Author's response to reviews

Title: Factors associated with delayed treatment of tuberculosis in hospitalized patients: a retrospective cohort study.

Authors:

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Version: 3 Date: 5 February 2012

Author's response to reviews: see over
Reviewer's report

Title: Factors associated with delayed treatment of tuberculosis in hospitalized patients: a retrospective cohort study.

Version: 2 Date: 8 January 2012

Reviewer: Susanna Sophia van Wyk

Reviewer's report:

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

METHODS:
1. With regard to laboratory turn-around time. I assume that the 2 hours, mentioned at the end of paragraph 2, apply to direct tests only and not culture. Extra-pulmonary TB and sputum smear negative TB (the two main factors associated with diagnostic delay) are usually diagnosed on culture. What is the average turn-around time for culture (Löwenstein-Jensen medium) in your laboratory?

The average turn-around time for culture is 4 weeks. We included this information in the article.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

RESULTS:
2. Third paragraph, first sentence: According to table 1 “Cough and night sweats were more common in patients with a diagnosis in less than 6 days...” Why do you say “less than 24h”?

We corrected the sentence.
DISCUSSION:
3. First sentence: Change “retrospective study” to “cross sectional study” or just remove “retrospective”.

We changed “retrospective study” to “cross sectional study”.

4. Paragraph 6: “...less than 24 hours after admission” is not consistent with the results. Should this not be “...less than 6 hours”? We changed “24 hours” to “6 days”.

RESULTS:
6. Paragraphs two to four are duplication of Table 1. I would suggest highlighting only the factors that are significantly associated with delay in the text.

We included only factors significantly associated with delay in these paragraphs.

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
Reviewer's report

Title: Factors associated with delayed treatment of tuberculosis in hospitalized patients: a retrospective cohort study.

Version: 2 Date: 8 January 2012

Reviewer: John Ayisi

Reviewer's report:

1. Is the question posed by the authors well defined? No. The authors have to justify why they have not presented data on facility specific factors associated with delay. They need to clearly define delay and just imply.

This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).

2. Are the methods appropriate and well described? Yes

3. Are the data sound? No. There is no denominator. Did all the suspects test TB positive? Was there a difference in delay with regard to TB test done etc…

As stated in Methods section, “we included only the patients who began treatment for TB after hospitalization.” We did not include TB suspects. Patients with sputum smear negative or not performed (didn’t produce sputum) were more frequently diagnosed more than 6 days after admission, using other tests like positive acid-fast bacilli in induced sputum or bronchoalveolar lavage, PCR, presence of granuloma and positive acid-fast bacilli in biopsy specimens, and culture. Only 32 patients were diagnosed exclusively by culture. We included this information in the text.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes, but have to present complete data as suggested in major revisions below

See answers below.
5. Are the discussion and conclusions well balanced and adequately supported by the data? No. The discussion is very weak as suggested in the major revisions e.g. no data is supporting their conclusions and statements they make

See answers below.

6. Are limitations of the work clearly stated? No. why was data on healthy facility not presented?

This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes. They appear do have a limited understanding of statistics and need to read more on this subject to able to address the issues I have raised

We revised again all statistics aspects of this article.

8. Do the title and abstract accurately convey what has been found? Title is ok.

Abstract has problems indicated below.

See answers below.

9. Is the writing acceptable? Only if issues raised have been fully addressed.

- Major Compulsory Revisions

Abstract:

Results;

1. I thought at day 6 (the median), 50% of the cases should have been diagnosed. The authors report 33.2%, and in addition their values 33.2% and 45.6% do not add to 100%. What is the explanation for missing data (21.2%)
Sorry, this was a mistake. Some percentages of the old delay classification were maintained. The correct percentages are 54.4% (≤ 6 days) and 45.6% (>6 days).

2. Line 11. What is the definition of diagnostic delay? If it is >6 days that should be stated.
We included the definition of diagnostic delay in line 11.

3. Line 11, regarding main factors associated with delay, did the authors address the effect of HIV status, if so what was it?
HIV was not a factor associated with delay in the present study.

4. Conclusion, last sentence. The authors need to allude to what facility specific factors contributed to delay otherwise why was the study done among hospitalized patients?
This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).

Introduction:
3rd paragraph, after last sentence, the authors have to include provider/facility factors that can cause delay otherwise why was study done on hospitalized patients only?
This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).
Methods:
1. 2nd paragraph. Line 2, during the period of three years, kindly specify the period e.g. January 2001-December 2003.
   We included the period: “January 2008 - January 2011”.

2. 2nd paragraph. Line 14, sentence ending with location [11]. It looks an incomplete sentence.
   We changed the sentence: “The diagnosis of extra-pulmonary TB was based on clinical and/or complementary tests according with the location of TB”.

3. 3rd paragraph. Line 12, after discharge. What is the discharge policy in Brazil/study hospital? Was it e.g., after the intensive phase of treatment?
   The discharge policy is “as soon as possible”, once patients are expected to be treated in outpatient’s clinics. They remain hospitalized only if their clinical condition does not allow discharge.

