Author’s response to reviews

Title: TB treatment delays and associated factors within the Zimbabwe National Tuberculosis programme

Authors:

Kudakwashe C Takarinda (ktakarinda@theunion.org)
Anthony D Harries (adharries@theunion.org)
Barnet Nyathi (bnyathi@theunion.org)
Mkhokheli Ngwenya (mkhongwenya@gmail.com)
Tsitsi Mutasa-Apollo (tsitsiapollo@gmail.com)
Charles Sandy (dr.c.sandy@gmail.com)

Version: 2
Date: 29 November 2014

Author’s response to reviews: see over
Dear Editor in Chief

Please find below a reply letter to our submission, titled:

**TB treatment delays and associated factors within the Zimbabwe National Tuberculosis programme**

We thank the Editor and the reviewers for their valuable comments to our initial submission. We have attempted to address all the queries made. We provide below a point-by-point response, and we have made tracked changes to the revised paper and also provided another clean version of the manuscript with all changes made highlighted in red font.

**Reviewer:** Anamarija Jurcev-Savicevic

**Reviewer's report:**

***Minor Essential Revisions***

I read this report with interest because it is addressing a very important issue in the context of TB control. Although the findings are not surprising or absolutely novel, this study took significant effort to consider the TB treatment delay and associated factors within the Zimbabwe National Tuberculosis Programme. However, I found that the manuscript needs some minor revisions.

**Comment 1**

1. Abstract
   
   It would be interesting to include in the abstract section proportion of the patients who experienced delays >30 days for PD and 15 days for HSD, especially because you chose these cut-offs as delays to understand abstract conclusion accordingly.

   **Response**
   
   Thank for noting the omission. We have since added the information by rephrasing the 3rd sentence of the results section as follows: “There was a median of 28 days (IQR, 21-63) for patient delays and 2 days (IQR, 1-5) for health system delays with 188 (49%) and 22 (6%) TB patients experienced health system delays >30 days and health system delays >15 days respectively.”

**Comment 2**

2. Introduction
   
   Provide the TB data from the newest Global TB Report.

   **Response**
We have updated TB data with the 2014 Global TB Report information as per your request.

**Comment 3**
3. Results
What was the refusal rate?

**Response**
We did not encounter any refusals to participate in the survey as all 383 smear-positive patients who met the study criteria voluntary consented to participate in the survey. We have added this information in the first paragraph of the results section.

**Comment 4**
4. Discussion
Could you explain in more detail uncommon practice to take self-medication for TB-related symptoms (any reference?)

**Response**
The uncommon practice of taking self-medication is in reference to the finding that only 12.5% of our study respondents had sought medication from a pharmacy prior to first presentation at a health facility. No references for purposes of comparison where identified in our literature search.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests

**Reviewer:** Mareli Claassens

**Reviewer's report:**
Major compulsory revisions

**Comment 5**
1. Methods:
a. Study participants and sampling: Were all districts/health facilities in Zimbabwe included in the sampling frame? Because of the multi-stage design, would clustering per facility not be expected? Is there a possibility of missing data, i.e. are all cases diagnosed/started on treatment registered?

**Response**
As mentioned in the section on “Study participants and sampling”, not all districts/health facilities in Zimbabwe were included in the sampling frame. Because of the multi-stage design, there is the possibility of clustering per facility. To correct for this, we have redone our statistical analysis where we weighted our dataset using proportional weighting in order to adjust for the
clustering effect in the survey. It is possible that there may be some diagnosed TB cases that may be started on TB treatment but not registered. Although we could not get access to the full article, a study done in one province of Zimbabwe by TC Murimwa et al. (Int. Health (2012) 4 (4): 320-322.) reported that 43% of 574 TB diagnosed cases who were treated during the first 6 months of 2010 were not registered. We have therefore stated the possibility of having missed some cases under limitations in the discussion section as follows: “Our study could have failed to capture information on confirmed TB cases who were started on TB treatment but were not registered as shown in a study conducted in one province of Zimbabwe whereby 43% of treated TB cases were not registered. [Murimwa, 2012]”

Comment 6
b. TB diagnosis under the NTP: For the facilities included in the study, were all Microscopy centres or were the primary healthcare facilities’ samples sent to other facilities? Is there a possibility that some patients could not be traced and therefore not registered/included in the study?

Response
27 of the 48 health facilities included in this study were TB microscopy centres and we have included this in the 5th line of the first paragraph in the “Study participants and sampling” section. Furthermore as mentioned in the results, 279 (74%) respondents were receiving TB treatment at the same facility where their sputum was analyzed for TB. Also as mentioned under the “TB diagnosis under the National TB Program” section, TB microscopy centres are often located at selected primary level health facilities, all secondary level health facilities (i.e. district & mission hospitals) in each district and all tertiary level hospitals (i.e. provincial and central hospitals).

Given that patients recruited in the study were only those who were registered as starting TB treatment in the health facility TB register, it is possible that those who could not be traced after a confirmed TB result were not included in the study. We focused on those registered in the TB register because that is the only way we could establish health system delays by determining the difference between their date of first visit to the health facility upon exhibiting TB symptoms from their patient notes and the date of initiating TB treatment.

Comment 7
c. Statistical analysis: Please clarify why a cut-off point of >15 days were used to investigate health system delay when the median in this study was 2 days (refer Finnie et al. where most of the quantitative studies used the median as cut-off). Were different cut-off points investigated? Especially since laboratory turnaround time for sputum samples (smear and GeneXpert) is expected to be less than 72 hours, so in effect patients should be started on treatment before 15 days after presentation to the facility. Account for missing data, i.e. which patients were included in the logistic regression models? Only those with no missing values for any of the variables?

Response
In view of your suggestion, we have revised the health system delay cut-off from >15 days to >4 days since we would expect that on day 1 sputum is collected, whilst day 2 & day 3 are
reserved for turn-around time of sputum results and day 4 for initiation of confirmed smear-positive TB patient on TB treatment. This timeline for initiation of smear-positive TB patients on TB treatment would be the most ideal for purposes of infection control though in practical terms it can be longer since not all facilities have a TB diagnosing centre on site and in certain settings, sputum transportation runs are erratic.

In terms of our data, there was an average of 3.2% of all variables missing in the analysis with a range from 0.52% to 14.36%. In order to limit case-wise deletion in the logistic regression, we coded all missing data for each variable as 9 in order to maintain all 383 respondents in our analysis.

**Comment 8**
2. Results:
   a. Patient characteristics: how many patients did not give consent to take part in the study? Could this have influenced the results?

**Response**
We did not encounter any refusals to participate in the survey as all 383 smear-positive patients who met the study criteria voluntary consented to participate in the survey. We have added this information in the first paragraph of the results section.

**Comment 9**
   b. Patient delays and associated factors: Did the patients accessing rural facilities also access traditional healers or other healthcare providers first? Is there any information available on the patients’ perception of rural facilities, i.e. that they might choose to access district/mission hospitals rather than primary healthcare facilities? Are the district/mission hospitals better funded or managed? Are these hospitals in general further away from patients compared to primary facilities? Add the significant association “visited a drug store yes/no”.

**Response**
Your questions have resulted in us adding text to our results and we have therefore expanded our discussion in context to this as follows:

On further analysis, those patients who started TB treatment at rural facilities accessed traditional healers more than those accessing other types of health facilities although the association was not statistically significant (14.2% vs. 8.4%, p=0.192). Seeking of treatment at private practitioners was also similar for both those who were treated at rural facilities and other types of health facilities (7.8% vs. 7.5%, p=0.937).

There is no literature in our extensive search which highlights patients’ perceptions of rural health facilities that may lead them to seeking treatment from district/mission hospitals rather than primary health care facilities. However in Zimbabwe’s four-tier referral system, district/mission hospitals are second-level health facilities and may therefore be preferable to primary care facilities or first-level health facilities since they manage referral cases not managed at primary care facilities and have a staff complement of medical doctors in addition to nursing staff and also provided specialized services to periphery first-level health facilities within the
district such as laboratory services and ART prior to decentralization. As such these
district/mission hospitals are centrally located within the district and therefore usually better
resourced or managed and generally further away from patients in comparison to primary
facilities.

**Comment 10**
c. Health system and associated factors: Patients with >4 visits to facilities, were
these patients also those accessing primary healthcare facilities or other
(traditional, private practitioners, pharmacies) first?

**Response**
On further analysis, those that visited traditional healers, pharmacies and private practitioners of
the 47 patients who had ≥4 health facility visits prior to starting TB treatment were only 5
(10.6%), 11 (23.4%) and 7 (14.9%) respectively.

