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: 2  Date: 26 December 2011

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: 1 Date: 28 November 2011

Reviewer: Ramona Finnie

Reviewer's report:

Minor Essential Revisions

1) The second paragraph under Methods states PTB was diagnosed "according to the following criteria established in the Brazilian Guidelines for Tuberculosis". It looks like the diagnosis required 1 of the 5 requirements and that the list starts from the most preferred method. Is there a hierarchy in how diagnosis is made? If so, this should be stated.

**Pulmonary TB was diagnosed according to any of those criteria, and there is not a preferred method. We changed the sentence: “Pulmonary TB was diagnosed according to any of the following criteria…”**

2) In the discussion, you make connections between patient (help seeking) delay and treatment delay (citing studies of patient delay to confirm this study's findings for treatment delay). It is important to explicitly state that patient delay may effect diagnostic or treatment delay when making these connections. That is why the findings for patient delay are important for diagnostic/treatment delay.

**As suggested by another reviewer, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article. Therefore, we made many changes in discussion section.**

3) Please check for typos in the paper.
The paper was checked for typos.

Discretionary Revisions

1) Is the term in-hospital diagnosis more widely used vs in-patient diagnosis?

Yes, as we have seen, in-hospital is more common.

2) Inclusion criteria: what age classifies as adults in this population (15 and up or 18 and up)?

We classified adults as 18 and up. We included this information in the text.

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.

Ramona K.C. Finnie
Reviewer's report
Title: Factors associated with delayed treatment of tuberculosis in hospitalized patients: a retrospective cohort study.
Version: 1 Date: 16 November 2011
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)
INTRODUCTION:
1. First 2 sentences need to be referenced.

2. Second paragraph, second sentence is not supported by a relevant reference.
   Please provide a relevant reference to this statement.

METHODS:
3. Setting: Please elaborate on setting. What are the TB caseload, cure rate and HIV-TB co-infection rate in this setting? Also say something about the laboratory facilities and what TB tests are routinely done at the lab.
   We included more data on setting: “Porto Alegre is the city with the highest incidence of TB in Brazil (115 cases/100,000 population), with a cure rate of 67%. Also, the TB-HIV co-infection rate is the highest in the country (35%).”
   We included information about lab facilities and TB tests: “In addition to the most common tests as acid-fast bacilli smear, culture, drug susceptibility test and tuberculin skin test, our hospital has all the standard major equipment to conduct biomedical research studies (ultracentrifuges, HPLC, PCR, electrophoresis, cytometer, etc). Induced sputum and Bronchoscopy Unit are also available.”
4. First paragraph, second sentence: Adult patients with TB that were hospitalized...during what period? You also need to describe inclusion criteria and exclusion criteria, e.g. age.

We included information about the period of hospitalization: “Adult patients with TB that were hospitalized during the period of three years were identified retrospectively.”

We described inclusion and exclusion criteria: “Adult patients (≥ 18 years old) with all forms of TB that were hospitalized during the period of three years were identified retrospectively. We included only the patients who began treatment for TB after hospitalization. Patients who were already receiving treatment at admission were excluded from this study.

5. Third paragraph, first sentence: What do you mean by data were collected in a standardized questionnaire. Does the hospital routinely collect data in a standardized questionnaire when patients are admitted? Or do you mean data were collected from patient records using a standardized data extraction tool?

Data were collected from patient records using a standardized data extraction tool. We changed the sentence in the article.

6. Do you have any data on laboratory turn-around time? When were specimens sent to the lab and when were results reported by the lab? Did patients initiate treatment on the same day results were reported? The question here is, does the lab play an important role in the delay in treatment or is it only the clinical team that plays a role? If data on this is not available, it should be discussed in the limitations.

The specimens were sent to the laboratory as soon as they were collected. Typical turn-around time in our laboratory is 2 hours. Patients initiate treatment in the same day results were reported. We included this information in the text.

7. Statistical analysis: You might have more power using delay as a continuous variable rather than categorising it. Also, it is difficult to interpret results if unadjusted analysis was conducted using 3 categories of delay, but adjusted analysis was conducted using only 2 categories of delay. You should either use delay as a continuous variable or you should categorize delay into the same
number of groups throughout.

We decided to categorize delay into two groups, according to median delay.

