Author’s response to reviews

Title: Risk Factors for Tuberculosis Treatment Failure, Default, or Relapse and Outcomes of Retreatment in Morocco

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Author's response to reviews: see over
To the Editor-in-Chief:

Thank you for your thoughtful review of our manuscript number 1036667033461546 entitled, “Risk Factors for Tuberculosis Treatment Failure, Default, or Relapse and Outcomes of Retreatment in Morocco”. My colleagues and I are re-submitting the manuscript, with modifications suggested by the reviewers, to be considered for publication in the journal *BMC Public Health*. We are submitting the manuscript in “track changes” format so that modifications can be readily found by your editorial staff. Point-by-point responses to specific comments and suggestions by the reviewers are detailed below.

I will be the corresponding author, and my e-mail address is kdooley1@jhmi.edu. Should you be unable to reach me immediately, my colleague, Dr. Rajae El Aouad, is also at your disposal for queries at rajaelaouad@yahoo.fr. My co-authors and I appreciate your consideration of this manuscript and are available to answer any questions that might arise in the review process.

Best regards,

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Reviewer: Michelle Elisabeth Kruijshaar

Reviewer's report:
This study addresses the important problem of the effectiveness of tuberculosis retreatment regimens and risk factors for retreatment in Morocco. It describes treatment outcomes for retreated TB cases, risk factors for retreatment and use of DST. Currently, its messages overlap partly with the earlier study by Ottomani et al (reference 5), describing treatment outcomes of retreatment cases in a much larger sample. The key new elements of this study, I believe, are the DST results and risk factor analysis, but due to the small sample size these have to be interpreted with care. I think the paper should focus more on the new information and acknowledging more clearly the limitations of the small sample size.

Detailed essential revisions

Abstract:
- The abstract seems quite long.
The abstract has been modified to focus more strongly on the new information that derives from this study and has been streamlined, as per the reviewer's suggestions.

- The conclusion presented in the abstract should focus more on what is new.
Ottomani et al already show that failure is more common in those who previously failed. Focus, acknowledging limited power, on the risk factors and limited DST.
The conclusion has been revised to focus more on what is new, including very high default retreatment rates in the urban “hot spots” where the study was conducted, the risk factor analysis, and poor uptake of DST.

Background:
- I would shorten the background but add the higher rate of failure/default after initial failure/default from Ottomani. Remove the repeated reference to the three subgroups of retreatment, only mention these once or twice. After para 1 I would move immediately to para 3, and add in at the end that DST is not always available, include results of Ottomani (retreatment outcomes), and that risk factors for retreatment groups have not been investigated. Para 2 is then no longer needed. Para 4 – the efficacy of standard treatment is already shown by Ottomani, focus this paper on use of DST and identification of risk factors.
We appreciate these thoughtful comments and have revised the background section to describe Ottomani’s findings, decrease references to the three subgroups, mention poor access to DST, and focus on DST and risk factor identification as strategies to improve outcomes as well as potentially decrease morbidity and transmission.

- TB is a global public health problem (add public)
The word ‘public’ has been added, as recommended.
• DOTS is the WHO recommended TB control strategy of 5 elements, it is not the same as DOT (directly observed therapy) alone. The words ‘short-course’ have been added to be more precise.

Methods:
• Yes, relapse cases could be reinfected cases, so the 2 year cut-off seems sensible.
• Relapse is defined as initial treatment success after treatment of sufficient length. This is a bit confusing for two reasons. Firstly, treatment success is a specific outcome category, so this could mean that other patients who completed tx would not be included. Secondly, how long is sufficient length? Relapse is defined as recurrent disease after initial treatment success (which includes those with cure or treatment completion) among patients who received an adequate course of TB treatment. In Morocco, those with ‘serious’ TB, defined as CNS TB, renal TB, multiple lobe pulmonary involvement, disseminated TB, or other categories receive 9 months of treatment whereas others with a new TB diagnosis that is not ‘serious’ receive a standard six-month regimen. The text has been modified to clarify this.

• Retreatment patients were those with first retreatment: do you mean those who were retreated for the first time? Yes, the text has been modified to clarify this.

• ‘Controls were chosen among patients with successful initial treatment, without failure, default or early relapse’ - This is confusing, are you choosing controls that had an initial outcome of treatment success (i.e. sputum smear conversion seen), or all patients completing treatment? Controls were chosen from among patients with initial treatment success, with success defined as cure (those who were able to produce a sputum sample and that sample was negative) or treatment completion (those who completed treatment but were unable to produce a sputum sample for analysis).

• ‘Controls (…) selected from the same centre and treatment period’ – I guess you need to add the word random, or did you include all? There must be a large number of patients in each centre in the 1 year period? We chose controls with treatment initiation dates that were the closest to the cases’ treatment initiation dates. The text has been modified to make this clear.

Results:
• Table 1 can be omitted, the numbers by retreatment group are given in the text and the sites where these patients come from are not relevant for most readers. We agree and have removed Table 1.

• The comparison of retreatment failure and default in the three retreatment groups is probably hampered by small expected cell sizes (I am assuming this is X2 test and e.g. 4% overall failure would give less than 5 expected failures in the failure and default groups).
For comparisons in which there were cell sizes of five or fewer, the Fisher’s exact test was used; the use of this test is described in the methods section.

The outcomes of retreatment cases were also already studied by Ottomani in a much larger sample, so are not that relevant. Instead, I would suggest to present a table with some patient characteristics (the population description), the DST results (see comment below on table 2) and outcome of all 291 retreatment cases. E.g.

<table>
<thead>
<tr>
<th>Retreatment group</th>
<th>Gender</th>
<th>Age</th>
<th>Sputum smear</th>
<th>DST tested</th>
<th>Outcome (retx)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-mono (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-MDR (+/-S)</td>
<td></td>
</tr>
</tbody>
</table>

We have modified the text to focus more on the differences between Dr. Ottmani’s study and ours, including the higher default rate among retreatment cases in our study, which may result from period differences (his study was performed in 1996-2003) or, more likely, from differences in populations, as we focused on urban TB “hot spots” where TB incidence is high. Patient characteristics of the retreatment population have been added to the manuscript.

You could mention in the text the different proportions failure relapse and default, but I would leave it to the discussion to say that numbers were too small to test for significance, but already shown by Ottomani et al that the risk is higher. As our study had individual-level data rather than population-level data, we were able to report individual-level retreatment outcomes, and we could evaluate risk factors for the need for TB retreatment, but our power to conduct subgroup risk factor analyses were limited, as the reviewer suggests and we have made sure to highlight this important limitation.

- Table 2 contains several rows with only 0s and very small numbers especially in the failure and default groups. I suggest to omit this table and include the key result in the new table suggested above. I.e. Total number (all retreated cases) tested, % sensitive, % mono-resistant, % MDR (with or without other resistance to also S, HRS is also MDR). Also, any abbreviations have to be explained in the footnote.

Table 2 has been omitted, as per the reviewer’s suggestion.

- ‘Though numbers were small’ – even saying this can still be misleading since there are only 3 cases in this group. I think it would be better to give the exact numbers, and use discussion to say that although the numbers are very small other studies suggest ….

The exact numbers have been inserted into the text as per the reviewer’s suggestion to avoid the possibility of misinterpretation by the reader.
• Risk factors for initial outcomes: 104 patients had completed initial TB treatment. This would mean that this group can only include relapse patients, as default and failure patients did not initially complete treatment?
Thank you, this is a good catch. The text has been modified as follows, “Of 291 retreatment patients, 104 (36%) had started a retreatment regimen within two years of completing or stopping an initial TB treatment regimen…”

• The multivariable analysis for retreatment (the 3 groups combined) should be included in table 3, as this is the more powerful analysis.
We agree that the multivariable analysis is the most informative analysis, and the results of multivariable analysis for those factors that remained in the model after model selection procedures were completed are reported in the text. Since few factors remained in the model, we chose to report these individually in the text rather than in a separate column in the table.

• The risk factors for the different subgroups will be limited by power. Also, it is not clearly described what the case and what the control group is for these in the methods. I presume the controls are the same, and the numbers of cases limited to the specific group.
Yes, this is correct. We have modified the text to emphasize more strongly that the ability to evaluate risk factors for the different subgroups is limited by power constraints given the small sample sizes in these subgroups.

Discussion
• Focus less on the outcomes by group, which are already shown by Ottomani et al, and more on the risk factors. The message that the 3 sub-groups will benefit from different strategies fit with both (although of course the multivariable analysis in the subgroups is limited by power).
More detail regarding the risk factor analysis and the implications have been added. For example, in Morocco, if missed doses early in treatment are associated with subsequent treatment default, coordination of provision of medical care and dispensing of medications (which are done in two different places) may be a helpful country-specific strategy. Similarly, making sure that those with positive sputum smears after 3 months of treatment undergo DST will help identify patients with resistance earlier rather than later.

• ‘Default patients may require additional surveillance’, maybe you could say instead intensified case management?
We agree and have changed the wording as suggested.

• Rather than saying ‘All failure patients’ in the DST is underused section, I think the small number issue will be better acknowledged by saying ‘All three failure patients …’. Similarly, I would say ‘While these DST results were only available for three patients, and therefore not representative…”
We agree and have modified the text accordingly.
• The mention of the population based study showing 12.2% MDR-TB raises the question why this information could not be combined. Could the clinic registries not be combined/link to national surveillance data or data from this population based study to obtain a larger sample of retreatment cases with DST results? Although we did link the clinic registries to national and regional reference laboratory results, there was little overlap between DST testing performed in our study patients and that performed as part of the population-based study. The national surveillance study was performed in 2007, and our study covered 2007-2008.

• The paragraph about risk factors for failure or relapse is a bit unclear, possibly because it starts with what is known from the literature rather than what was found in this study, so it is not so clear what this study adds and where it deviates. I would expect here a discussion of the risk factors for retreatment as found for the three groups combined.

The paragraph has been modified to clarify that the initial sentences describe the published risk factors for failure/relapse/default. The paragraph has been further modified to discuss more clearly differences in risk factors found in other studies and those found in the current study and ways the findings can inform strategies to reduce the need for retreatment.

• Foreign birth is probably only a risk factor in certain countries.

It is a common risk factor, particularly among immigrants moving from countries where TB is more highly endemic to countries where it is less so, but this is not universally the case.

• ‘Thus, risk factors … vary by setting …’ – It is not really clear to me how this is shown in the study, all nine clinics were in urban areas in Morocco, so that is kind of a similar type setting?

By this, we mean that the risk factors in Morocco, a Muslim country in North Africa where HIV and alcohol use are uncommon, differ from risk factors in other parts of the world and may be trickier to uncover. We have added some description of the differences along with a query about whether or not this would also be true in other North African or Middle Eastern countries.

• I don’t think the data support the statement that weight gain occurred late. Can this paragraph be omitted?

We agree and have omitted this paragraph.

• ‘While prediction of failure/relapse is challenging, patients at risk of treatment default may be easier to identify.’ I find this sentence possibly misleading. Part of the reason that it is difficult to identify is the small number of cases, this is in my view definitely the reason you are not finding any significant factors for the smallest group.

We agree and have changed the wording in this paragraph substantially.

• Male sex was not significant in the multivariable model for default. Tobacco use
and illicit drug use are mentioned separately here, while the analysis looks at tobacco, alcohol or illicit drug use, i.e. the presence of one or more of these, rather than the effect of each of them separately.

There was a trend toward increased risk of default among men but this missed statistical significance. We have changed the text of the manuscript so that substance use is consistent with that described in the table.

- I think the risk factors for the three separate groups need to be presented with a lot of care and further investigation with a larger study required to confirm.

We agree and have stated that larger trials will be better suited to answering subgroup-specific risk factor questions in the text.

- Can you please elaborate a little bit more on the small sample sizes.

We have altered the text to emphasize this more strongly.

- ‘Risk factors for TB treatment failure or default vary by setting’ — I don’t think that is shown in this study, so this should not be part of the conclusion.

We agree and have modified the conclusions accordingly.

Reviewer: Reinout R van Crevel

Reviewer’s report:

1. The question posed by the authors is not 100% clear from title, abstract and background. The authors seem to be looking for factors related to failure of primary TB treatment and to evaluate outcome of retreatment of TB for various subgroups. the study would benefit from more focus. I would suggest the following title: "Factors associated with success of retreatment of TB in Morocco; a retrospective cohort study."

The text has been modified to be more focused, as per the reviewer’s suggestion, and to more clearly articulate the goals of the study, which are to address the following two questions: (1) What are retreatment outcomes among Moroccans living in urban settings with high TB incidence? and (2) What were the risk factors that led them to require retreatment in the first place?

2. The study suffers from the limitation of a relatively small and retrospective cohort study using routine medical records. Patients coming for retreatment were included; outcome of primary treatment for these patients was retrieved from previous records. Drug resistance testing, a major contributor to success of retreatment was only performed in 10% of cases, and very little information is provided on the method of DST, and no data are presented regarding quality control. other possible confounders including HIV-status and diabetes are lacking. a nested case-control seems appropriate to examine what factors affect outcome of primary treatment, but I wonder if this separate question should be
included in a paper on retreatment. The most important conclusions seem justified: those who default during primary treatment have a higher chance to default during retreatment; those who fail initially have a higher risk to fail during retreatment.

The manuscript has been modified to describe the methods of DST and details regarding quality control. Information has been added describing HIV incidence, which is less than 1% among TB patients in Morocco, as per the national TB program. Only 3 individuals in the study had diabetes, and 1 had HIV; these data were added to the manuscript.

3. presentation of data:
the result section could be shortened and improved.
the added value (other than for the Moroccan NTP) of Table 1 is unclear. similarly, the results of DST on this small sample of strains can be summarized in the text instead of Table 2.
the results of retreatment (stated in the abstract and the result section) could be summarized in a table.
There are many missing data in table 3, for which little explanation is given. the authors acknowledge themselves that subgroup analysis is limited by the small numbers of patients included in the study. in the final paragraph of the text it is stated that male gender is an independent risk factor for default, however this is not significant (table 4). there is more discrepancy between table 4 and text.
the abstract mentions 292 patients presenting for retreatment, the result section 291

Thank you for these thoughtful suggestions. The result section has been shortened and streamlined. Tables 1 and 2 has been removed from the manuscript, and the results of Table 2 have been moved to the main body of the text. The manuscript has been revised to include only the 291 patients for which full treatment information was available so that the sample size is consistent throughout the manuscript. The statement regarding male gender as a risk factor for default has been changed to make it clear that though there was a trend towards male gender being an independent risk factor, the subgroup analyses were limited by small numbers.

major revisions;
4. I think the study would gain much from focusing solely on outcome of retreatment (leaving out the analysis of factors related to outcome of primary treatment), and clarification of the study objective in title, abstract and background.

The manuscript has been modified to clarify the study objectives and to link more clearly the analysis of retreatment outcomes and the risk factors for requiring retreatment in the first place. Of note, reviewer 2 recommended focusing on the risk factor analysis, but this reviewer found the retreatment outcomes data more compelling. To address both reviewers’ suggestions, we have endeavored to make it more clear that the study findings of most interest, we feel, are (1) retreatment outcomes among patients living in
urban TB hotspots where TB control has proven difficult and high default rates are of particular concern and (2) the risk factors that led people to need retreatment, as the latter can inform TB control strategies in these regions where incidence, alarmingly, is rising rather than falling.

5. Second, the manuscript would be much stronger is drastically shortened, in balance with the amount of data included and the novelty of findings. the current tables could be replaced by one table related to retreatment (comparing successful and unsuccessful retreatment).

Tables 1 and 2 have been removed, as per Dr. van Crevel's suggestions, and the manuscript has been streamlined.