Reviewer's report

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

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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 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.

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.
• TB is a global public health problem (add public)
• DOTS is the WHO recommended TB control strategy of 5 elements, it is not the same as DOT (directly observed therapy) alone.

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?

- Retreatment patients were those with first retreatment: do you mean those who were retreated for the first time?
- ‘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 (…) 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?

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.
- 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).

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>

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.

- 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.

• ‘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 ….

• 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?

• The multivariable analysis for retreatment (the 3 groups combined) should be included in table 3, as this is the more powerful analysis.

• 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.

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).

• ‘Default patients may require additional surveillance’, maybe you could say instead intensified case management?

• 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…’

• 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/linked to national surveillance data or data from this population based study to obtain a larger sample of retreatment cases with DST results?

• 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.

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

• ‘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?

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

• ‘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.

• 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.

• 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.

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

• ‘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.

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

Quality of written English: Acceptable

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.