8. Last paragraph, fourth sentence: Should it not be “...using selection of factors associated with delay (rather than death) in univariate analysis”? If it is “death”, then this is inconsistent with the study question and results.

We changed “death” for “delay”.

9. How did you establish a significant level of 0.20 to determine the variables that would remain in the model?

We decided to adopt a more traditional level ($P < 0.05$). We included this information in the text.

RESULTS:

10. First paragraph, third sentence reads “The overall delay until initiation of treatment was 6 days (2-12 days)”. This is unclear. This should be changed to “The median/average delay from hospital admission until initiation of TB treatment was 6 days (IQR/Range 2-12 days)”

We changed the sentence: “The median delay until initiation of treatment was 6 days (IQR: 2-12 days).”

11. You’ve included 16 covariates in your multivariate analysis. Did you have enough power to look at so many covariates?

As we decided to adopt a more traditional level ($P < 0.05$) to determine the variables that would remain in the model, fewer covariates were included in multivariate analysis.

TABLE 2:

12. Footnote: The footnote is unclear. What does “p for the comparison between groups 1 and 2” and “p for the comparison between groups 1 and 3” and “p for the comparison between groups 2 and 3” mean? In the table you report only 1 p-value for the 3 categories.

As we have modified the analysis for two categories of delay, this footnote was also excluded.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

INTRODUCTION:
13. Second paragraph, last sentence: Put it in context. Consider changing it to “According to 2 studies....” or “According to a systematic review conducted by....the main factors associated....”

We changed the sentence: “According to 2 studies, the main factors associated with diagnostic delay included HIV infection, negative sputum smear, extra-pulmonary TB, old age, and female sex [8,9].”

METHODS:
14. Design: Is this really a retrospective cohort study? Patients were sampled according to their TB status and hospital records were reviewed thereafter to collect data on risk factors for delayed treatment. I would call this a cross sectional study of hospitalized TB patients. Data were collected retrospectively.

We agree. We changed the title and methods section.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

15. Title: Consider including the country or “high TB burden setting” in the title.

We changed the title: “Factors associated with delayed treatment of tuberculosis in hospitalized patients in a high TB and HIV burden setting: a cross-sectional study.”

INTRODUCTION:
16. Last paragraph, last sentence: Remove the “Then” in front of the sentence.

We removed the “Then”.

TABLES:
17. Consider merging table 1 and 2.
We merged the table 1 and 2.

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

Quality of written English: Needs some language corrections before being Published

The manuscript was revised and some language corrections were made.

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: 1  Date: 25 November 2011
Reviewer: John Ayisi

Reviewer's report:

1. Is the question posed by the authors well defined? No. Its not clear whether the authors are addressing diagnostic or treatment delay and whether all patients were admitted due to TB or other conditions.

The patients were admitted with a clinical suspicion of TB. After diagnosis in the facility, treatment is initiated immediately, that’s why we used both terms. However, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article.

2. Are the methods appropriate and well described? No. If it was a retrospective cohort, there is no clear definition of what an actual TB case was in this study.

As suggested by another reviewer, this is considered a cross-sectional study. Then, we changed the title and Methods section. Pulmonary TB was diagnosed according to any of those criteria cited in the Methods section, and there is not a preferred method. We also included more information on laboratory facilities, as suggested by other reviewers.

3. Are the data sound? Yes. But what criteria were used to get the three classifications of delay?

We changed this classification, as suggested by another reviewer. Now, we have two classifications based on the median delay.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data? No. Major shortfalls of discussions are indicated in the major compulsory revisions below
6. Are limitations of the work clearly stated? No. Regarding mortality, were there patients who might have been discharged, died but were not captured by this study?

No. Data after discharge were obtained from SINAN’s database (National System of Information on Noticeable Disease). SINAN is a database from the Brazilian government which stores information concerning all notifiable infectious and contagious diseases. Also, we contacted by telephone the outpatient primary health care units where patients received the treatment after discharge, in cases without an outcome in this database. We included this information in the article.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.

8. Do the title and abstract accurately convey what has been found? No. refer to my remarks on major compulsory revisions below

9. Is the writing acceptable? Yes

- Major Compulsory Revisions
1. There is confusion from the Title and the contents of the manuscript. Were all patients admitted due to TB diagnosis but treatment initiation was delayed in facility?

