Author's response to reviews

Title: Time Delays in Diagnosis of Pulmonary Tuberculosis: A Systematic Review of Literature

Authors:

Chandrashekhar T Sreeramapreddy (chandrashekharats@yahoo.com)
Panduru V Kishore (pandu_vki@yahoo.com)
Jef Van den Ende (jvdende@itg.be)

Version: 2 Date: 4 March 2009

Author's response to reviews: see over
Dear Editor

BMC Series of Journal

Thank you for considering our manuscript “Time Delays in Diagnosis of Tuberculosis: A Systematic Review of Available Evidence”. We have now prepared the replies to the reviewers’ comments and have revised the manuscript according to the reviewers’ suggestions. We have also made the corrections suggested by the editorial team to confirm the manuscript with the Journal style. We made suggested changes in abstract, main manuscript section and we added acknowledgements and sources of funding.

We are resubmitting the revised manuscript for further consideration for publication in BMC Infectious diseases. We hope that the revisions are acceptable to the reviewers. We look forward for a favorable consideration.

Ps: We have included Joris Menten as a co-author who earlier had assisted in data analysis and revised the manuscript for content in interpretation of the results. This time during the revisions he rewrote the results and methods section.

Best wishes

Chandrashekhar T Sreeramareddy
Kishore V Panduru
Joris Menten
Jef Van den Ende

Reviewer's report

Title: Time Delays in Diagnosis of Tuberculosis: A Systematic Review of Available Evidence

Version: 1 Date: 19 January 2009

Reviewer: Joseph Beyene

Reviewer's report:
The manuscript presents a systematic review with the objective of summarizing patient, health-care system and total delays to diagnosis of pulmonary tuberculosis; and compares low and middle against high income countries with respect to delays. Overall the manuscript is written very well.

Dear Joseph Bayene,

Thank you for your time reviewing our manuscript. We have now provided answers to the issues raised by you. Our replies are in italics bold and underlined. Hope these revisions are acceptable to you.

Kindly note that we have made some revisions as suggested by another reviewer.

Major Compulsory Revisions

1) The authors have not included EMBASE as one of the databases for their search. EMBASE is a widely used database in doing systematic reviews. My experience is that the overlap between MEDLINE and EMBASE can at times be very small. By excluding EMBASE, the authors may have potentially missed many useful studies that could have been included in the systematic review to answer their scientific question, which will make the review less rigorous than a high quality systematic review would be expected. Is there a reason why the authors chose not to include EMBASE?

Thank you for the suggestion. There was no particular reason for not including EMBASE in the search. This time around we have included EMBASE and also following another suggestion we extended the search from 1990 to December 2008.

2) The Medline search is limited to the time period from 1990 to 2006. Is there any rational why the search went only as far as 2006? One of the strengths of a systematic review is that it is often up-to-date by the time the review appears in the literature. I strongly suggest making the search as up to date as possible.

Thank you for the suggestion. There was typographical error in the previous version you reviewed actually the search was done until 2007. This time around we have included EMBASE and also 2008.

3) The “Methods” section is limited in describing the analytical strategies the authors used for summarizing data. For example, data are described graphically using Box plots. This and any other data summarization approaches should be described in the “Methods” section. Issues around sensitivity analysis and potential for publication bias should be described adequately.
As suggested a section of one paragraph has been included in the methods data analysis and details explained about Box plots along with statistical tests of significance as suggested by another reviewer.

Minor Essential Revisions

1) The title doesn’t need the qualifier “of Available Evidence”.

*Yes, we agree with you and removed it from the title. The revised title says”…………… a systematic review of literature.”*

2) The 1st sentence, 1st paragraph of the discussion section gives the impression that a meta-analysis was included in the manuscript. The manuscript includes ONLY a systematic review without a formal meta-analysis.

*No, meta-analysis was not done. So we have removed it from the sentence.*

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests
Reviewer's report

Title: Time Delays in Diagnosis of Tuberculosis: A Systematic Review of Available Evidence

Version: 1 Date: 27 October 2008

Reviewer: Alan Altraja

Dear Alan Altraja,

Thank you for reviewing our manuscript and also for the insightful comments and suggestions. We agree with most of the points raised and have provided answers to the same in this letter. Please find our responses as italicized, bold and underlined sentences.

Please note that the references have been updated for this systematic review including EMBASE and the year 2008. This is in accordance with the suggestions of the other reviewer.

Reviewer's report:

The manuscript “Time Delays in Diagnosis of Tuberculosis: A Systematic Review of Available Evidence” by Chandrashekhar T. Sreeramareddy, Kishore V. Panduru and J. Van den Ende takes together data on patient delay, health system delay, and total delay in pulmonary tuberculosis. This is an interesting study with a pretty well-written, reading-prompting abstract, which picks up an interesting topic of challenging the effectiveness of passive case finding.

However, this is a type of analyses, where methodological aspects are of sensitive nature, and several concerns arise in association with the core manuscript.

We agree that methodological aspects are rigorous for such reviews. We have tried to answer all you questions below

Major Compulsory Revisions.