**Comment 11**
d. The tables should be clarified in the sense that all variables are not accounted
for in tables 1 (ever heard of TB diagnosis before), 2 (type of diagnostic test,
diagnostic centre, marital status, self-medication, number of healthcare visits)
and 4 (previous contact with TB patient, marital status, self-medication, traditional
medicine, private practitioner). Why were certain variables left out?
e. For the figure, it would be interesting to split the columns according to patient
and health system delay to visualise the cut-off values used in the logistic
regression.

**Response**
We thank you for raising the above questions and we have attempted to address all of them
below:
Table 1
- We added “ever heard of TB diagnosis before” to table 1.
Table 2
- Type of diagnostic test was left out as we feel it is not related delays in making first visit
to a health facility from the time of onset of TB symptoms.
- “diagnostic centre” is in the table and is phrased as “TB diagnosis centre on site”.
- “Marital status” has not been shown as risk factor for patient or health system delay (refer
to Finnie RKC et al, 2011) and when we conducted univariate logistic regression in using
our data set it was not significant hence was dropped to limit no. of variables in our
paper.
- “self-medication” is included in the model as “visited drug store”. We have rephrased it
as “took self-medication from pharmacy”.
- “Number of healthcare visits” was not included as these were not a determinant of delays
in making a first visit to a health facility from the time of onset of TB symptoms but is
rather related to health system delays.
Table 4
- “previous contact with TB patient” was not included as this is a determinant of patient
delays rather than health system delays according to our study definitions.
- “marital status” was excluded for reasons stated for its exclusion from Table 2 above.
- “Self-medication” was included as “visited drug-store” but now rephrased as “took self-medication from pharmacy”.
- “traditional medicine” was included in the table.
- “private practitioner” has been added to Table 4, though it is not significantly associated with health system delays.

We have also included the cut-offs values used in the logistic regression for Tables 2 to Table 5.

Minor essential revisions

**Comment 12**
1. TB diagnosis under NTP: clarify the algorithm for the use of GeneXpert – are all smear negative and all HIV positive patients investigated with GeneXpert? Were patients who were GeneXpert positive all smear negative?

**Response**
A point of correction; Gene Xpert is currently recommended as the initial TB diagnosis among presumptive TB patients who are HIV-infected or who have risk factors for drug-resistant TB. In patients who are known to be HIV-negative and/or who have no risk factors for DR-TB, sputum smear microscopy is the diagnostic method of choice. We have amended the manuscript to highlight this. All the 29 patients who had a positive Gene Xpert result had had this test as the initial TB diagnosis test hence had no sputum smear-microscopy done.

**Comment 13**
2. Study definitions:
   a. Patient delay: clarify whether “registered nurse or medical doctor” refers only to NTP staff members or to private practitioners as well. When a patient visited a pharmacy, traditional healer or private practitioner first, was this visit defined as the “first visit” or only visits to NTP facilities?

**Response**
Contact with a health worker was defined as a nurse or medical doctor stationed at a public health facility, which in Zimbabwe provides TB treatment and these health workers excluded pharmacists, traditional healers or private practitioners. We have clarified this under the section on Study Definitions.

**Comment 14**
3. Results: clarify that “taking self-medication” refers to “visiting a drug store” in the tables.

**Response**
Yes, “taking self-medication” and “visiting a drug store” are the same. We have since rephrased either of the 2 statements as “took self-medication from pharmacy”.

**Comment 15**
4. Tables: include N= total no and N=total yes for patient delay and health
system delay in tables 2 and 4. Account for missing data.

**Response**
We have included the totals for patient delays (yes/no) and health system delays (yes/no) as suggested. All missing data has also been accounted for in tables 2, 4 and also table 1.

5. Discussion:

**Comment 16**
a. With regards to limitations, the sample size to determine patient delay was adequate according to the sample size calculation, but the number of participants who experienced health system delay (n=22) and had >4 visits (n=8) was small, limiting the interpretation of those results.

**Response**
Indeed the number of participants experiencing health system delay >15 days was small (n=22) and furthermore those with ≥4 clinic visits. However, in line with your recommendation, we have redefined health system delays as >4 days and therefore the number of participants experiencing this delay becomes 118, of which 20/45 (44%) who had ≥4 clinic visits experienced health system delays thus resulting in reasonably more precise results.

**Comment 17**
b. Was there a validation done of the questionnaire to curb the possibility of bias because of healthcare workers administering questionnaires?

