PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence, duration and risk factors associated with delayed and missed diagnostic opportunities associated with Tuberculosis: A population-based longitudinal study
AUTHORS	Miller, Aaron; Arakkal, Alan; Koeneman, Scott; Cavanaugh, Joe; Gerke, Alicia; Hornick, Douglas; Polgreen, Philip

VERSION 1 – REVIEW

REVIEWER	Nathan Ford WHO, Switzerland
REVIEW RETURNED	11-Nov-2020

GENERAL COMMENTS	Congratulations on a well conducted study describing the important issue of missed opportunities in TB service delivery

REVIEWER	Joyce Der London School of Hygiene & Tropical Medicine, UK
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	General comments This study sought to estimate the frequency and duration of diagnostic delays among patients with active pulmonary tuberculosis and the risk factors for experiencing a diagnostic delay using longitudinal insurance claims data. The study showed that TB patients experienced missed opportunities for early diagnosis and established the duration for delay. It also showed some patient and context specific risk factors associated with diagnostic delay. Findings highlight some context and healthcare-setting factors that when addressed might improve diagnostic delays. Specific Comments Abstract 1. Pag2 2, Line 33-37: the confidence level for the confidence intervals reported should be indicated for clear interpretation. Background 2. Page 4, Line 11: should the word be familiarly or familiarity? 3. Page 4, Line 43: the word this has been repeated Methods 4. Data source: some information on the kind of population that is covered by this insurance should be provided 5. Even though the study is deemed as non-human subject research, the authors should at least provide information on where permission to use the data was sought from. 6. On page 5, line 24-25 “If treatment began prior to the initial tuberculosis diagnosis, we used the treatment start date as the index diagnosis date” What could be the possible explanation for patients initiating TB treatment before diagnosis?

	Results 7. Page 8, line 16-17: "……prior to the index tuberculosis patients". The word "patients" should be diagnosis to make the sentence clearer. 8. Page 8, line 6-9: "We also estimated that approximately 528 missed opportunities occurred in inpatient settings, 9,001 in outpatient settings, and 589 in ED settings" Percentages should be added to the counts to make it more meaningful. Discussion 9. Page 10, line 18-19: "One-hundred-twenty days prior to the index diagnosis…" In the results section on page 8 line 46 it was stated that the change-point analysis detected an increase in number of SSD visits occurring 127 days prior to index diagnosis. How can the 127 days be reconciled with the 120 days stated in the discussion? Tables 10. Table 1: Page 18, line 27: for clarity the word diagnosis should be added to the sub-heading to show what the index is referring to. 11. What informed the choice of categorization of the enrollment time? Can the authors consider categorizations that do not overlap so the counts (%) in each category are distinct? 12. Table 2: the level of confidence for the confidence interval should be indicated in the heading in column 3 13. In the first column, are the unit of measurement for row 22-24 different from that of row 20-21? Labelling of units should be consistent for clarity.

REVIEWER	Juan Fernando Vesga Imperial College London, UK
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	The authors have assembled a retrospective cohort of patients from insurance claims records in the US from 2001 to 2017 to assess the incidence and risk factors of missed opportunities in TB diagnosis. The problem they address is clearly stated and the aims are aligned with the results and the discussion. The statistical methods used for assessing trends of missed opportunities and the simulation approach are robust and very clearly explained in the methods section. It is, in my opinion, a very robust analysis of an important (and rather unexplored) subject: the cascade of TB care in the US. Also, the methodology used for this analysis, particularly how they address potential misclassification of missed opportunities, can be an important reference for further studies in different settings. I have the following comments/suggestions: 1) It is clear that a spike in related visits starts ~130 days prior to index diagnosis, but is plausible that the tail before the 365 days is longer than we expect(?). It seems plausible that one symptomatic person can spend more than a year before being diagnosed as has been observed in other settings. Perhaps won't make a large difference in final results, but either a sensitivity analysis on this period (perhaps 2 years) or a more robust explanation of why a 365 days cut-off point was selected. 2) This is at the end a reconstructed observational study and as such it is in my view a better practice to have the study individuals

	flow diagram in the main text (fig S1) . If it comes down to a number of figures allowed, perhaps figures 2 and 3 can be merged?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Reviewer Name: Nathan Ford
Institution and Country: WHO, Switzerland
Please state any competing interests or state 'None declared': None declared

Congratulations on a well conducted study describing the important issue of missed opportunities in TB service delivery.