4. 5th paragraph. Line 7, p# 0.05 is too conservative for inclusion in a multivariate analysis. It’s usually 0.10 or even 0.20. Same line after univariate analysis, add -- or those known to have clinical significance.
   OK, we choose p< 0.10 for inclusion in multivariate analysis.
   We added “or those known to have clinical significance.” after univariate analysis.

Results:
1. 1st paragraph. Line 1, what was the denominator of your three hundred and five, since you were dealing with TB suspects, did they all have TB?
   As stated in Methods section, “we included only the patients who began treatment for TB after hospitalization.” We did not include TB suspects.

2. Note that apart from current smokers your table 1 has no results on the behavioural factors.
   OK, we included alcoholism and injection drug use in the Table 1.

3. 2nd paragraph. Line 1, highlight the significant findings first, and mention the ones not significant.
We changed the order of sentences in the 2nd paragraph.

4. 2nd paragraph. Line 1, the variable age had p=0.079, this can’t be ignored as not significant.
   **OK, we changed the sentence.**

5. 3rd paragraph line 2, data is misleading as 89 (53.6%) refers to #6days and not 24h.
   **We changed “24h” to “6 days”.

6. 3rd paragraph line 2, sentence starting There was no significant----, should be re-written as: Even though patients diagnosed #6days were more likely to be febrile 111 (66.9%) vs 79 (56.8%), the difference was not significant p=0.072
   **We excluded this sentence, as suggested by other reviewer.

7. 4th paragraph lines 6 and 7. All patients with ---- extra-pulmonary TB. Add (data not shown).
   **We included “data not shown” after this sentence.

8. 5th paragraph line 2. Re-write as in 6 above. HIV sero-positivity was more common in group 1 than group 2, though this difference did not reach statistical significance (p=0.059).
   **We excluded this information from the text, as suggested by other reviewer.

9. 5th paragraph line 3, comment on the fact that chronic renal failure numbers were too small.
   **We included this information.

10. 5th paragraph last sentence starting with Age > 60 years----. This information is obvious and since it adds no value to the study in question I would suggest it be entirely deleted.
    **We excluded this sentence.

11. 6th paragraph line 5, ---- adjusted by age and sex. This makes no sense. The
purpose of a multivariate analysis is to determine for independent explainable variables for the study question as all variables in the model adjust for each other. So those that remain significant have been adjusted for all variables that were in the model.

**OK, we changed the sentence.**

12. 6th paragraph line 7, ---- The statement starting The following variables ---- should read-- The following variables remained significant in the final ----

**We changed the sentence.**

13. Since this study was facility based, the results would be incomplete without the authors mentioning provider/facility based factors that could have contributed to delayed diagnosis.

**This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).**

14. Table 1. Under demographic characteristics, Age >60 years is missing data on totals column. Replace (-) with data.

**We included n (%) on total column for age > 60 years.**

15. Table 1. Footnote, Data are presented as mean ±SD, clearly clarify that continuous variables (age) are presented as mean ±SD, and not blanked as currently presented.

**We changed the footnote.**

Discussion:

1. The last sentence of your results (6th paragraph lines 8 and 9) contradicts your discussion (1st paragraph line 4) as diabetes and chronic renal failure were not significant in your final model.
We changed the sentence.

2. 2nd paragraph line 2, ---- The statement starting—we found unacceptable time delay ---- is totally misleading as the authors do not provide other comparative data from Brazil and/or other similar settings elsewhere to justify their statement. In addition, information in line 10 confirms that their findings agree with other studies referenced [14-18].
OK, we excluded the sentence.

3. Again depending on diagnostic method used (e.g. culture), your observed delay may be acceptable.
Patients with sputum smear negative or not performed (didn’t produce sputum) were more frequently diagnosed more than 6 days after admission, using other tests like positive acid-fast bacilli in induced sputum or bronchoalveolar lavage, PCR, presence of granuloma and positive acid-fast bacilli in biopsy specimens, and culture. Only 32 patients were diagnosed exclusively by culture. We included this information in the text.

4. 2nd paragraph line 7, does 2-87 days refer to patient or facility delay?
As stated in the cited article, it refers to health system delay.

5. 2nd paragraph, line 10, sentence starting. Another warning ----, does not make Sense
OK, we excluded the sentence.

6. 2nd paragraph, line 10, your findings of 45.6% and 30% from Canada (line 12) contradicts your information as cited by Ward and others [12], as presented in line 4, sentence of Ward and others [12] -----
OK, we changed the sentence: “Despite a high incidence of TB, as suggested by Ward and others [12], 45.6% of patients in our study had diagnosis delayed by more than a week.”

7. Were the 30% in Canada duet to pulmonary or extra-pulmonary?
Treatment was initiated after a week or more in 30% of all patients with pulmonary TB. We included this information in the text.

8. 2nd paragraph line 14, --- diagnosis was probably ----. Why use probably and yet you have results??

