Author's response to reviews

Title: Effects of introducing Xpert MTB/RIF test on multi-drug resistant Tuberculosis diagnosis in KwaZulu-Natal South Africa

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Version: 2 Date: 18 July 2014

Author's response to reviews: see over
Dear Editor-in-Chief

We are delighted to resubmit this manuscript entitled “Effects of introducing Xpert MTB/RIF test on multi-drug resistant Tuberculosis diagnosis in KwaZulu-Natal South Africa” for publication. We are very grateful for the constructive comments provided by the reviewers which have certainly added much value to the quality of our manuscript. After careful consideration, we have tried our best to address every concern that was raised in the manuscript and in the point by point response below.

Yours sincerely

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Response to reviewer’s report

Title: Effects of introducing Xpert MTB/RIF test on multi-drug resistant Tuberculosis diagnosis in KwaZulu-Natal South Africa

Reviewer: Prince James

1. In Abstract section - results - it becomes a little difficult to relate that confirmatory test is actually culture and DST. Methods section in Abstract should be expanded a little more.

Response:
Thank you for pointing out this oversight, confirmatory tests have been changed to “phenotypic and genotypic tests” instead of culture and DST or line probe assay. We have also expanded on the methodology section.

2. In Abstract section - conclusion - Though Xpert provides results in few hours only, there was delay of 1 to 3 months in starting MDR TB treatment. I think this should be highlighted more clearly in conclusion.

Response:
We agree that this was not pointed out clearly on the conclusion and we have added it.

3. In Main article - result section - It will be good to know actually how many samples were totally tested with Xpert over one year study period - out of which 637 were found to have Rifampicin resistance.

Response:
The total number of patient samples tested on Xpert was 34444, of which 5870 were positive for TB. This data has now been included in the revised manuscript.

4. In discussion section of main article - 2nd paragraph - large number of patient did not have confirmatory test - This is an important finding - Authors can also write some suggestions to rectify this problem, like - to put the necessary follow up date in Xpert request form, so that patient can be informed to come for follow up the results by that date.

Response:
We have highlighted a new development by the department of Health and the laboratory which was introduced to address this problem.

“In recognition of this, the provincial department of health in collaboration with the laboratory services has recently established an alert system where health care workers at patient facilities are alerted of MDR TB results. This should lead to prompt tracing of patients for further management.”
5. Main article discussion 3rd Paragraph - A large number of patient culture was done on same day sample - It's an important finding - authors can give some suggestions to rectify this problem.

**Response:**
Here we have recommended the adoption of the Western Cape policy where two samples are collected at the same time, but the confirmatory sample is only processed if the rifampicin result is showing resistance.

“A significant number of samples were submitted simultaneously for both Xpert and culture. While this may have ensured timely confirmation of Xpert rifampicin resistant cases, both tests were performed concurrently without considering the Xpert results. This practice could lead to wastage of resources where culture is not required. The Western Cape which is one of the provinces in South Africa has a protocol where two samples are submitted concurrently, one for Xpert and should the rifampicin be resistant, the second sample is used for confirmation using LPA or APM.”

6. Main article discussion 4th paragraph - starting MDR TB treatment within 5 days - Authors can give some suggestions like - may be a good standard protocol and monthly audit will help to trace patients and problems in system.

**Response:**
In addition to the initiative above in point number 4, we have also suggested decentralization of Xpert and MDR TB initiation sites to near patient point of care. It would also be good to adopt the practice done by the TB/HIV care of actively communicating results to the patient using cell phones to link patients with community health workers, clinics and laboratory.
This paragraph has been moved from the 3rd place to the 9th to allow flow of the discussion following changes from the reviewer.
Response to reviewer’s report

Title: Effects of introducing Xpert MTB/RIF test on multi-drug resistant Tuberculosis diagnosis in KwaZulu-Natal South Africa

Reviewer: Keertan Dheda

1. In the abstract background section the sentence needs to be reworded as both line probe and phenotypic testing is a form of DST.

Response:
The sentence has been reworded to “phenotypic and genotypic susceptibility testing”.