Response: No changes requested.

Response to Reviewer 2

Reviewer Name: Joyce Der
Institution and Country: London School of Hygiene & Tropical Medicine, UK
Please state any competing interests or state 'None declared': None declared

General comments
This study sought to estimate the frequency and duration of diagnostic delays among patients with active pulmonary tuberculosis and the risk factors for experiencing a diagnostic delay using longitudinal insurance claims data. The study showed that TB patients experienced missed opportunities for early diagnosis and established the duration for delay. It also showed some patient and context specific risk factors associated with diagnostic delay. Findings highlight some context and healthcare-setting factors that when addressed might improve diagnostic delays.
Specific Comments

Abstract
1. Pag2 2, Line 33-37: the confidence level for the confidence intervals reported should be indicated for clear interpretation.

Response: We have added these confidence levels (corresponding to 95%) to the abstract. We also made a few additional edits to improve the readability of the abstract.

Background
2. Page 4, Line 11: should the word be familiarly or familiarity?

Response: Yes, this was a typo and we have corrected it in our revised manuscript

3. Page 4, Line 43: the word this has been repeated

Response: We have removed this repeated word in our revised manuscript

Methods

4. Data source: some information on the kind of population that is covered by this insurance should be

provided

Response: In our revised manuscript, we have provided additional details on the types of enrollees that are represented in both the commercial claims and Medicare supplemental databases.

5. Even though the study is deemed as non-human subject research, the authors should at least provide information on where permission to use the data was sought from.

Response: We have added a statement regarding the authorization to use these data in our revised manuscript.

6. On page 5, line 24-25 “If treatment began prior to the initial tuberculosis diagnosis, we used the treatment start date as the index diagnosis date” What could be the possible explanation for patients initiating TB treatment before diagnosis?

Response: If TB is strongly suspected based on clinical presentation and risk factors for TB are present (e.g., known exposures), TB treatment may be started before final culture results are available.

Results

7. Page 8, line 16-17: “……prior to the index tuberculosis patients”. The word “patients” should be diagnosis to make the sentence clearer.

Response: We have changed the text in our revised manuscript to clarify this sentence.

8. Page 8, line 6-9: “We also estimated that approximately 528 missed opportunities occurred in inpatient settings, 9,001 in outpatient settings, and 589 in ED settings” Percentages should be added to the counts to make it more meaningful.

Response: We have added these percentage values (out of all visits) to our revised manuscript in order to make the counts more interpretable.

Discussion

9. Page 10, line 18-19: “One-hundred-twenty days prior to the index diagnosis…” In the results section on page 8 line 46 it was stated that the change-point analysis detected an increase in number of SSD visits occurring 127 days prior to index diagnosis. How can the 127 days be reconciled with the 120 days stated in the discussion?

Response: We apologize for not being clear; this was a rounding error in our original manuscript. We had intended to say “approximately 120 days” however we have now corrected this to reflect the 127-day change point that we had reported elsewhere.

Tables

10. Table 1: Page 18, line 27: for clarity the word diagnosis should be added to the sub-heading to show what the index is referring to.

Response: We have made this correction to our revised manuscript.

11. What informed the choice of categorization of the enrollment time? Can the authors consider

categorizations that do not overlap so the counts (%) in each category are distinct?

Response: We changed the enrollment categories in Table 1 so they are no longer overlapping in our revised manuscript. Please see our comments to Reviewer 3 (below) for additional details explaining why we selected the 1-year window for study.

