Author's response to reviews

Title: Time to first consultation, diagnosis and treatment of TB among patients attending a referral hospital in Northwest, Ethiopia

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Author's response to reviews:

Dear Editor,

First and foremost we would like to thank the reviewers for their constructive comments regarding our manuscript. We have now revised the manuscript based on each of the reviewer's comments. The necessary corrections and newly added texts have been shaded in yellow in the manuscript. Please find below our responses to the reviewers' comments in italic right after each comment/question.

Sincerely yours,

Solomon Abebe Yimer

Corresponding Author

Reviewer's report

Reviewer 1: Sven Gudmund Hinderaker

1. The pages MUST have side numbers! It is cumbersome to comment without line numbers or page numbers.
Comment accepted, page numbers inserted on each page of the manuscript.

2. For the content I suggest you drop the TOTAL DELAY. The more specific patient and HS delay is much more informative, and total delay is redundant. OK for conclusion.

We would like to keep total delay as we have additional information resulting from newer analyses to report to the reader.

3. Analysis you must do again. You cannot use health post as reference category; there are TOO FEW non-delayed in health-post so that the estimates are TOO WIDE intervals. I suggest you look at ALL your categories and check that you have chosen a good reference value. In selecting reference you must also include some statistical perspectives! It may be more natural to select HIV neg than pos as reference?

Comment accepted and analyses have been performed

4. Many results have too many digits, giving an impression that your precision is MUCH higher than it is! E.g. AOR 3.39, 95% CI 1.29-8.93, say AOR 3.4, 95% CI 1.3-8.9.

Comment accepted, and numbers have been rounded off to one decimal place as suggested

TITLE

5. Delete name of facility. Say “referral hospital in northern Ethiopia”.

Comment accepted, correction made in the title.

ABSTRACT:


Comment accepted, correction made in the text.

7. Results: abbreviations first time give full, e.g (Interquartile range IQR 7-60days)
Comment accepted, correction made as suggested.

8. Avoid words like «Inadmissibly», try be scientific. If interviewed be “politician”

Comment accepted, correction made in the text.

9. “TB test will reduce…” this is NOT what you have shown. May be true. But dont claim!

Comment accepted, correction made in the manuscript.

10. In conclusion you have not even mentioned that the important determinant of delay is RURAL living, most consistent! In all tables that is obvious! Focus on this. HS+pt delay both!

Comment accepted, correction made in the text as suggested

11. In conclusion of abstract you indicate that pt delay is acceptable, but HS delay is not acceptable. Fairly equal size. Reader may wonder why.

According to the literature review that we performed, there is no standard cutoff point to divide delay periods into acceptable- and unacceptable delays. Based on consultations of treating physicians and previous studies, a delay of 30 days for patient delay is commonly considered acceptable. For health systems delays, a delay of up to two weeks is also considered acceptable. These were the reasons for our claim.

INTRO:

12. There is nothing about HIV in the intro, only TB. HIV must be mentioned! This is an important addition to make. Need not be long.

Comment accepted and a text about HIV is included in the introduction section.

13. In SAME paragraph you need not refer to a paper TWICE even if different sentences.

Comment accepted, correction made in the text.

14. «Delay studies…» You talk about it as if known. Your reader may not know.
Rephrase it maybe «Studies on delay in starting TB treatment …» or similar

Comment accepted and correction made in the text.

15. EPTB contagious: yes they have sometimes cough! As you show in table. EPTB can often have an UNRECOGNISED PTB in addition, which would be potential transmitter. Not surprising as they are all infected via lungs before disseminating, but EPTB itself can hardly do so. ALWAYS suspect concomitant PTB! That is why sputum always should be taken from EPTB!

Comment accepted.

METHODS

16. The setting needs MUCH more info. Where do people live? How do they live rural/urban? Standard of living? What do they do when sick? How far must they go? Do they all use modern health system? Traditional healers? Transport systems! Cars? Buses? Trains? Bikes? Rivers? Distribution of health facilities? Hospitals? How to get there? Rural/urban? Make this interesting so that people understand why urban/rural is a risk factor. This is important because the only important determinant is rural/urban living. You MUST give more info about it. Likely cultural differences rural/urban? E.g. use of traditional more in rural? Rural people less used to health care and get lost? A qualitative study would be nice as additional info.

Comment accepted, and more information have been added regarding the setting of the study.

17. You indicate details of demographic and clinical characteristics. They are in the tables and need not take space here. Refer to table 1.

Comment accepted, the text has been reduced as suggested

Data analysis:

18. You say in line 3: «A and delay of more…» delete «and»

Comment accepted and correction made in the text

19. «Patients with a median delay…» should be «patients with delay», delete Median
Comment accepted and correction made in the text

20. You say you use multivariate log.regression. In abstract univariate. In tables both. Be consistent!

Comment accepted and correction made in the text

21. You must mention how you adjusted, what was your regression model? Did you adjust for ALL variables? Selected some? How selected?

