Author's response to reviews

Title: Diagnostic Accuracy of Quantitative PCR (Xpert MTB/RIF) for Tuberculous Pericarditis Compared to Adenosine Deaminase and Unstimulated Interferon-gamma in a High Burden Setting: A Prospective Study

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Response to reviewers' comments

Diagnostic Accuracy of Quantitative PCR (Xpert MTB/RIF) for Tuberculous Pericarditis Compared to Adenosine Deaminase and Unstimulated Interferon-gamma in a High Burden Setting: A Prospective Study

Dear Professor D’Souza,

Once again, we thank the reviewers for their helpful comments. We have addressed all the three outstanding comments by (1) moving the Limits of Detection (LOD) figure (Figure 2) from the main manuscript to the supplementary material, (2) by supplying additional information on the InterGam Ultrasensitive Rapid Immuno-suspension assay by Antrum Biotech, and (3) by providing commentary on the novelty of this manuscript compared to other publications on diagnostic tests in other body fluids for extra-pulmonary tuberculosis. Please find our responses to the three queries outlined below (changes in the manuscript are highlighted as tracked changes) as well as being presented below, where required, with each response).

Thanking you in anticipation.

Yours sincerely

Bongani M Mayosi, DPhil, FCP(SA)
Reviewer #1: Padmapriya Banada

General comments:
We appreciate the acknowledgements that ours is an interesting manuscript and that can have a good impact on the study of extrapulmonary TB diagnosis. We have responded to the comments as follows:

Comment #1: “I think Fig. 2 is not important as an LOD graph in the current manuscript, since it can be mistakenly used as a reference by future studies. Since the authors report it as a proof-of-principle data, because of its low number of replicates, it is best put as supplemental information. The statement of no major difference in LOD between PF and sputum can still be supported without this figure in the main manuscript.”

Response #1: We agree with the reviewer that it is not essential to include the figure of the LOD graph in the main manuscript and have therefore moved it to the supplementary material (Online Supplementary Material Page 11 of 12, Line 163).

Comment #2: “I could not find much detail about the InterGam Ultrasensitive Rapid Immuno-suspension assay by Antrum Biotech anywhere on web. It would be essential that we understand the principle of this kit for scientific advancement. Authors can provide more details if they have and if this is not currently available commercially, please provide the way researchers can procure it. Without that information, it would be difficult for anyone else to use or replicate this data.”

Response #2: Antrum Biotech (Pty) Ltd is a University of Cape Town spin-out company licensed to commercialise the InterGam Ultrasensitive Rapid Immuno-suspension assay (IRISA™-TB), diagnostic test for extrapulmonary TB. Details of the assay and additional information pertaining to Antrum Biotech (Pty) Ltd and IRISA™-TB is now available at: www.antrumbiotech.com. The weblink to the website has been inserted in the manuscript on page 8, line 148.

Comment #3: “There is a similar publication in BMC Pulmonary Medicine 2014, 14:58 doi:10.1186/1471-2466-14-58 by Meldau, R et al., with similar conclusions as this study. Can you highlight the novelty of this manuscript over the published one?”
Response #3: Thank you for raising this question. The novelty of our work rests on at least four pillars. First, this is the first paper to comprehensively evaluate Gene-Xpert in a large cohort of pericardial TB patients in a setting of high TB endemicity. Second, it is the only paper to directly compare several diagnostic approaches in TB pericarditis, including an established screening test (ADA) and a new test, IFNgamma. Third, the majority of the patients have HIV-associated TB pericarditis, which is the entity that is very relevant to many TB endemic regions of the world. The last major studies of the diagnosis of TB pericarditis involved a small number or no HIV infected patients. Finally, we show clearly that IFNgamma is a superior first line test and this has immediate implications for clinical practice. Therefore, our findings are clinically useful, will probably lead to a change in clinical guidelines, and our study is likely to be highly cited.

In addition, TB is a heterogeneous disease whose presentation ranges from latent TB infection, pulmonary TB, smear negative TB, sputum scarce TB, HIV-TB co infection, and various forms of extra-pulmonary TB. Even within extra-pulmonary TB (i.e. meningeal, pleural, pericardial, abdominal or lymphatic TB), the unique nature of the compartment and pathological characteristics translates into different performance outcomes and algorithms when using diagnostic tests. Thus, Gene-Xpert performance can vary greatly in between the different compartments. Deriving the compartment specific performance is an unmet diagnostic need. For example, we have recently published a paper in PLoS Medicine about Gene-Xpert performance in TB meningitis (Patel VB et al. PLoS Med. 2013 Oct;10(10):e1001536. doi: 10). Here Gene-Xpert seems to perform well but this was a seminal paper despite prior small published data sets because it informed clinical practice in a specific subset of patients. Thus, Xpert performance in pleural TB is a separate issue and is not directly relevant to the current paper under review. In fact there have been several prior papers on Gene-Xpert in pleural TB and these were not cited in our manuscript as it is a different compartment. Incidentally Gene-Xpert performance in pleural TB is poor compared to pericardial TB and TB meningitis. This highlights the point that compartment-specific outcomes are different and distinct. Thus it does not follow that Gene-Xpert performance in pleural TB can be extrapolated to pericardial TB. Therefore our publication in pleural TB does not diminish the current paper in any way. Rather, it is complimentary and of critical importance to guide clinicians in the appropriate use of Gene-Xpert in TB endemic settings.
The response stated above is summarised in the main manuscript in the first paragraph of the discussion section (page 14 line 283):

The performance of the new WHO-endorsed, Xpert MTB/RIF assay has recently been reported for some types of extra-pulmonary tuberculosis such as TB lymphadenitis [22], pleural TB [23], and TB meningitis [24]. However, there are no comprehensive data about TB pericarditis to guide clinical practice. Here we report on the first large comprehensive study of Xpert MTB/RIF assay for the diagnosis of pericardial TB [5, 10]. It is also the first study to compare Xpert MTB/RIF to several alternative diagnostic assays including ADA and IFN-γ, and to evaluate test performance outcomes in a TB and HIV-endemic setting.

Reviewer #2

Reviewer: Pierre Goussard

Reviewer's report:
Dear Editor

The authors have responded to all the points and have improved this manuscript. The manuscript can be accepted in its current form

Response: Thank you for accepting the changes that we have previously made.