Reviewer's report

Title: Intensified specimen collection to improve tuberculosis diagnosis in children from rural South Africa, an observational study.

Version: 2
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Reviewer: Christina Lancioni

Reviewer's report:

This is a well-written and organized manuscript detailing the findings of an observational study designed to investigate the diagnostic yield of multiple specimen collections for childhood TB. Strengths of the study include the inclusion of children from both inpatient and outpatient settings in rural South Africa, inclusion of children with TB-HIV co-infection, and a comprehensive approach to specimen collection in most children. The authors’ emphasize on the feasibility of performing induced sputum in the out-patient setting is also important and adds to the growing body of literature on the safe implementation of sputum induction in young children. The major weakness of the study is the very low number of children with confirmed-TB disease, thus making it impossible to actually determine the diagnostic accuracy of the investigated tests. However, as the authors’ acknowledge, the low number of children with culture-confirmed disease reflects the reality of pediatric tuberculosis and is not due to flaws in the study design or execution. There are several points in the manuscript that require clarification, as well as some additional discussion points that could strengthen the manuscript.

Major Compulsory Revisions:

1. The authors state both in the abstract and the methods section that “All participants had blood, urine, and sputum collected.” However, in Figure 1, it shows that only 34/51 outpatients and 61/67 inpatients had sputum collected; in addition, urine was not collected from all subjects and 3/67 inpatients did not have blood cultures. The authors need to clarify this point and explain why some specimens (specifically sputum) were not obtained in all subjects.

2. Regarding patient recruitment in the Methods section, the paragraph describing enrollment is somewhat confusing. From reading this statement it sounds like all patients were recruited from the district hospital (ie, inpatients), but this clearly was not the case. The authors should explain how outpatients were recruited and clarify this paragraph.

3. In the results section, the authors state that the sensitivity of CXR was 100% to diagnosis probable/confirmed TB; however, they admit this is likely due to the WHO case definition for probable TB (that includes an abnormal CXR). Given that CXR are used to categorize children as probable TB, I believe it would be best to not attempt to apply sensitivity/specificity analysis as it is misleading.
4. It was remarkable to see in Table 1 that 31% of all children reported “Prior TB.” It would be appropriate for the authors to comment on how a history of prior TB was obtained (and if it was verified), and why such a large proportion of their children report a history of prior TB.

5. Given only 50% of all children with suspected TB were actually treated for TB, it would be appropriate for the authors to include a summary statement or additional table detailing the non-TB diagnosis for children not treated for TB.

6. Was TST testing included in this study? If yes, TST results should be included in Table 1. If TST testing was not included, the authors should state this and provide an explanation as to why TST was not included.

Discretionary Revisions:

7. The authors mention the limitations of the WHO classification for childhood TB, as well as other scoring systems in their discussion. They should emphasize in this section that 4/8 children with confirmed TB were only considered to have “possible TB”—further emphasis that clinical scoring systems are very limited.

8. Although this study was performed prior to roll-out of Xpert TB/RIF testing, it would be appropriate for the authors to include some discussion of how this technology may assist in pediatric TB diagnostics, including its use on non-conventional clinical specimens (such as urine or stool).

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

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.