**Response**
Unfortunately only validation of the information that was abstracted from patient clinical records was done.

**Comment 18**
6. Conclusion: consider recommending a qualitative study to elicit patient responses on why they thought delay was associated with access to primary healthcare facilities.

**Response**
We thank you for this suggestion, and we have therefore included it in our study conclusions.

**Discretionary revisions**

**Comment**
Please consider using line numbers in future submissions.

**Response**
We have added line numbers to the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests
Reviewer: James Mancuso

Reviewer's report:

Overall I thought this was a very well-written paper with some solid, clinically useful results. I had a few thoughts which the authors may wish to consider addressing.

Discretionary revisions:

Comment 19
1. Why did the authors choose to use chi-square analysis for time to treatment rather than the more commonly accepted Kaplan-Meier survival analysis? Cox regression would also seem to be more suitable for multivariate regression.

Response
We used logistic regression because it allowed us to set a particular time period as the cut-off points for both patient delays and health system delays from which findings can be compared with other existing literature. Also survival analysis is better suited for prospective cohort studies whereby we are able to follow up a cohort of study participants from date of entry into a study to the time they develop the outcome of interest, which was not possible in our study.

Comment 20
2. The authors should comment on why those who lived farther from the facility were less likely to experience delays, since this finding is counter-intuitive.

Response
We attempted to explain this observation which indeed is counterintuitive. However it is likely that higher patient delays among those with shorter travel time to a health facility and those accessing treatment at lower-level health facilities are attributed to more health conscious patients seeking treatment sooner at higher-level hospitals even though they may be further away whilst those patients who are less health conscious seek treatment late at nearby lower-level clinics. This is given that Zimbabwe has a four-tiered referral health system and district/mission hospitals which are at the second level are preferable since they manage referral cases not managed at primary care facilities at the first level as they have a staff complement of medical doctors in addition to nursing staff and also provide specialized services to periphery first-level health facilities within their district such as laboratory services and ART prior to decentralization. As such, these district/mission hospitals are centrally located within the district and therefore usually better resourced or managed and generally further away from patients in comparison to primary facilities, particularly in rural settings.
Comment 21
3. The authors should comment on the finding that > 4 visits were associated with health delays. Although this is very logical and intuitive, some more information about these cases (there were very few) would be helpful. Were they diagnostic dilemmas, atypical presentations, HIV infected, bad doctors, etc? The only information presented is that half saw physicians only in one facility.

Response
In total there were 45 cases that had >4 clinic visits prior to commencing TB treatment with and of these 20 (44%) encountered health system delays after we had redefined health system delays as >4 days as recommended by previous reviewers. Unfortunately we do not have more information to explain the reasons for these numerous visit in terms of diagnostic dilemmas, atypical presentations and whether the doctors where bad or good. The only information has you have highlighted was that those with more than >4 clinic visit and had experienced health system delays, there were 8 (42%) who had seen different health workers in the same facility and 11 (58%) who had seen different health workers in different health facilities.

Comment 22
4. How can the median total delay be 36 (page 11) when the medians for patients is 28 and the median for health system is 2 days. What were the other 6 days?

Response
Please note that the total delay is a function of adding the patient delay and the health system delay per individual. However, despite doing so, the median total delays do not literally translate to addition of the median patient delays and the median health system delays since each individual has varying patient delays and health systems hence the distribution obtained from a plot of total delays is different from that obtained for a plot of patient delays and that of health system delays. I hope the above explanation clarifies our point.

Comment 23
5. Page 12 discusses the lower than expected system delays of 2 days. Might this finding be the result of the increased scrutiny from enrolling patients in the study (Hawthorne effect)?

Response
Generally, health workers are aware of the urgency of tracing and initiating smear-positive TB patients on TB treatment once the results are communicated from the laboratory (more commonly by cellular phone) for issues of infection control hence this may not be a very surprising observation. However it is indeed possible that the hawthorne effect may have been at play in this study and we have acknowledged this possible limitation in our discussion. Another follow-up records-review study may better validate whether our findings were a true reflection of the situation on the ground.

Comment 24
6. Much recent interest in the use of presumptive treatment has been raised by the experience with GeneXpert. The authors should consider commenting on the use of presumptive treatment in this population and how it may affect study findings and conclusions.

**Response**

Thank you – this is an important point but as we are already at the limit of the word count we would prefer not to get involved in this discussion.

