Author’s response to reviews

Title: Epidemiological profile of tuberculosis patients by HIV status in Brazil: a retrospective cohort study

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Author’s response to reviews: see over
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Re: MS: 3215530541241648 Epidemiological profile of tuberculosis patients by HIV status in Brazil: a retrospective cohort study

Dear Editor:

We would like to thank you and the reviewers for their thoughtful comments on our paper and the opportunity to improve it.

Our point by point responses to the editor’s and reviewers’ comments is below and the revised paper is attached.

Thank you for considering our paper for publication in BMC Infectious Diseases.

Best regards,

Ethel Maciel for the Authors

REVIEWER’S REPORT

Reviewer #1

I) Major Compulsory Revisions

1) Abstract: 1st sentence..."The prevalence of TB-HIV co-infection was 10.8% (95% CI, 10.7% – 12.9%) among adults # 15 years of age" ... If HIV status is known only for 46,466 subjects, shouldn't then TB/HIV prevalence = 46,466/243,676 = 19.1%??

Author’s response: We have made change as you suggested

2) Discussion/conclusion..."HIV-related TB has not declined in Brazil over the past decade, despite significant declines in overall TB rates"... This conclusion seems beyond the scope of the study (data available, analyzed and presented). Thus, the sentence need to be re-phrased based on the data and findings of the study. It would be more informative if the trend in TB and TB/HIV during the study period (2007-2011) is analyzed, and then discussed as compared with previous data.

Author’s response: We have made change.
II) Minor Essential Revisions
1. Methods/Study population... line 103 "...... whose HIV status of TB transmission # 15 years old..." ... lacks clarity, need to be re-write
   Author's response: We re-wrote this sentence as you can see below:
   The population of the study included TB cases aged ≥15 years reported in Brazil between January 1st, 2007 to December 31st, 2011.

2. Data Analysis and Statistics... line 133 "....We compared TB subjects with TB with HIV subjects.." ... lacks clarity, need to be re-write
   Author's response: We re-wrote this sentence as you can see below:
   We compared subjects with TB and HIV (TB – HIV) with those who only had TB (TB only) according to socio-demographic characteristics, comorbidities and TB features.

• Discretionary Revisions
  Level of interest: An article whose findings are important to those with closely related research interests. Author's response: Thank you
  Quality of written English: Needs some language corrections before being published
  Author's response: We have made changes. The manuscript was edited by a native-English speaker with scientific expertise, who is a co-author of the paper.
  Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Reviewer #2

I) Major Compulsory Revisions
Before a final decision is taking on its acceptance or otherwise, the authors need to have the paper edited proficiently in order to make the take home message clearer. In its present form, it is not. A number of these are highlighted for their consideration

**Author's response:** We have made changes. The manuscript was edited by a native-English speaker with scientific expertise, who is a co-author of the paper.

**Line 83** Studies performed … should read, “Studies conducted …”

**Author's response:** We have made change

**Line 91** “Thus, models of analysis using the hierarchical multivariable analysis, could be explain or determining a causal model of TB-HIV” needs revision

**Author's response:** We have deleted this sentence

**Line 105** (TB – HIV) should be deleted

**Author's response:** We have deleted this sentence

**Line 123** should be revised: “inclusion” and “included” – one should be deleted.

**Author's response:** We have deleted “inclusion”.

Perhaps, it could read “Directly observed therapy (DOT). Besides, there’s a need to justify why DOT subjects are treated as covariates.

**Author's response:** We decided to treat DOT subjects as covariates, because in Brazil the strategy is not fully implemented and other studies shown the important of DOT to outcome.

**Author's response:**

Line 126 “abandoned” is not the right terminology – default, I guess is the right concept

**Author's response:** We have made change

**Line 137 – 143** I counted 9 or more uses of “plus”. This makes reading monotonous. The authors are encouraged to vary the language or may perhaps rephrase to simplify the whole paragraph.
Author's response: We have change this sentence as you can see below:

In the hierarchical analysis, the following covariates were included: step 1 (Gender + age + school level + skin color + Area of residence); step 2 (variables retained from step 1 + Institutionalization + DOT); step 3 (variables retained from step 2 Diabetes); step 4 (variables retained from step 3 + treatment type + TB form + Tuberculin Skin Test + smear + culture + pathologic examination + X ray suspicious for TB); and step 5 (variables retained from step 4 + outcome).

Line 145 should read, “Due to high missing information on HIV status, we carried out polynomial analysis based on the following TB treatment outcomes (default etc.) vis-à-vis HIV status (negative etc.) …”. Cured TB status was used a reference category instead of the present rendition.

Author's response:
Thank you. We have made change

Line 168 on should be replaced “in”

Author's response:
We have made change

Line 198 add “group” to age to read age group

Author's response: We have made change

Line 207 like should be “likely”

Author's response: We have made change

Line 211 “Since” should replace “As”

Author's response: We have made change

Some other issues the need to pay attention to include the use of indefinite article “The”. Sometimes, it is misplaced. Also, some capitalizations are misplaced because they are not proper nouns.

Author's response: We have made change.
Reviewer #3

This MS has used a large data base of surveillance information from Brazil, a high TB burden country. The topic of this MS is important addition to the existing literature, but the MS writing and some analysis issues are to be addressed before publication. Detailed specific issues are detailed below.

One major issue for credibility of results by multivariate analysis (hierarchical) is missing data for certain variables. I see table 1 & 2 where authors have shown samples (numbers) included in the analysis for each of the variables. All the data was not available for all variables, including some as less as 50% of cases included in the final analysis. Data on skin test, Culture, histopathological report was available for <50% of the cases included.

**Author's response:** We included as limitation of our study the missing data for certain variables. Nevertheless, our large sample size still allowed us to maintain a high statistical power. Besides, the quality of the utilization of data base of surveillance information from Brazil was confirmed in previous studies.

Authors only had HIV information for just over 50% of the all TB cases captured from SISAN/TB database (43% missing from figure) but authors wrongly, state prevalence of TB-HIV co-infection as 10.8% by not excluding all TB cases for whom HIV status was unknown. The actual proportion (not prevalence since this isn't a survey using representative sample) is 19.07% shown in the figure.

**Author's response:** We agree with you and we have made change.

Indeed, all TB cases included in the analysis are not representative of TB cases in Brazil since all TB cases and those with and without HIV co-infection may not be reported to SINAN/TB as both conditions have social stigma.

**Author's response:** In Brazil the treatment of TB and HIV patients is offered free of charge by the National Tuberculosis and AIDS programs. So, the treatment is available unique by public health services. The patients have to be notified in National Surveillance System to receive these medications. This strategy reduces underreporting of TB patients. As we said above the quality of the utilization of data base of surveillance information from Brazil was confirmed in previous studies.
Thought this MS generally follows STROBE guidelines, most important missing information is about how SINAN/TB is organised in Brazil, what information is gathered, flow of the information i.e. health management information system (HMIS) and how authors collected this data from SINAN for this MS.

**Author's response:** We have included this information in method section as you can see below.

SINAN was developed in the early 90s, with the objective of collecting and processing data on disease notification throughout the country. SINAN is the primary information system from which data are extracted for epidemiological analyses [13]. This system is available in the website [http://dtr2004.saude.gov.br/sinanweb](http://dtr2004.saude.gov.br/sinanweb)[14]. Although for this particular study, data were obtained from the Tuberculosis National Program at the Ministry of Health in order to avoid replication and misclassification. These databases support the improvement of health care systems in Brazil by increasing the capacity of health care workers to make decisions based on accurate information.

The design is not retrospective cohort, but is a secondary data analysis for operational research as admitted by authors under limitations.

**Author's response:** We have made the change. We consider our study as a cross sectional study as requested by another reviewer.

Information about general health services from which surveillance information tricked into SINAN/TB and TB control program, HIV testing policy in Brazil need a mention in the MS for international readers to comprehend their findings.

**Author's response:** We have made the change on the MS. About HIV testing policy, Brazilian National Tuberculosis Control Plan which recommends that all patients diagnosed with TB be submitted to serological investigation for HI.

Title suggests epidemiological profile but, article presents factors associated with TB-HIV co-infection relative to TB only.

**Author's response:** We have changes the title to Factors associated with TB by HIV status in Brazilian National Surveillance System: A cross sectional study
Authors should consider presenting descriptive picture of TB-HIV situation in Brazil in graphically without venturing into logistic regression analysis for factors associated with TB-HIV relative to TB (HIV-ve). This shed light on non-reporting, non-testing of HIV among TB and vice versa. Social and demographic profile of patients ofTB, EPTB and TB+EPTB with or without HIV would be interesting considering serious data limitations for logistic regression analysis.

Author's response: Our research group published two manuscripts about the theme EPTB using the Brazilian National Surveillance System (SINAN). The first was published by Plos one entitled Extrapulmonary Tuberculosis: *Mycobacterium tuberculosis* Strains and Host Risk Factors in a Large Urban Setting in Brazil. Second paper was published recently on BMC infectious diseases Epidemiology of extrapulmonary tuberculosis in Brazil: a hierarchical model, in this paper we proposed to examine the epidemiology of EPTB in Brazil between 2007 and 2011. We observed that the patients with EPTB were mainly white (16.7%), and most (29.1%) patients had five to eight years of education. Among comorbidities, HIV infection was prominent (OR 2.15; 95% CI 2.09 – 2.21), although the proportion of cases awaiting test results or untested was high (39%).

Authors present both epidemiological (social, demographic), clinical and also treatment outcomes. Hence title is not apt and authors should reconsider this.

Author's response: We have made change the title as you suggest above.

Another problem with the analysis is extra-pulmonary TB is more common in HIV+ve, but authors both forms regression analysis for factors associated with TB-HIV relative to TB alone (HIV-ve).

Author's response: We explained above that the issue was addressed in another article.

Background does not provide a sound rationale about which gaps in research on factors associated with TB-HIV co-infections this study aims to fill. Two of the cited references are too outdated.

Author's response: We have made changes.

Overall, MS writing is very poor, riddled with many spellings and typos. It is hard for reviewer to highlight all those in the comments. Results are presented in great details with too many numbers for odds ratios and p-values. Instead present
significant ones succinctly. I have not commented on the discussion but will if I re-
review a revised version.
Author's response: We have made changes

Reviewer #4

I) Major Compulsory Revisions

Abstract

• Present key findings only in the abstract so that the message is communicated clearly.

Background/Introduction

• The authors have rightly confirmed the available literature on TB/HIV but clearly failed to state the gap in knowledge
• The research question is not well defined or does not come out clearly in this section
• Objectives are either not clearly stated or unclear

Methods

• Study design is not appropriate. The authors carried secondary data analysis of a TB cohort from 2007 to 2011 using a comparative cross sectional study and not a cohort study.
  • Author's response: We have made the change

Results

• Table 4. Under treatment outcomes. Suggest the author includes all treatment outcomes used in the reporting of TB treatment outcomes

Discussion

Lines 226 to 233 are a repetition of the results. This is not necessary and the authors are encouraged to just discuss the results

Author's response: We have made change

Not all results are discussed, of key interest include:

• The observation that TB/HIV co-infected patients were more likely to be AFB positive that TB patients only. This must be discussed in relation to TB infection
prevention and control and the need to develop more sensitive diagnostic
techniques to confirm TB among HIV co-infected.

**Author's response:** We have discussed this finding

- The authors contradict themselves by stating the huge number of patients
  without HIV status and at the end say the strength of the study was due to the
  large sample size. It is also not clear how the stated limitations affected the
  research question

  **Author's response:** We have made change

- Discuss why the retention in DOT for TB/HIV co-infected patients was poor
  in relation to available AIDS and TB treatment models in Brazil. Is there no
  encouragement for patients on HAART to receive treatment supervision in the
  community (community model)

  **Author's response:** We have made changes as you can see below:

Because of this difficulty and poor adherence to tuberculosis treatment, new
strategies for monitoring treatment should be devised, taking into account the
characteristics of the co-infection as recommended by Brazilian National
Tuberculosis Control. However, in our study the TB – HIV subjects were less
likely to be covered under the DOT, although it was not statistically significant.
This retention in DOT for TB/HIV co-infected patients was poor in relation to
available AIDS and TB treatment models in Brazil. In addition, in Brazil some
cities there is no encouragement for patients on HAART to receive treatment
supervision in the community such food vouchers and transportation subsidies.

**Conclusions and Recommendations**

- Conclusions seem to imply that there are specific reasons why HIV related TB
  remain relatively high in Brazil, but the reasons are not obvious in the article.

  **Author's response:** We have made the change

- There were no recommendations suggested, based on the significant findings
**Author's response:** We have made the change

- The author must be specific in terms of which targeted interventions are recommended for TB/HIV co-infected populations in Brazil
  
  **Author's response:** We have made the change

**Minor Essential Revisions**

- Typos on lines 39, 68, 74 and 103 require corrections
  
  **Author's response:** We have made change

- Use available Microsoft office tools to correct grammar
  
  **Author's response:** We have used this tool to correct grammar. Besides, the manuscript was edited by a native-English speaker with scientific expertise, who is a co-author of the paper

- Line 78, the correct terminology is “isoniazid preventive therapy” and not “isoniazid preventive”. Suggest correct
  
  **Author's response:** We have made change.