Reviewer’s report

Title: Utility of the REBA MTB-Rifa(R) Assay for early detection of rifampicin resistant Mycobacterium tuberculosis and correlation with multi-drug resistance

Version: 1 Date: 12 August 2013

Reviewer: Susan S Dorman

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The authors report results of a diagnostic accuracy study that assessed the REBA MTB-Rifa assay using a large set of Mtb clinical isolates as well as microscopy smear positive sputum specimens. As applied to Mtb clinical isolates, sensitivity and specificity of the investigational assay were 98.1% and 100%, respectively. As applied to smear microscopy positive sputa, sensitivity and specificity of the REBA assay were 100% and 100%. Several novel mutations associated with phenotypic resistance to rifampin were identified and the implications were discussed. Strengths of this study include the number of specimens tested among which a high proportion were rifampin resistant, and the comprehensive assessment of the tested specimens (i.e. MICs determined, DNA sequencing performed, phenotypic DST performed).

MAJOR COMPULSORY REVISIONS

1. In the results section, please provide results for the specificity of the REBA test.

2. Some of the Conclusions in lines 341-344 are not clearly justified by the data and results presented. Specifically, the results do not address ‘utility’, ‘availability’ or timing of the REBA test, and do not really address testing of isolates from the Korean peninsula and surrounding regions. The sentence might be more accurately changed to ‘The findings reported herein support the accuracy of the REBA MTB-Rifa assay for the detection of RIF resistance on clinical isolates and smear positive sputum samples in South Korea.’

MINOR ESSENTIAL REVISIONS

1. Inclusion of a flow diagram would be helpful to a reader in keeping track of the specimens tested and the results of investigational and conventional assays, and would be in keeping with the STARD recommendations for reporting of diagnostic accuracy studies.

2. Please clarify if tested sputa were from some of the same participants as the tested Mtb isolates – the Methods section is not clear on this point. The STARD diagram could include this information.

3. Please provide the confidence interval (e.g. 95% CI) around estimates of sensitivity and specificity. Also, recommend handling proportions consistently
throughout with respect to number of places after the decimal point and with respect to inclusion of numerators and denominators.

4. In lines 264 and 266, it is unclear why the MIC values are provided as 'less than or equal to'. The alamar blue method should have provided an MIC value (or a narrow range of MICs). Does less than or equal to 12 mean that the MIC might be 0.25, or 1, or 2 or 12?

DISCRETIONARY REVISIONS
1. Lines 272-274: would consider replacing 'detection rate' with 'sensitivity' or perhaps more correctly 'sensitivity for detection of rifampin resistance'.

2. Discussion lines 330-338: in support of the applicability of the REBA test beyond the NMH population is the specificity of the assay as determined by your study: 277/277 (100%) as performed on clinical Mtb isolates. This might be worth mentioning.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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.