We first performed uni-variate analysis on each variable to calculate crude odds ratios. Epidemiological and clinical significance were considered to include variables in the final regression model. The goodness of fit of the multiple logistic regression model was assessed using the Hosmer-Lemeshow test. A two-sided p value of less than 0.05 was considered statistically significant.

Definitions:

22. Patient delay indicate only time since started COUGH! In EPTB only 3 patients

Patient delay indicates the time from the start of TB symptoms until first visit to medical providers

23. Sample size considerations have not been mentioned!

Study participants were enrolled in the study from January to August 2010 in a consecutive manner, the total number of patients enrolled in the study represent nearly 50% of the cases for the year 2010.

RESULTS

24. You state that age among PTB and EPTB was significantly different and you give CI 2.15-9.06. You do NOT indicate what this number represents.

Comment accepted and correction made in the text

25. You could consider baseline info to show if categories are significantly different. In Table.

Comment accepted, P-values included in table one.
26. You give symptoms for Sm+ and SmNeg patients + EPTB. Therefore «all PTB» not needed, delete.

Comment accepted correction made in the text

27. Are symptoms recorded «present symptom» or «FIRST symptom» or otherwise?

Symptoms recorded were symptoms at presentation

Predictors of delay:

28. In your text there are too many numbers, they are all in the table! Do not repeat all the numbers. Only sufficient to get the message and refer more to table.

Comment accepted. Only significant findings are included in the text.

29. If you MUST give numbers make it more readable e.g : adjusted odd ratio (AOR) 3.4; 95% CI 1.3-8.9. Try make it pleasant to read it.

Comment accepted, correction made in the text.

30. I suggest you drop TOTAL DELAY, delete table and text. It does not give more than you have in pt and HS delay. Redundant.

We think it is still relevant to keep total delay; we got additional information when the analysis was re-done, and it is important to report that for the reader.

DISCUSSION

31. Delete the first paragraph in discussion.

Comment accepted and the suggested paragraph has been deleted

32. In para 2 you say: «Our findings indicate…» Actually you claim that main problem is HEALTH SYSTEM delay, and not patient delay. But they were not very different, 27 and 21, and you give no reason for your claim. You consider it obvious. And you even use in abstract.
As mentioned earlier, a median patient delay of 30 days is considered acceptable according to opinions of treating physicians and previous studies. It is crucial that patients get timely diagnosis when presenting to medical providers. Our finding of median health systems delay of 27 days is unacceptable.

33. Drop total delay.

Please see comment to number 32

34. In para 4 you say “.may result in …MDR...”. I suggest you rather state the generic fact that is can lead to drug resistance (which then may be MDR).

Comment accepted, correction made in the text.

35. Para 5: You say “Urgently needed”. Delete “urgent”. There are many things more urgent than treating a chronic disease. It is not an emergency admission. You are a scientist, not politician.

Comment accepted, correction made in the text.

36. Para 6. You talk very little about rural residence as a risk factor. This is your most consistent finding. There must be several cultural factors involved, aren’t there? Do rural people feel less welcome at health facilities? More use of traditional healers? Perhaps suggest “more research is needed”, e.g a qualitative study? Perhaps rural people do not have relatives working there and helping them around, as many “urbanites” have? They don’t understand system? MUCHless exposure to it??

Comment accepted and further study has been recommended as suggested

37. Total delay drop it.

We have earlier mentioned our reasons for keeping total delay

38. Para 11 conclusion. Sentence starting “Patients with EPTB.” is too heavy and can be rephrased, “higher risk of increased delay” is same as “longer delays”.

Comment accepted correction made in the text.

39. Do not say “Urgently needed…”, “highly recommended”. It is very good if we get it, and same day referral would be lovely, but for a chronic disease it is not
emergency.

Comment accepted the word “urgently” is removed from the text.

40. Do you find it surprising that HIV gives surprising results? HIV NEG have higher risk of HS delay, is it because HIV pos are always suspected of TB? What about patient delay? The estimate of pt delay suggests lower risk in HIV neg than pos, but not statistically significant. Be VERY careful stating NO ASSOCIATION in your study, your POWER to claim no association is fairly low.

Comment accepted! We are not surprised with the result related to HIV serostatus. We just wanted to report the finding!

REFERENCES:

41. Do references correctly. Do not trust the electronic reference manager. Look at every one. Especially those documents that are not journal papers.

Comment accepted.

42. Take a look at these references:: #1, 2, 11 need bold title, 20 bold author, 31bold title.

Comment accepted, and the necessary corrections have been made in the references.

TABLES:

43. Give tables number!

Comment accepted, corrections made in the tables.

44. Table 1. Baseline characteristics. This gives the same info in many tables. The only reason to keep it is if you check whether the categories in each variable are similar or significantly different, creating a potential confounder in regression analysis. Do you adjust for ALL variables in baseline in adjusted log. regression?

All in table? All in baseline table?

We have added p values f in Table one. We have adjusted for all variables in the tables during the regression analysis.

45. Table 2. Patient delay. Title OK, column headings have errors:
Comment accepted, corrections made in table 2

46. % delayed should be delayed (%)

Comment accepted, corrections made in the table

47. Table 3. Health system delay: Column 3 Heading says P-value. Delete.

Comment accepted, corrections made as suggested.

Should be only Delayed (%). The analysis must be done again. FHP visited uses as reference HEALTH POST. Only one was not delayed. This cannot be used as reference! Perhaps also change reference in HIV variable as mentioned above.

Comment accepted, analysis redone as suggested.

48. Table 4. Total delay: This table can be deleted. There is no additional info in this table. Errors: used comma not fullstop. “P-value” in column heading misplaced.

Comment accepted, and correction made in the table. We have kept the table because of the reasons mentioned earlier.

Reviewer 2: Matthew Arentz

Abstract

1. A better clarification of the meaning of total delay is needed (presuming this is not the patient delay + the systems delay). Perhaps ‘total delay in time to initiating treatment’.

Comment accepted, and correction made in the abstract.

Introduction

2. Please either write out or use numerical numbers, not both (see line 1).

Comment accepted, and correction made in the text.
Methods

Data analysis

3. In the data analysis section you comment on a 30 day cutoff as being an acceptable patient delay. Why is this considered acceptable? Why not 14 days (HIV positive) or 21 days (HIV negative). Why is the system delay set at 14 days? Please clarify. Please also expand on what you considered patient delays (i.e. delay in evaluation, delay in follow up, ect.) and system delays (i.e. diagnostic delay, delays in referred to clinic for treatment initiation… especially in smear negative cases). This is not intuitive to the reader and is ambiguous in the text.

As far as our literature review is concerned, there is no standard cutoff point to divide delay periods into acceptable- and unacceptable delays. Our cutoffs are based on opinions of treating physicians, and results of previous studies. A thirty days cutoff point has commonly been used as an acceptable delay period for patient delay in many previous studies. For health systems delay, a delay of up to two weeks is also considered acceptable. We consider patient delay as the time from the start of TB symptoms until first visit to a medical provider, and health systems delay covers the time from first visit to a medical provider till first initiation of treatment.

4. When analyzing the relative importance of factors in delay, why not use time delay as a continuous variable (as opposed to a dichotomous variable)? You say that longer delays may be associated with more transmission and worse outcomes. Yet you use time cutoffs (i.e. 30 days, 21 days and the median total delay) as your division.

Yes, we agree that delay can be analyzed as a continuous variable as suggested. In this study however, we used dichotomous variables to run logistics regression analyses and analyze factors associated with delay.

Definition of variables

5. This needs some clarification for me. Couldn’t patient factors (i.e. slow to follow up, failure to promptly present for diagnostic work up following initial presentation) be important in what you define as “health systems delay”. Could health care factors (i.e. number of clinics, distance from clinic) be important in your definition of “patient delays”? How to patient and system delays factor into the time from evaluation for diagnosis to initiation of treatment (i.e. your total delays)? Please clarify why you chose these definitions as your Conclusions/discussions are largely based on these/
Comment accepted! We agree that “slow to follow up, failure to promptly present for diagnostic work up following initial presentation” should be considered when analyzing health systems delay. Number of clinics and distance also affect patients delay. Unfortunately, we have not documented this in the current study, and these factors should be investigated in future studies.

The definitions we used for patients, health systems and total delays have been used in a number of previous studies. We used these definitions to compare our results with similar former studies.

Results

TB Symptoms

6. Where there significant differences in TB symptoms among your patient groups? If so, it would be useful to highlight them.

Yes, we observed significant differences in TB symptoms among PTB and EPTB patients. We have included a new text regarding this in the results section.

Length of delay

7. Did length of health systems delay increase for smear negative cases? Some national guideline recommend a trial of antibiotics in smear negative, HIV negative TB suspects with low/intermediate suspicion of TB. This could be an appropriate reason for delay in some smear negative cases.

Yes, some former studies have shown increased health systems delay among smear- negative cases compared to smear- positive cases. However, this was not the case in our study.

Discussion

8. Can you clarify if your HIV positive patients were more often smear negative? Either way, provider education on the importance of TB in HIV could explain why they experienced no delay in diagnosis.

Yes, there were more smear –negative cases among HIV-positive patients in our study.
9. There are a number of other important issues raised here, but there are two major points that I believe need to be addressed.

a. When one discusses patient and health care delays in TB diagnosis and treatment, the most important question is, “What can we fix?” Many of the delays you highlight (i.e. rural vs. urban setting, pulmonary vs. extrapulmonary TB) are not alterable. How might you intervene to decrease delays (other than point of care testing)? Strengthening health care systems is not specific enough. Where and how might you strengthen those systems?

Comment accepted, and we have now included specific recommendations in the text.

b. It is important to note that while you observed relatively short patient delay times, both recall bias and attrition bias (i.e. only patients who seek out care and follow up in clinic are included in your cohort).

Comment accepted! We agree that these are important limitations of the study and have been mentioned in the manuscript.