**Comment 25**

7. In particular, the conclusion could be strengthened with specifics. The authors state the need for increased advocacy, communication and social mobilization. What about targeting the drug stores and pharmacies as per the results? Recent HIV diagnosis, recent start of ART, and timing of ART would be other known confounders that could impact TB diagnosis. Were any of these patients contacts of known TB cases and was routine TB screening performed among the HIV patients as per WHO guidelines. To what extent were these factors considered and how might they impact delays?

Are there patients that can be identified who should be screened more frequently? Perhaps those initiating ART after initial diagnosis?

**Response**

We have added a recommendation to the conclusion that there is a need for engagement and training of pharmacy staff so that they can accurately identify people with TB-like symptoms and effectively explain to them that TB diagnosis and treatment are offered for free at public health institutions as this may lessen patient delays.

In our study we noted that 9.1% of respondents were currently staying with someone on TB treatment and 45.2% had previously had contact with a TB patient. However, these two variables were not associated with encountering patient nor health system delays.

We also found out that prior uptake of HIV testing and receiving HIV treatment and care services where not associated with both encountering patient and health system delays and we also adjusted for their potential confounding in the multivariate analysis. According to the Zimbabwe national TB and HIV programmes all HIV-infected individuals should be routinely screened for TB at every review visits or encounter with a health worker using the the 4 TB-symptom screening checklist. Also recently, use of Gene Xpert machines for TB screening among HIV-infected individuals has been recommended and may explain why those screened for TB using Gene Xpert encounter less health system delays. We have outlined these points in the manuscript narrative.

**Comment 26**

8. Generalizability. The authors should consider commenting further on
generalizability. This study was done in smear positive largely HIV positive population. This does not represent the full spectrum of TB cases, and in particular the HIV patient population which is largely smear negative. Delays in smear negative are likely to be much more complex, longer, and difficult to address.

**Response**
Our study was specific to smear-positive TB cases since they are at higher risk of transmitting TB in the community if they are not quickly diagnosed and started on TB treatment. However it important to highlight in the conclusion that our findings do not represent the full spectrum of TB cases (in particular those with smear-negative TB) which is indeed more complex, longer and difficult to address. We have therefore added this statement in our conclusion section.

**Level of interest:** An article of importance in its field
**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:** Paulo de Tarso Dalcin

**Reviewer's report:**
This is a very interesting study evaluating the extent of both patient and health system delays in accessing TB treatment within the public health facilities under the Zimbabwe National Tuberculosis Programme. This manuscript is addressing a very important issue in the context of TB control. In this study, the median patient delay was 28 days and the median health system delay was 2 days. Starting TB treatment at district / mission vs rural primary healthcare facilities was associated with shorter patient delays whilst taking self-medication increased patient delays. Four or more visits to health facilities prior to TB diagnosis were associated with health system delays.

# Major Compulsory Revisions

**Comment 27**
1) In a previous study, the factors that were independently associated with patient delay for TB treatment were cocaine and crack. The authors did not analyze these variables in the present study. They should discuss this issue in the limitations of the study.

**Response**
Whilst injecting drug use is associated with patient delay for TB treatment, their use is prevalent in other parts of the world such as Eastern Europe and are uncommon in Sub-Saharan Africa (Mathers BM et al, 2008). Given this, we did not analyze this variable in our study.

**Comment 28**
2) I am not sure if the authors included only pulmonary TB in the study. They should clarify this in the Methods section.

**Response**

Our study referred only to confirmed pulmonary tuberculosis (PTB) as mentioned in the Methods section under “Study participants and sampling”.

**Level of interest:** An article of importance in its field  
**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:** Sven Gudmund Hinderaker

**Reviewer's report:**
This is a nice paper about treatment delay in Zimbabwe, interviewing patients about their symptoms and diagnosis. Delays at health facilities were short, but patient delay before contacting the health system averaged a month. Text is good, with some minor issues for your consideration.

Major revision: None

Minor essential revisions:

**Comment 29**
There are more tables than needed for the paper. I suggest you reduce number of tables, combine 2+3 and 3+4. Some columns can be deleted: p-values and NO-columns.
The column heading remaining are:
Tables 2+3: Characteristics-Total- Patient delay>30d - OR(95%CI) - AOR(95%CI)  
Tables 4+5: Characteristics- Total- Health system delay>15d - OR(95%CI) - AOR(95%CI)

**Response**
Thank you for your suggestion. However we had included separate tables for Table 2 & 3 and 4& 5 since some of the variables in tables 2 and 4 were not included in the multi-variate analysis. This was meant to cater for any queries about variables that were not included in the analysis. We do hope this response is satisfactory.

The column headings for the tables 3 and 5 have been amended so that they read as shown above. We thank you for your suggestion.

Discretionary revisions and pages:
Response
We thank the reviewer for above comments. We have addressed all of these comments. However, we are unsure what is meant by the comment for page 12 and have therefore not been able to accept this recommendation. We hope the editor is alright with our stance here.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

Reviewer: Chandrashekhar Sreeramareddy

Reviewer's report:
MS 'TB treatment delays and associated factors within the Zimbabwe National Tuberculosis programme'
Authors: Kudakwashe C Takarinda, Anthony D Harries, Barnet Nyathi, Mkhokheli Ngwenya, Tsitsi Mutasa-Apollo and Charles Sandy

This MS reports about an important areas of operational research about TB care from high burden African country. The research seems well designed covering a large geographic area one country and obtaining a representative sample of TB (pulmonary) patients. The whole article is succinctly written but has not cited some important literature about this area of research. The authors have used sound analysis techniques, but I suggest a different (details below) suggestions for analysis and tables.
I would for classify my comments/suggestions as major or minor revisions since this article from national sample has merit for publication.

Comment 31
Abstract:
Background could be cut down to say "insufficient (no) literature from Zimbabwe and state their objective. state smear positive pulmonary TB cases in the
Response
We thank this reviewer for the suggestion and we have amended the background to the abstract accordingly. We have also stated “microbiologically confirmed pulmonary TB” instead of “confirmed TB” or “smear-positive pulmonary TB” since those patients who were included in our study were either Gene Xpert positive or smear-positive PTB patients.

Comment 32
Methods: Suggest to write two-stage, random sampling technique to obtain a nationally representative sample.
Should write 'smear positive pulmonary TB cases' here as well. Provide briefly how patient and health care system delay.
Typo (95% CIs)
Patient characteristics is not a suitable term as they have other factors related to health system as well.

Response
Thank you once more for the suggestions. We have made necessary amendments in line with your suggestions.

Comment 33
Results: Inconsistency in provide number and % for background characteristics. Conclusions as high or low or majority (even if not 80%) should be avoided. mission vs primary health care facility and increased patient delay are incorrect interpretations. please modify. aOR and 95% CIs are standard acronyms. To avoid double brackets.

Response
We have ensured that all provided numbers and percentages for background characters are consistent.

Comment 34
Conclusion:
Health system delay was uncommon (short) is mainly due to recruitment of the patients within the framework of national TB control program framework. 4 or more visits was associated with health system delay. So the authors first conclusion is both right and wrong (read the following by Lambert et. al. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2005.01485.x/pdf )
Last conclusion "who should be trained? Staff of NTP or private sector or missionary or government hospital staff. What was the basis from the results for this?

Response
In view of the article by Lambert we note that it provides a critique of studies that recommend improving awareness of TB in the community of reducing long delays to TB treatment yet these have weak evidence on patients’ knowledge of TB. This however was not the case in our study since our study shows that 88% of respondents had heard of TB prior to them being diagnosed with TB disease. Furthermore, our recommendation was not aimed at education of the community about TB since we do not have adequate evidence of lack of TB knowledge but instead our recommendation was to educate communities to seek timely and appropriate medical consultation upon exhibiting symptoms suggestive of TB. In addition we have added a recommendation that pharmacy staff should be educated and engaged about referring clients with TB suggestive symptoms to public health facilities since our results show that those who sought self-medication where more likely to encounter patient delays.

The recommendation on training was directed at health workers implementing NTP activities in the form of providing TB diagnosis and treatment services. The basis of this recommendation was the finding that having >4 clinic visits prior to commencing TB treatment was a risk factor for encountering health system delays. As stated in the discussion section of the manuscript, we speculated that these frequent visits could highlight missed opportunities for screening TB in presumptive cases or poor documentation or misplacing of patient records which may have resulted in each follow-up visit being like a first visit.

We also do acknowledge that our study had limitations since it only focused on those patients who reported to the health system and were diagnosed and started on TB treatment. In view of this we have highlighted in our limitations that our study may have missed those who did not seek health care on developing TB symptoms and also those who might have been diagnosed with TB but did not show up for commencement of TB treatment.

Main MS.

Comment 35
Background:
2st and 3Rd paragraphs should be combined. Last sentence of 2nd and first sentence of 3rd paragraph are the same and should be cited. Importantly 2-3 systematic reviews (Sreeramareddy et. al. Storla et. al and Finnie et al. and their conclusions should be cited since this research is conducted within the framework of studies included in these systematic review.

Response
We have deleted the last sentence to paragraph 2 as this is similar to the first sentence in paragraph 3. However we feel merging paragraph 2 and 3 will make the combined paragraph too long. The above mentioned systematic reviews have been referenced in the manuscript.

Comment 36
Results from some studies from Africa (or Zimbabwe) should be brief in the background.

Response
We have referenced the important factors identified in the meta-analysis by Finnie et al which was specific to sub-Saharan Africa.

**Comment 37**
1979-2004 is not recent but 10 years old. Please update these numbers.
Authors should be consistent with the terminology throughout the MS. treatment delays are different from diagnostic delays i.e. Patient delay, health system delay as mentioned in abstract. Please read Sreeramareddy et. al. 2014

**Response**
We have added 2013 TB mortality estimates from the WHO TB Global report 2014 in place of the 1979-2004 review paper by Dlodlo et al. We have also ensured that there is consistency in use of patient and health system delays instead of treatment delays.

Methods:

**Comment 38**
Which random method (Simple, systematic, stratified) was used?
It is not clear which type of health facilities were selected. Private, Public Mission hospitals, etc. Were these urban or rural health facilities. Were they primary care or secondary/tertiary care hospitals? The delay would be longer tertiary care, rural hospitals? So it is important to know these since seeking care depends a lot of health services (type, number, accessibility, user fees, quality etc).
Microbiologically confirmed (either sputum smear or gene expert) Pulmonary TB cases should be written clearly.

**Response**
A two-stage random sampling criteria was used to identify the provinces and districts where the study would be conducted whilst the high volume sites were selected for inclusion into the study regardless of type of health facility. At the sites, patients were sequentially recruited into the study upon voluntary informed consent as highlighted in the methods section.

Of the selected facilities, 3 were provincial hospital (3rd level health facilities in urban settings), 15 were district/mission hospitals (2nd level health facilities with all mission hospitals in rural setting and district hospitals having a rural/urban mix), 10 were urban clinics and 19 were rural primary health care facilities. Find the insert under section titled “Study participants and sampling”

Below is an extract from Table 1 showing the distribution of respondents:

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Count</th>
<th>Total</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provincial hospital</td>
<td>18</td>
<td>383</td>
<td>4.7% (3.1-6.9)</td>
</tr>
<tr>
<td>District/mission hosp</td>
<td>237</td>
<td>383</td>
<td>61.8% (58.5-64.9)</td>
</tr>
<tr>
<td>Urban municipal</td>
<td>73</td>
<td>383</td>
<td>19.1% (16.7-</td>
</tr>
</tbody>
</table>
The term microbiologically confirmed PTB has been used throughout the manuscript in place of sputum smear or gene expert pulmonary TB.

Comment 39
Authors wrote a good description about NTP some of which are beyond the scope of this MS. For example smear-negative TB definition and EPTB case definition and the next paragraph starting with "Once traced.........."

Response
We have removed irrelevant information on smear-negative and EPTB case definitions. However the paragraph starting with “Once traced” has remained since we feel it shows the processes that happen within the health facility setting once a patient is traced from the community upon having microbiologically confirmed PTB.

Comment 40
Variables: Abstracted or extracted
The last sentence about questionnaire translation should be written before questionnaire piloting for correct sequence of activities. Sex is missing in the list of variables and once again authors fail to explicitly write smear-positive Pulmonary TB.

Response
Thank you for noting the above. We have amended the mentioned text accordingly. Please refer to the manuscript.

Comment 41
Number is visits occurs twice in one paragraph. Statements about consent appear thrice in the MS.

Response
We have deleted the repeated text on number of health facility visits and statements about consent.

Comment 42
I have an important suggestion about use of an arbitrary cut-off for delay. Read the systematic review and editorial in this topic. I would suggest the authors to use time durations between onset of symptoms until first contact with nurse/medical doctor and there onwards until treatment initiation as continuous (though skewed) variable to test associations in their multivariate a models. For HSD, they had very small number of cases leading to wide 95% CIs due to

| Rural primary healthcare facility | 55 | 383 | 14.5% (11.4-18.2) | 21.8) |
categorization of a continuous variable (loss of data) and probably not detecting any associations.

**Response**
Whilst the reviewer suggests that we use the outcome of delays (particularly patient delays) as continuous variables we feel this may not be the best approach. If the outcome is left as a continuous variable it is not clear to us what type of multivariate analysis will be used and how the results will be interpreted and in relation to what reference.

Since we have redefined our cut-off for health system delays from >15 days to >4 days there are now more cases encountering health system delays (30.7%) hence the 95% CIs are narrower and we were able to detect more associations.

**Comment 43**
Also tables 2 and 3 and tables 4 & 5 are redundant.

**Response**
This comment is not very clear since removing tables 2 to 5 would leave the manuscript with the table on descriptive patient and health system characteristics. We would like to retain these tables and hope the editor can accept this.

**Comment 44**
Present the time durations (in days) according to variables tested for associations for patient, health system (if required total delays) in one table for a comparison of delays (days) according to variables tested. If overall median (IQR) values for delays are provided in this table figure 1 is not necessary. Later one table for associations

**Response**
The above suggestion can indeed assist in cutting down on the number of tables however we opted to have the tables separate since you will notice that not all variables linked to patient delays are linked to health system delays and vice-versa. We hope this is justifiable.

**Comment 45**
Table 3
Smoking is not reported whereas alcohol is reported. Studies show smokers may seek care very late attributing the cough to their smoking but not TB (Bam et al.). Took traditional medicine, visited drug store, and consulted private practitioners should be one variable as first action taken after onset of symptoms. I am not sure how the question/s were phrased.

**Response**
Indeed smoking is an important variable to assess and we have now included it though it was not statistically significant in our study. The variables that patients took traditional medicine, patients visited drug stores and consulted private practitioners were all asked as separate questions and had overlap hence they cannot be lumped together as one variable.
**Comment 46**
Definition of patient delay: It should refer to onset of first symptom.
Health system delay TB treatment or anti-TB treatment?
Criterion for Fisher's exact test? How small was small?

**Response**
Below are the definitions for patient and health system delay as written in the manuscript:

*Patient delay* – the time period in days between the onset of TB symptoms and the patient’s first contact with a health worker of >30 days

*Health care system delay* – the time period in days between the date of first contact with a health worker and date of start of TB treatment of >4 days. This is assuming that laboratory turnaround times for sputum samples are expected to be less than 72 hours and coupled with immediate tracing of patients for start of TB treatment for purposes of infection control.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**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:** Sayoki Mfinanga

**Reviewer's report:**

**Comment 47**
1. The description on study participants and sampling: In the multistage sampling, it is not clear on whether stratification was done to ensure an equal chance of selecting primary, secondary and tertiary health facilities. Also stratification into rural and urban facilities is not clear. The overrepresentation of district/mission hospitals and underrepresentation of primary health care facilities should be justified.

**Response**
Selection of study sites was independent of type of health facility (i.e. primary, secondary and tertiary health facilities) but instead a two-stage random sampling of provinces and districts where those sites with >30 smear-positive PTB cases per quarter were selected. Overall, 47 health facilities were included in the study of which 3 were provincial hospital, 15 were district/mission hospitals, 10 were urban clinics and 19 were rural primary health care facilities hence no overrepresentation of district/mission hospitals and under representation of primary health care facilities was done in site selection. We have, however, weighted our data in the analysis to account for the over-sampling in the district/mission hospitals. It also important to note that the majority of TB cases are recorded at these district/mission hospitals and are compared to primary health care facilities at national level in Zimbabwe.
Comment 48
2. A minor correction is needed on results section, under Health system delays and associated factors; the [AOR 3.34, 95% CI 1.11-10.03, p=0.031] should be changed to [aOR 3.34, 95% CI 1.11-10.03, p=0.031}. Also on discussion paragraph two: “Whilst the majority of our study participants were rural patients, distance to a DOT facility was not associated with patient delay and in fact those taking a longer time taken to reach a DOT facility were less likely to experience patient delays.” The word ‘taken’ should be deleted.

Response
Thank you for noting those grammatical errors. We have corrected them accordingly.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

We thank the reviewers for their useful comments in improving the quality of this paper. We hope that it is now satisfactory.

Best regards
Kudakwashe C Takarinda
On behalf of the co-authors