1. The study handles pulmonary tuberculosis. This should be mentioned also in the Title and “Abstract”.

The suggested change has been made in the title, manuscript and abstract.

2. Page number are missing, thus making references to the text is somewhat
complicated.

**Apologies for that error. In our revised manuscript we have included the page and line numbers.**

3. Paragraph “Data extraction and analysis” in the “methods” section: the authors have thoroughly written, how they have defined the end of the delay period. However, how did the authors define the onset of symptoms (i.e. the beginning of the delay)? From the onset of whatever symptom related to TB the patient experienced first or several symptoms that might have lead to a suspicion of TB?

**We have modified this aspect as either first the symptom of TB or several symptoms starting together as it may happen sometime. We have clarified the definition in the text of Methods section.**

4. Same page, “Operational definitions”: clear definitions of LMIC and HIC should be provided.

**We have referred to World Bank website and used the definitions provided by world bank for the same and included them in the methods section.**

5. There are no statistical calculations used to substantiate the facts the authors claim in “Results” and comment in “Discussion”. E.g. comparisons between LMIC and HIC for different aspects of the delay etc.

**In the revised manuscript we have done the statistical tests of significance and provided p-values which of course not significant i.e. the differences between HIH and LMIC for different types of delays.**

6. The authors claim about having performed their analysis on studies carried out on smear/culture-positive tuberculosis. However, “smear/culture-positive” does not appear anywhere in “Methods”.

**We apologize for not mentioning that in the previous version of the manuscript. However now we have included that in the revised manuscript.**

7. “Results”, “Search results”: it is not common and does not facilitate understanding, if this section begins just only with a reference to a figure (“Figure 2 shows…”).

**We agree that enough details were not provided earlier. In the revised manuscript we have provided more details of the results of the search for**
In the earlier version there were some typing errors which did not facilitate comprehension. Now we hope it is clear. However the numbers have changed since references were updated and EMBASE and 2008 were also included in the search.

As said before the earlier version had some typing errors which did not facilitate comprehension. 52 studies included were of different study designs. Now we hope it is clear after this section has been described in separate paragraph.

As shown in figure 1, only 98 studies were possibly relevant. Of the excluded studies, only 8 studied delay within the strictly applied inclusion rules. Inclusion of these studies in a separate analysis for patient delay would probably not have changed our overall results or conclusions. If you insist, we might do a separate analysis…

11. In “Results”, paragraphs “Patient delay”, “Health care system delay”, and “Total delay” contain very homologous presentation of data, which may better fit
into a table, to facilitate understanding. There, also statistical differences could be provided smoothly.

*We apologise, we think providing a table will not add much to the readability of the article, since these results are also shown clearly in the figures (Box Plots). However now the statistical differences are also provided.*

12. The use of terminology is vague throughout the manuscript, without defining them. Particularly, it concerns usage of “diagnostic delay”. The results of this research article provide data divided as “Patient delay”, “Health care system delay”, and “Total delay”. This issue should be corrected or definitions should be provided.

*This word has been corrected to “time delay in diagnosis” wherever it was appropriate.*

13. The “Discussion” of the manuscript should be strengthened in many of its parts. For example, 1st paragraph, last sentence: “When the diagnostic delays were compared it was expectedly higher among LMICs.” Why “expectedly”? Further, in “Weaknesses in our methodology”, 2nd paragraph: “If studies which did not find a longer diagnostic delay might not have been published ...”: why do the authors think that results not showing extremes in delay have probably not published?

*As suggested we have removed the statement “... expectedly higher...” in the revised manuscript as also judged inappropriate.*

*We think that studies which did not finding longer delays may not have published (like the negative results as in clinical trials). This is what we mean by publication bias in our discussion/limitations. Mention about publication bias was suggested by other reviewer.*

14. Why Table 1 only contains diagnostic delays among pulmonary tuberculosis patients in low and middle income countries? Again, what is meant by “diagnostic delay” (title of the table)?

*We have changed the term “diagnostic delay”. We wanted present briefly all the studies selected for the review in separate tables for LMIC and HIC.*

15. The figures should have footnotes rather than titles, containing explanations of abbreviation used etc. to make any figures a self explanatory unit.

*Yes, we have made them foot notes for all figures (not as a title) and written out abbreviations full.*
16. Figure 3: it could be presented as figure 3a, 3b and 3c (indicating total delay). What do the bubbles indicate on Figure 3 (on Patient delay)? Statistical comparisons and asterisks to indicate significant findings could be of value.

Yes we agree with you. The tables have been provided separately now for each type of delay. Statistical comparisons, with p-values and 95% confidence intervals have been provided (although none were significant).

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

1. “Discussion”, 2nd paragraph, reference [57] should better follow the previous sentence.

Suggested change was made.

2. The text contains some incorrect grammar.

We have revised the manuscript to correct incorrect grammar.

Prof. Alan Altraja, M.D., Ph.D. Department of Pulmonary Medicine, University of Tartu 8 Puusepa St., 51014 Tartu, Estonia Fax Int.: +372 7 318 905 Tel. Int.: +372 7 318 901 E-mail: alan@kliinikum.ee Mobile phone: +372 50 71 941

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

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests