Author's response to reviews

Title: Performance Evaluation of the Xpert MTB/RIF Assay according to Its Clinical Application

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Author's response to reviews: see over
**Responses to the reviewers’ comments:**

**Reviewer #2**

Huh et al. retrospectively evaluated the Xpert MTB/RIF assay in a routine clinical setting at a tertiary health institution in Korea using four different criteria i.e. (i) diagnosis of TB in highly probable cases, (ii) exclusion of TB in clinically indeterminate cases, (iii) differentiation of M. tuberculosis from nontuberculous mycobacteria in acid fast bacilli positive smears and (iv) detection of rifampicin resistance using standard culture and drug susceptibility testing as reference methods.

The manuscript is well written and the authors acknowledge some shortcomings of their study.

Major Compulsory Revisions:

None

Minor Essential Revisions:

1. Some specimen descriptive information from lines 147-156 would benefit the manuscript to be included in the abstract as well.

   **Reply:** Specimen information has been added in the Methods section of the Abstract (page #2: line #31-32).

2. Lines 76-78; The information is not very clear; can the authors consider rephrasing/combining the two sentences to read “A total of 398 respiratory specimens were evaluated consecutively using the Xpert assay between Oct. 2012 and Feb. 2014” if this is what they intended to state?

   **Reply:** Rephrased according to the Reviewer’s suggestion.
3. Lines 95-97: Where respiratory specimens collected in a uniform manner? This
would plausibly influence the quality of category 2 specimens. Also, had AFB smears
been done on all of these samples, if so can the authors provide some information on
grading of these smears to assess the bacillary load, which may affect the results?

   **Reply:** Of a total of 103 specimens in category 2, 84 were sputum and the
   remaining 19 were BAL, which have been collected in a uniform manner. We
   provided the data on the grading of the AFB smears for category 2 in the Results
   section of the manuscript. Among 5 smear-positive samples, one was grade 4,
   another was grade 2, and the remaining three were grade 1.

4. Line 170-173: Can the authors provide the data on the grading of the AFB smears for
these samples to support their speculation since the data is available. How long into
treatment were the study subjects from whom these samples were taken?

   **Reply:** We have provided the data on the grading of the AFB smears for false
   positive samples for category 4 in the manuscript. Of a total of 14 false positive
   samples, 8 samples (57%) were smear-positive: 1 sample of grade 3, 4 samples
   of grade 2, and 3 samples of grade 1. Also, all 14 false positive samples were
   from patients who were currently receiving tuberculosis treatment, in the 60
days prior to testing and started > 48 hours ago.

5. Lines 178-181: Was minimum inhibitory concentration testing done to assess
whether this could be associated with low rifampicin resistance?

   **Reply:** We performed drug susceptibility test for rifampin using two methods;
the MGIT 960 system and the absolute concentration method. DSTs using the
two methods were done in only the critical concentrations for rifampin; 1.0
μg/mL in the MGIT 960 system and 40 μg/mL in the absolute concentration
method, respectively. The DST results of both methods were concordant in
isolates from specimens exhibiting a discrepancy between the Xpert assay and
the phenotypic DST results. However, we could not perform further minimum inhibitory concentration testing in this retrospective study.


Reply: Corrected.

7. Lines 253-254: The authors should consider relooking at their conclusion as it appears to more strongly worded compared to the limited data (at least in some categories) from which inference is being drawn from.

Reply: In response to the Reviewer’s comments, we have modified the conclusion in order to avoid over-interpretation, as follows:

“The retrospective study present here revealed that the Xpert assay exhibited variable performance according to its clinical application in an intermediate-incidence, high-resource setting. The finding in this study cautions that careful interpretation for the results of this assay would be needed in the light of the intended purpose of the test.”

Editorial requirement:

- Acknowledgements

By way of a section Acknowledgements, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for
the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible. The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.' Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Reply: We added the Acknowledgements in the revised manuscript.