Reviewer's report

Title: Molecular detection of rifampin and isoniazid resistance to guide TB chronic patients’ management: a feasibility study in Burkina Faso

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Reviewer: Hendrik Simon Schaaf

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Molecular detection of rifampin and isoniazid resistance to guide chronic tuberculosis patients' management: a feasibility study in Burkino Faso

The authors present a study of laboratory evaluation of sputum samples of chronic TB patients, identified by sputum smear-positive results after failing a retreatment regimen, and how these results can help to improve the management of the chronic TB cases, would these tests be available in Burkino Faso. The reviewer’s opinion is that the study was not very well designed, as it seems that specimens were obtained far into WHO regimen IV therapy in quite a large proportion of cases, which definitely could play a role in the study outcome. There were also other limitations as mentioned below. Despite this, there is merit in the study and the results are interesting – especially if it can be presented in a clear way.

The reviewer has the following comments:

Major compulsory revisions:

Abstract and title:

1. Title and elsewhere in manuscript: Should change “TB chronic patients” to “chronic TB patients”. I think that the title is somewhat misleading as the laboratory part of the study was done in Italy and not in Burkino Faso – it would only be feasible if the laboratory work can be done in Burkino Faso itself.

2. The aim in the background seems to be the wrong way round: As I understand the study, the researchers “…evaluated the molecular assay Genotype MTBDRplus for detecting DR-TB directly in clinical specimens as a means to a more accurate management of chronic TB patients in Burkino Faso.”

3. The method in the abstract does not clearly state on what grounds patients were selected as “chronic TB patients” – were they all supposed to be sputum smear-positive on microscopy? This is what I gather from the results because almost half the patients were not “reconfirmed as sputum smear-positive” which places some doubt on the accuracy of the initial smears?

Methods (Main body of manuscript):

4. Methods, page 5, study setting: The authors need to say what the HIV prevalence in the country/setting is where the study was done. Looking at the high rate of NTM infection in the chronic cases, the authors should give some
information about NTM infection rates in the area. Lastly, the second part of the first sentence should be deleted because it is repeated in the third sentence.

5. Methods, page 5, 2nd paragraph: What, in these patients, is category IV regimen? This is not a standard regimen, but could be different regimens as far as I understand. The readers not familiar with WHO TB guidelines will also not know what regimen IV is – please define accurately.

6. Methods, page 5, 3rd paragraph: Why were all patients not enrolled at the beginning, before starting follow-on therapy? Was there any cut-off time for not further enrolling a patient, or were they all still smear-positive by the time of enrollment (not clear from current methods)? I think that two different early-morning specimens were sent to the two laboratories (same morning or different days?) can also be a limiting factor giving different results.

7. No mention is made of ethics or institutional review board approval for the study, especially in the light of taking specimens out of the country.

Results:

7. Results, page 8, first paragraph: The authors state that all chronic TB cases were confirmed sputum smear-positive when diagnosed – were these smears checked by the research team or were these the results from the local laboratories? It is quite concerning that there is such a big difference in smear results with 1/3 of patients not yet on treatment having a smear-result discrepancy?

8. Results, page 8, sputum smear positive sample analysis: This part is difficult to follow. Most of the numbers of the GenoType MTBDRplus test results again appear in Table 1, but then the percentages are different because different denominators are used, which is confusing. I think that it may be better to present numbers and percentages only in table 1, not to be repeated in text, and to add the culture results to the table (or if too difficult, only present the culture result comparison in text), showing how these compare. The text can then be used to mention the complexities of the results. Some important findings are presented, such as discrepancies between culture and GenotypeMDR TBplus methods, but it gets lost in a maze of results and grammatical problems. Table 2 is very helpful and clear.

9. Results, page 9: Frequency of mutations: last sentence of 1st paragraph: Were these rifampicin-resistant strains diagnosed by the absence of WT probes confirmed by culture and DST?

Discussion:

10. Discussion, paragraph 3. The study method was not very inductive for good results from the GenoType MDRTBplus, as many of the specimens were obtained (long?) after category IV treatment was initiated – the results obtained could therefore be incorrect, with original organisms already been removed. I think these results should therefore be interpreted with some care.

11. Discussion, page 11, 4th paragraph: the results mention 2 rifampicin mono-resistant cases by MDRTBplus method being identified as MDR TB by
culture (therefore two INH resistant cases missed)

12. Discussion page 12, 2nd paragraph: The authors need to explain better why there were such huge discrepancies between sputum smear microscopy results between Burkino Faso and Italy – sampling time is not clear, and in many cases both samples were taken before treatment was initiated (according to metods)

13. Discussion page 12, 3rd paragraph: Why were suboptimal methods of transportation used?

14. Discussion page 12, 1st paragraph – the results presented in this paragraph need to be moved to the results section

15. The conclusions on page 14 should be part of the discussion – as in my second comment I think that the aim should be turned around. Further in the same paragraph, the authors now call it the Hain molecular test, while previously (and more correctly) referring to the Genotype MTBDRplus test. At the end there is another conclusion which is more correct.

16. The manuscript needs major grammatical revision

Minor comments
1. Abstract, results, 5th line: no-tuberculous mycobacteria (not uppercase M)
2. Abstract, results, page 3 – INH mutations – need to see the numbers
3. Abstract, conclusions: should state “sputum specimens”. Also, it may contribute to limiting the emergence of drug resistance (although this is logical, it is not part of this study’s results and therefore can probably not be a conclusion)
4. Background, page 4, ref 4-6: There also exists evidence in some recent articles that cure rates are not necessarily very low – this should also be presented
5. Background, page 4, 3rd paragraph, last line: change “MTB drug resistant strains to “drug-resistant MTB strains”
6. Page 6, 2nd paragraph, 3rd line: abbreviations should first be written in full before used, e.g. DOT. In the following paragraph, what does (M0) stand for?
7. Page 8 and elsewhere – the authors should decide to use drug susceptible or drug sensitive – the first is preferred (WHO guidelines). Using both terms interchangeably causes confusion.

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

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'