The patients were admitted with a clinical suspicion of TB. After diagnosis in the facility, treatment is initiated immediately, that’s why we used both terms. However, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article. The title was also changed: “Factors associated with delayed diagnosis of tuberculosis in hospitalized patients in a high TB burden setting: a retrospective cohort study.”

2. The authors are mixing treatment delay as in the Title and diagnosis delay as in discussion paragraph 1, line 4. Their definition of treatment delay must come out clearly.
The patients were admitted with a clinical suspicion of TB. After diagnosis in the facility, treatment is initiated immediately, that’s why we used both terms. However, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article.

Discussion section
3. In Abstract (line 12) and in discussion section (paragraph 1, line 4 and paragraph 3, line 1 it is wrong to state female gender was associated with delayed treatment. This has not been shown in your multivariate analysis. We decided to categorize delay into two groups, according to median delay, as suggested by another reviewer. Then, female gender was not associated with delayed treatment anymore.

4. It looks like female gender is confounding HIV. Authors should therefore present results of HIV status of the study group, by gender. We decided to categorize delay into two groups, according to median delay, as suggested by another reviewer. Then, female gender was not associated with delayed diagnosis anymore.

5. Paragraph 2, last sentence give the likely explanation for differences observed in Brazil (45.6%) and Canada (30%).

We changed the last sentence: “In a population-based study in Canada, treatment was initiated after a week or more in 30% of all patients [14], which could be attributed to the relative rarity of active TB in this country, resulting in a lack of awareness of TB. However, in our study delayed diagnosis was probably related to extra-pulmonary TB and smear-negative pulmonary TB, which frequently carry diagnostic difficulties.”

6. Paragraph 3, line 2 what do figures 500 in parenthesis indicate? 

There was an error in the number “100”; the correct sentence is: “A cross-sectional survey of 1000 newly diagnosed pulmonary TB patients (500 women and 500 men)...”

7. Paragraph 3, line 5 the cited study from Tanzania, did authors address patient
and provider delay in their current study? They need to be careful in their writing.

**We excluded this paragraph, once female gender was not associated with delayed diagnosis anymore.**

8. Paragraph 3, last sentence, ending with ---- explain our finding. There is no evidence from their data to support this statement.

**We excluded this paragraph, once female gender was not associated with delayed diagnosis anymore.**

9. Its not plausible as to why age should delay treatment initiation among TB diagnosed patient, but can impact health seeking (can delay). Authors need to clarify this.

**We included this sentence at the end of paragraph: “This finding can be explained by the fact that old age is more closely related to patient delay, and not health care system delay, which was not evaluated in the present study.”**

10. Paragraph 9, line 1, is delay of treatment or diagnosis? In same paragraph line 3, HIV is known to delay TB diagnosis due to non-specific results and not what the authors are alluding.

**This paragraph was changed once HIV was not associated with delayed diagnosis in the new analysis.**

11. Paragraph 10, line 7, authors to keep in mind that age affects care seeking, not treatment initiation in a health facility, and at the same time it is a risk factor for chronic diseases like diabetes. The argument regarding age and initiation of treatment in a health facility is not consistent with what is in the public domain.

**We excluded the sentence: “Age > 60 years was more frequent in these patients, although this was not a risk factor for delayed diagnosis in our study.”**

12. Paragraph 11, this paragraph need re-writing unless it is clarified what delay in treatment in this study means, the discussion is misleading if patients started treatment immediately upon diagnosis in the facility after being admitted. Were all patients admitted due to TB or it was due to other medical problems?
The patients were admitted with a clinical suspicion of TB. After diagnosis in the facility, treatment is initiated immediately, that’s why we used both terms. However, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article. The paragraph was rewritten: “Our data did not show an increased mortality in patients with retard in diagnosis. Controversy still exists on the role of delay in TB diagnosis and treatment in the mortality rate. Although some authors demonstrated an association between diagnosis delay and mortality [20,38-40], in other studies delayed diagnosis was not a risk factor for mortality [16,38,41].”

13. Paragraph 12, line 1, the limitation between diagnostic and treatment delay must be made by the authors for this study to have value. Otherwise, the conclusions may be misleading.

After diagnosis in the facility, treatment is initiated immediately, that’s why we used both terms. However, in order to avoid misunderstanding, we choose to write delay in diagnosis all over the article.

14. Paragraph 12 last sentence starting with Delays in diagnosis---- is misleading since the study only addresses health facility delay in treatment and not patient delay, thus one can’t tell whether most delay was due to patient or provider, hence source of delay may not be captured from admitted patients.

We excluded this sentence.

15. Paragraph 13, second line linking delay with female gender is wrong as this did remain significant in multivariate model. In addition studies on health seeking, especially by HIV status may be warranted in the study setup as a recommendation.

We decided to categorize delay into two groups, according to median delay, as suggested by another reviewer. Then, female gender was not associated with delayed treatment anymore.

We included the sentence: “In addition, studies on health care seeking may be warranted in this setting.”
- Minor Essential Revisions

Discussion Paragraph 9, line 5 has a typo error

**We corrected the error.**

Methods:

First paragraph

1. 3rd line southern in Southern Brazil should start with a lower case.

**We corrected that.**

2. Last sentence starting with ethics committee to be moved to after the end of 4th paragraph after the words ---- and group 3 (> 6 days).

**We moved the sentence.**

Second paragraph

1. Last sentence ending with location (line 10) needs a reference

**We put a reference (number 11) after the sentence.**

Third paragraph

1. Second line, variables from smoking to injection drug use should referred to as behavioural, while from clinical form TB to outcome of after discharge should be medical history.

**We changed the sentence:** “…behavioral data (smoking status, alcoholism, injection drug use), and medical history (clinical form of TB, symptoms at admission, methods of diagnostic, presence of comorbidities, prior TB treatment, drug regimen, interval from hospital admission until initiation of treatment, length of hospital stay, intensive care unit [ICU] admission, length of mechanical ventilation, hospitalization outcome [death or discharge], and outcome after discharge [cure, dropout, death]).”

Results:

2nd paragraph line 3--- current smokers (and in Table 2) appear to be fewer in group 3 (p=.082). The issue may be small numbers affecting your statistical test. Clarify this fact.

**These results changed after the new analysis.**
5th paragraph lines 5 and 9 add % to figures e.g. 56.8% and 36.8% respectively

**We added % to figures.**

6th paragraph, last sentence that starts with--- The following variables remained----, need to show these results as Table 3.

**We merged Table 1 and 2, as suggested by another reviewer. Then, we included the data from multivariate analysis in Table 2.**

Table 1. Include the median delay and IQR.

**We included median delay and IQR in Table 1.**

Level of interest
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- An article of importance in its field

Quality of written English
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- Needs some language corrections before being published

**The manuscript was revised and some language corrections were made.**

Statistical review
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- No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests
'I declare that I have no competing interests' below.
Reviewer's report
Title: Factors associated with delayed treatment of tuberculosis in hospitalized patients: a retrospective cohort study.
Version: 1 Date: 13 November 2011
Reviewer: Sarah Lou Lou Bailey

Reviewer's report:
Whilst this study does not produce drastically novel data, the study is well conducted, clearly presented and the findings do add to the body of existing data. In particular, the background section is clear and concise, and the methods section is detailed, clear and replicable.

Major Compulsory Revisions
Nil

Minor Essential Revisions
1. Some very minor attention to grammar is required, for example abstract, line 3.
We corrected grammar errors in abstract and also reviewed all the manuscript.

2. In the results section of your abstract you need to define what the values are that are given in line 1. Is this mean delay (and standard deviation)? Also, the separation of participants into group 1, 2 and 3 does not make sense in the abstract, though is clear in the full methods section.
This is median and IQR. We corrected the sentence: “The median delay until initiation of treatment was 6 days (IQR: 2-12 days).”
We changed the sentence that separated participants into groups: “Sixty seven (21.9%) patients initiated the treatment ≤ 24 h after admission to hospital, 99 (32.5%) between 24 h and 6 days, and 139 (45.6%) > 6 days after admission.”

3. The results are mostly presented clearly, though I’m not clear about the legend in table 2. The star and crosses say that they relate to p-values but are located next to mean and standard deviations. Do you mean that the p-values for the comparison of these means are <0.05. If so, for what comparisons are the p-values that are presented? Or have I misunderstood this? Clarity on this would
be helpful.

We changed the presentation of data, as suggested by another reviewer, so the legend is also modified.

Discretionary Revisions
Nil

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

Quality of written English: Needs some language corrections before being Published
The manuscript was revised and some language corrections were made.

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