**OK, we excluded “probably”**.

9. 2nd paragraph lines 18 starting with In the multivariate analysis --- up to line 22, authors are repeating what they have already stated in lines 15-17

**We excluded the repeated information.**

10. 2nd paragraph line 23. In reference [18], what were health system factors in Rwandese study and can current study replicate them? The authors need to look at health system delay also as their study was facility-based as I have already stated earlier.

**In Rwandese study, health care system delay was the time from the first contact with a health care provider to the time of diagnosis, exactly the same factor that we looked in our study.**

11. 3rd paragraph line 3, reference [9], were participants hospitalized as is the case of the current study. Again delay in diagnosis among hospitalized cases cannot be due to age. I had stated this even in my earlier review

**We excluded 3rd paragraph.**

12. The whole paragraph 3 talks a lot about age as though this was the main aim of this study and yet it was not!!!!

**We excluded 3rd paragraph.**

13. 3rd paragraph last line (line 10) ending ---- which was not evaluated in the present study. This is the weakest part of your study as you must explain why you did not assess facility related factors contributing to diagnostic delay, otherwise why target hospitalized patients?

**We excluded 3rd paragraph.**
14. 5th paragraph line 6, ---- thought symptoms would go away has nothing with causing delay of diagnosis once a patient has been hospitalized/admitted as is the case with the study under review.

**OK, we excluded the sentence.**

15. 6th paragraph lines 1-2, there is no group diagnosed less than 24h as per your results.

**We corrected this information.**

16. 6th paragraph line 5, --- In the same way----default---. This sentence is poorly constructed as default of treatment and night sweat are not related to be in the same paragraph

**We excluded the last sentence of this paragraph.**

17. 8th paragraph HIV makes people more sick and you may be required to check for effect modification in your analysis.

**HIV was not a factor associated with delay in the present study**

18. 9th paragraph, Diabetes and chronic renal failure were only in the univariate analysis, and not multivariate analysis and thus one can’t rule out confounding, as these variables were not in the final model.

**OK, we excluded this paragraph.**

19. 11th paragraph 1st sentence is misleading as you have not provided any data on health system factors causing diagnostic delay

**This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t performed patient interviews. However, we evaluated health care system delay (the time from the first contact with a health care provider at the hospital to the time of diagnosis). Prospective studies will help us to understand what specific factors contribute to this health care system delay (e.g. low awareness of TB, atypical presentations, delayed results of diagnostic tests, etc).**

20. 11th paragraph line 4, you have not provided any evidence to show that TB
awareness was low among clinicians.

OK, we excluded this sentence.

21. 11th paragraph line 8, recall bias may not be an issue among newly
diagnosed patients

OK, we excluded this sentence.

22. 11th paragraph line 10, sources of delay need to be addressed by study
looking at both patient and facility/provider related factors

This was a retrospective study. We couldn’t evaluate patient delay, as we didn’t
performed patient interviews. However, we evaluated health care system delay (the
time from the first contact with a health care provider at the hospital to the time of
diagnosis). Prospective studies will help us to understand what specific factors
contribute to this health care system delay (e.g. low awareness of TB, atypical
presentations, delayed results of diagnostic tests, etc).

23. 12th paragraph line 2 ---- setting is long---. This is not true as studies you
have cited show that your observation is consistent with other studies (4-12.5
days [ref. 14-18])

OK, we changed the sentence.

24. There may have been no really delay in this study depending on methods
used to diagnose extra pulmonary TB, as it is hard to diagnose it, thus could
methodology of TB have been the issue?

Patients with sputum smear negative or not performed (didn’t produce sputum)
were more frequently diagnosed more than 6 days after admission, using other
tests like positive acid-fast bacilli in induced sputum or bronchoalveolar lavage,
PCR, presence of granuloma and positive acid-fast bacilli in biopsy specimens, and
culture. Only 32 patients were diagnosed exclusively by culture. We included this
information in the text.

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

Introduction

Line 7, what does 2010 stand for in inhabitants/year/2010?

**The correct is “in 2010”**.

Methods:

1. 2nd paragraph. Line 13, --- tests according with---, should be ---- tests according to--- [11].
   **We changed “according with” to “according to”**.

2. 2nd paragraph, line 15, --- our hospital has all ---, should be our study hospital has all –
   **We included “study” before “hospital”**.

3. 2nd paragraph, line 20, --- the word reported to be replaced by confirmed
   **We replaced the word “reported” to “confirmed”**.

Results:

1. 3rd paragraph line 1, --- patients whit, should be – patients with ---
   **We corrected the word**.

Discussion:

1. 2nd paragraph, line 4, the sentence starting, Ward [12] suggests ----should read: Ward and others [12] suggest -----  
   **We included “and others” after “Ward”**.

2. 7th paragraph line 2, sentence starting: In fact---, should read: A similar study has also shown that radiographic changes-----
   **We changed the sentence**.

- Discretionary Revisions

These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.
Please note that both the comments entered here and answers to the questions below constitute the report, bearing your name, that will be forwarded to the authors and published on the site if the article is accepted.

Based on your assessment of the validity of the manuscript, what do you advise should be the next step?

- Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions