Reviewer's report

Title: Drug resistance mutations and heteroresistance detected using the GenoType MTBDRplus assay and their implication for treatment outcomes in patients from Mumbai, India.

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Reviewer: Leen Rigouts

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In this paper the authors describe the prevalence of heteroresistance to rifampicine and isoniazide as determined by the molecular line probe assay and culture-based drug-susceptibility testing. As these molecular tests are endorsed by WHO for rapid detection of drug resistance and are frequently applied now, it is indeed important to have an idea of the prevalence, meaning and importance of detected heteroresistant profiles. However, little data is available on the prevalence of heteroresistant tuberculosis. Therefore, this paper has an added value. However, the paper requires a major revision before it can be accepted.

Major compulsory revisions

1. It is not clear how representative the convenience sample is. What were the selection criteria? Did the patients included differ from those excluded with regard to age, gender, treatment outcome and DST profiles? This is important to know as the study presents prevalence data.

2. The authors should clearly differentiate samples (= sputum specimen) from isolates (grown bacilli) when presenting the materials & methods and results. What was the starting material for molecular assays, bacilli grown on Löwenstein-Jensen?

3. P10 last line + P11 lines 2-3: ‘A comparison of the ….’ not clear

4. The study would be stronger if MIRU-VNTR typing was applied on the heteroresistant isolates.

5. P15: §2 first sentence: how was the link with RIF resistance and treatment outcome for these cases?

6. The study showed a high prevalence of heteroresistance as compared to other publications so far (e.g. Nikolayevskyy: 25% from sputum but only 6% from cultures). Do the authors have an explanation for this phenomenon? Was there a sample bias?

7. The paper needs English revision: examples given:
   a. P5 §2 line 4 rephrase ‘make it ideal’
b. P5 §3 line 2 rephrase ‘viz’
c. P5 last sentence; rephrase ‘Significantly’

8. Table 3 has no added value to the paper and could be omitted.
9. Table 4 should be rearranged to follow the sequence presented in the results (and discussion) part or another logic.
10. The numbers presented in Table 2 and 4 do not seem to match.

Minor essential revisions
1. P2 lines 2-3: need rephrasing
2. P2 line 7: specify the type of mono-resistance
3. P2 line 8: not clear what is meant by predetermined
4. P2 lines 8-9: these are results
5. P2 line 12 ‘absence of only WT8 …’ is not clear
6. Write abbreviations full out when used for the first time; thereafter systematically use these abbreviations
7. P4 INNO.LiPA.Rif.TB
8. P4 Add data/reference to the last sentence to document the statement that genotypic drug-resistance testing is more sensitive than phenotypic assays.
9. P5 ‘Certain mutations…’ not relevant here as MTBDRplus only identifies the 4 predominant mutations.
10. P5 ‘The application of …’ not relevant here
11. P6: RNTCP?
12. P14 lines 2-3: ‘during treatment’ not relevant
13. P14 §2: what about the 2 remaining that did not show a mixed profile
14. P15 §1: the link between the two last sentences is not clear
15. P15 last sentence: not clear
16. P16 lines 4-6: To my knowledge there is no direct link between the prevalence of TB and the prevalence of katG mutations (or INH-resistant TB). Many Sub-Sahara African countries have high TB incidences/prevalences and yet (relatively) low levels of drug resistance.

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

**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