Reviewer's report

Title: Use of the GenoType(R) MTBDRplus assay to assess anti-TB drug resistance levels and patterns among Mycobacterium tuberculosis isolates from TB patients in rural Uganda

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Reviewer: Hendrik Simon Schaaf

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Review: Use of the Genotype MTBDRplus assay to assess anti-TB drug resistance levels and patterns among Mycobacterium tuberculosis isolates from patients in rural Uganda

The authors present data on the occurrence of drug resistance among TB patients in rural Uganda. This kind of data is important as such data from African countries are scarce. In general the manuscript reads well but the reviewer has a number of concerns about the data and the interpretation. The title is very long and mentions tuberculosis three times, which seems unnecessary. The reviewer suggests something like the following: Use of the Genotype MTBDRplus assay to assess drug resistance among Mycobacterium tuberculosis isolates from patients in rural Uganda. The reviewer also has the following comments:

Major Comments:

1. The main problem is the numbers of drug resistant cases. The abstract indicates MDR-TB in 4 of 125 (3.2%) cases, INH mono-resistance in 5/125 (4%) cases and RIF mono-resistance in 7/125 (5.6%) cases. However, what is indicated as “mono-resistance” actually includes the 4 MDR-TB cases! In the manuscript (MS) in the results section under “Drug susceptibility” the authors indicate that there are only 6/125 RIF-resistant and 4 INH-resistant cases, of which all the latter 4 have MDR-TB, which adds up to 6 resistant cases in total. However, on the following page (Mutations associated…) suddenly there are 8 of 117 cases with drug resistance mutations (where did these extra ones come from and why only 117 isolates?). When one reads further, there most likely are 7 RIF-resistant isolates (if the #1 mutation is included), but no mention of the 5th INH resistant case? Finally, looking at the tables, hoping to get clarity, Table 1 indicates 5 INH-resistant, 7 RIF-resistant and 4 of these with combined resistance (MDR) which gives a total of 8 out of 125 drug-resistant cases. Table 2 agrees that there are 8 resistant isolates, but according to the reviewer’s understanding of this table, there are 6 RIF-resistant cases (no explanation given of the “-“ in cases 102 and 246), 4 INH-resistant cases, but now only two MDR-TB cases (cases 08 and 291). The reviewer is completely confused, and even if the interpretation may be slightly incorrect, the authors need to get their numbers correct and say exactly what they mean or how to interpret the data.

As part of the above confusion, it seems from the methods section that only the
MTBDRplus assay was used and no other intervention was done to confirm drug resistance – is this assumption correct?

2. The conclusion in both the abstract and the MS is not correct – there is definitely not a “substantial proportion of INH mono-resistance” and INH mono-resistance is not “the highest” according to the numbers provided – there are actually nil or maybe one case of INH-monoresistance according to most of the data. Mono-resistance means NO resistance to other first-line drugs.

3. Results, Study population…: Why were the 15 cultures not available for the study? Why were cultures only done on smear-positive cases and not on sputum smear-negative cases with suspected TB?

4. Discussion: the authors statistically compare three studies from Uganda, but the reviewer thinks that this cannot be done for the following reasons: a. no numbers (only percentages) are provided, and b. these are not comparable studies as they are from completely different settings. The reviewer suggests that the authors get a statistician’s opinion or delete the statistical comparison. They may, however, describe what was found in other studies in Uganda and say why it cannot be directly compared.

5. The reviewer is concerned about the cases with RIF monoresistance, especially as these cases seem not to be HIV-infected. Is this a limitation of the MTBDRplus test or a true reflection of resistance in the community?

6. The authors discuss and give the results of heteroresistance amongst their study isolates in the discussion. The results should be in the “results” section, otherwise it cannot be discussed.

Minor:

1. Abstract: Not all patients were tested for HIV, therefore 67.9% may be misleading suggest give numbers with percentage.

2. Abstract and MS: inhA is usually referred to as inhA promoter (region) mutation and not gene mutation.

3. Introduction, 1st sentence: The global rate of TB is actually declining from 2004 (see most recent WHO reports) but the total number of TB cases are still increasing – this has to do with growing population and not increasing TB rates.

4. The authors should indicate abbreviations with full description before using abbreviations in the MS (e.g. MDR, DST, PCR, AFB). Also, once abbreviated, do not repeat (e.g. NTLP in methods – already abbreviated in introduction, and tuberculosis – stick to TB).

5. The authors use “susceptibility” mostly (which is preferred) but then uses “sensitive” on a couple of occasions – need to use same terminology throughout the MS.

6. Was pre- and post-test counseling done and consent obtained for HIV testing?

7. Discussion: “Almost half of the study population…” This is not correct – of those tested two-thirds were infected, but a substantial number of patients were not tested for HIV and could also be dually infected. The authors also try to do
statistical comparisons (HIV-infected vs HIV-uninfected) but the numbers are really too small to make any reliable deduction.

8. Middle of 2nd page of discussion: A partial sentence hanging in mid air “MDR rate in Uganda…National survey.” Should be deleted.

9. The references need tidying up! Many “initials” with no authors, any number of authors from one to nine before “et al.”, style not consistent, etc. This does not look good.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**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'