2. The confidence interval around the discordance of 8.8% needs to be stated. Same for the RIF mono resistance.

Response:
Thank you for pointing out this omission from our side, confidence intervals have been inserted to table 2.

3. The key finding of the study is that a significant proportion of patients were only initiated on treatment weeks to months later despite having a rapid diagnostic tool with a turnaround time of 48 to 72 hours. The next step would to try and dissect out why this occurring? The turnaround time of the test result should be stated if possible. It should be relatively straightforward to know exactly when the sample was receipted in the lab and when the test result was generated? How was the result sent to the clinic and when was it sent?

Response:
The turnaround time at the time when the results used in the study were generated was not recorded, however the turnaround for the past year was monitored and it should not have been significantly different from the previous one. The monitoring is done by calculating the percentage of results that achieved the targeted turnaround time of 48 hours.

“An average of 71% of results achieved the targeted turnaround time of 48 hours at the study laboratory over the past year.” This has been included in the manuscript.

“The Xpert results are printed directly at the patient facilities using SMS printers, while printed copies are distributed from the laboratory to the healthcare facilities on the next day.”

We have included this on the under the laboratory procedures in the Methods section of the manuscript:

4. I feel that the conclusion could be worded much better. Message 1 should read something like: Despite having rapid diagnostic tools like GeneXpert, failure to address systems-associated delays will result in delays in treatment initiation.
The second key point is to point out that the discordance between Xpert and phenotypic testing is high enough to warrant DST being done.

Response:
Thank you for this comment; we agree that the conclusion was not clear. We have reworded the conclusion:
“*Our findings show a significant amount of discordance between Xpert and phenotypic and/or genotypic drug susceptibility testing which underscores the importance of taking a second sample in cases of Xpert rifampicin resistance. This will also assist in detection of the increasing rifampicin monoresistance. Studies ascertaining the causes and clinical significance of discordance between phenotypic and genotypic assays are warranted in order to solve the diagnostic dilemmas that often accompany such results. Despite having a rapid diagnostic tool which can generate results in a few hours, system associated challenges continue to result in delays in treatment initiation.*”

5. The authors need to discuss this discordance issue in detail in the discussion section. The key question is if a single DST and Xpert are discordant, how does one decide whether the Xpert or the DST is correct?

Response:
We have expanded on the discussion about discordance in paragraph four, five and six of the manuscript. The main point being that, even though we could not demonstrate this in our study, several studies have shown that molecular tests show a better concordance with the Xpert than phenotypic tests because of certain rpoB mutations that are missed by the latter. Therefore in cases of discordance between Xpert and phenotypic test, another molecular test should be done to confirm Xpert results.

6. There are a number of important publications (all done in South Africa) that have been left out and not quoted. These should be mentioned as they are directly relevant to the study and were done in South Africa. On having a quick look: there are two papers by Theron et al. One in the AJRCCM in 2011 validates Xpert positive culture negative discordance. A second paper published in The Lancet late last year, which would shed light on some of the issues discussed here.

Response:
Thank you for your recommendations, the studies were very helpful for our discussion. We have cited five more South African references (including the two suggested above) that are relevant to the manuscript.

7. In table 1, the proportion of samples that were paired, i.e. taken together at the time the Xpert was done, should also be mentioned.

Response:
The number of paired samples has been added to table 1

8. The authors should further suggest what recommendations arise from their findings about the delays? For example, how should the algorithm change so as to make sure a
sample is collected for potential DST should more than one sample be collected at the initial visit? In the Western Cape Province algorithms, for example, two samples are always taken. Should the RIF result be positive, then only is the second sample interrogated for DST (usually line proble) and a third sample is collected at the same time. If sample one and sample two are discordant, then DST is also done on the third sample. A final call on resistance or sensitivity is made depending on the second and the third DST (2 neg= stop MDR and follow up closely).

Response:
In addition to the recommendations made in point 5 above regarding discordant results, further suggestion was made in paragraph 3 of the discussion, of adopting the Western Cape protocol of sending two samples at the same time. Furthermore, the transfer of Xpert to a near patient point of care could bring significant improvements in these delays.