Reviewer’s report

Title: Underestimated pyrazinamide resistance may compromise outcomes of pyrazinamide containing regimens for treatment of drug susceptible and multidrug-resistant tuberculosis in Tanzania

Version: 0 Date: 29 Apr 2018

Reviewer: Lorenzo Guglielmetti

Reviewer’s report:

This manuscript describes the incidence of pyrazinamide resistance in DS- and DR-TB in the Kilimanjaro region of Tanzania. In addition, the authors aim to assess the impact of pyrazinamide resistance on MDR-TB treatment outcomes and the performance of the HRM technique in comparison to phenotypic DST. Overall, the manuscript is clear and well written. The conclusions, however, are considerably weakened by the low sample size (for MDR-TB cases) and in general only applicable to this specific epidemiological area.

I have the following major comments:

1. Title: I find the title misleading, as the shortcourse MDR-TB treatment is only mentioned in a couple of passages of the manuscript and patients in the study received the conventional treatment. I would rephrase the title by underlining the high incidence of pyrazinamide resistance in both DS- and DR-TB cases, and the potential impact on any pyrazinamide-containing regimen

2. Page 7, first paragraph of the results, and Table 1: the numbers in this section are unclear to me. The authors mention 23 discrepancies, when in Table 1 there are only 17. I don't understand what the authors refer to when they say "Those 14". In the footnote of Table 1, there is a reference to an asterisk which is not present in the Table; in any case, the results presented in the footnote should also be present, at least by a reference, in the text.

3. I could not find in the text a reference to how many DS-TB patients have been previously treated for TB; as the authors correctly mention in the discussion, this is a crucial element to interpret the incidence of pyrazinamide resistance; if this information is not available, this should be acknowledged in the limitations

4. Page 8, line 40-46: I suggest that the authors state clearly that the "important trend" did not reach statistical significance, mostly due to the small sample size; I would also be less assertive in the conclusions

5. In the Discussion, the authors should discuss the small sample size, in particular for DR-TB, as a major limitation
And the following minor remarks:

1. Page 1, line 35: I would suggest using the full word pyrazinamide, instead of PZA, throughout the text
2. Page 1, line 40, and page 3, line 23: replace "role-out" with "roll-out"
3. Page 1, line 47: I am not sure to see why pyrazinamide would be "increasingly important" in novel MDR-TB trials
4. Page 2, line 33: remove "even"
5. Page 2, line 38: remove "only"
6. Page 3, line 33: in the sentence as it is, it seems that WHO guidelines are followed mostly (or only) in TB endemic settings, which is not the case; please rephrase
7. Page 3, lines 38-43: Reference 6 does not appear to be appropriate for this sentence
8. Page 3, line 53: I would suggest replacing reference 8 with a reference to the WHO 2016 MDR-TB guidelines, which include guidance on the shortcourse treatment
9. Page 3, line 53: since you mention the synergy between pretomanid and pyrazinamide, I would suggest to briefly discuss also the one between pyrazinamide and bedaquiline, and the trials including this combination (ie, endTB)
10. Page 4, lines 50 and 52: replace "is" with "was"
11. Page 5, lines 48-53: the sentence starting with "previously" might be more suitable for the introduction than for the methods
12. Page 6, lines 21-26: the sentence starting with "fluoroquinolone" might be more suitable for the introduction than for the methods
13. Page 8, line 19: add "with" between "patients" and "treatment"
14. Page 8, line 21: remove "only"
15. Page 10, line 14: I suggest adding an appropriate reference after "previously"
16. Page 10, lines 21-30: I suggest dividing this sentence in two (stop the first after "common") to increase its clarity
17. Conclusions: I would stress that DST seems to be critical for both DS- and DR-TB care

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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