12. Table 2: the level of confidence for the confidence interval should be indicated in the heading in column 3

Response: We added this information to the heading in Table 2 in our revised manuscript.

13. In the first column, are the unit of measurement for row 22-24 different from that of row 20-21? Labelling of units should be consistent for clarity.

Response: We made this correction in our revised manuscript.

Response to Reviewer 3

Reviewer Name: Juan Fernando Vesga
Institution and Country: Imperial College London, UK
Please state any competing interests or state 'None declared': No competing interests

The authors have assembled a retrospective cohort of patients from insurance claims records in the US from 2001 to 2017 to assess the incidence and risk factors of missed opportunities in TB diagnosis. The problem they address is clearly stated and the aims are aligned with the results and the discussion.

Response: No changes requested.

The statistical methods used for assessing trends of missed opportunities and the simulation approach are robust and very clearly explained in the methods section.

Response: No changes requested.

It is, in my opinion, a very robust analysis of an important (and rather unexplored) subject: the cascade of TB care in the US. Also, the methodology used for this analysis, particularly how they address potential misclassification of missed opportunities, can be an important reference for further studies in different settings.

I have the following comments/suggestions:

1) It is clear that a spike in related visits starts ~130 days prior to index diagnosis, but is plausible that the tail before the 365 days is longer than we expect(?). It seems plausible that one symptomatic person can spend more than a year before being diagnosed as has been observed in other settings. Perhaps won't make a large difference in final results, but either a sensitivity analysis on this period (perhaps 2 years) or a more robust explanation of why a 365 days cut-off point was selected.

Response: We agree with the Reviewer, that delays lasting longer than our detected changepoint (occurring around 130 days) are plausible and have even been identified in prior investigations. There may in fact exist individual patients in our study population with diagnostic delays lasting longer than our window of opportunity, which are not detected by our approach because the volume of such SSD

visits may not be large enough to generate a detectable change in the aggregate trend prior to the index diagnosis. Thus, to some degree, our approach may be overly conservative and both the numbers of delays we report and our change-point may represent lower bounds on the total number of diagnostic delays. We have added a note to our limitations section highlighting this point.

In addition, as a sensitivity check, we evaluated the possibility of including a study period beyond 365 days prior to the index diagnosis. Specifically, we evaluated the effect of increasing the study window to 1.5, 2, and 3 years prior to the index diagnoses. The figure below depicts the estimated trends in observed and expected visits if we expand our analysis to 1.5, 2, and 3 years prior to the index diagnosis. However, by expanding this study window we tend to lose a significant number of case patients without sufficient enrollment. We lose approximately 15%, 30% or 50% of our study population by expanding to 1.5, 2 and 3 years respectively. In addition, increasing the study window beyond 1 year tends to exclude younger patients (age <55) at a greater rate than older patients. Because the observed and expected trends depicted below, which are used in our simulation, are not appreciably different with the expanded study window and because of the diminished size of the study population, we believe the 1-year enrollment window provides the optimal period for this study.

2) This is at the end a reconstructed observational study and as such it is in my view a better practice to have the study individuals flow diagram in the main text (fig S1) . If it comes down to a number of figures allowed, perhaps figures 2 and 3 can be merged?

Response: We agree with Reviewer 3. We have now included Supplementary Figure 1 in the main manuscript as Figure 3. To accommodate this change, we have moved Figure 2 to the supplement (now Supplementary Figure 1) and Figure 3 has been shifted to Figure 2. We also added a sub-figure to the new Figure 2 which depicts the baseline counts (A) before depicting the trends (B). In the heading for Figure 2, we also reference Supplementary Figures 1 and 2 which breakdown these counts by type of healthcare setting or type of SSD.

VERSION 2 – REVIEW

REVIEWER	Joyce Der London School of Hygiene & Tropical Medicine, UK
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	No comments.