Author’s response to reviews

Title: A Randomized Controlled Trial of Standard versus Intensified Tuberculosis Diagnostics on Treatment Decisions by Physicians in Northern Tanzania

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Author’s response to reviews: see over
Dear BMC Infectious Disease,

Thank you for the opportunity to again revise our submission. Taking into account the advice of the reviewer, we have made some changes to the manuscript which we hope will emphasize and highlight the key but unexpected finding of very high mortality in the study.

Please see my specific responses to the reviewer’s comments below, in italics and boldface type.

Reviewer’s report
Title:A Randomized Controlled Trial of Standard versus Intensified Tuberculosis Diagnostics on Treatment Decisions by Physicians in Northern Tanzania
Version:3Date:12 November 2013
Reviewer:Violet N Chihota

Reviewer’s report:
The authors set out to determine the impact of providing intensified diagnostic strategy (concentrated smear and culture) vs traditional method (smear only) on patient outcomes. The were therefore two arms (intensified diagnostic arm and standard of care arm) to which patients would be individually assigned. The randomised trial was powered at 80% and they need to enrol 120 participants (at least 60 per arm). However due to end of project funding the anticipated sample size was not achieved. In total 70 participants were enrolled, 37 in the standard arm and 33 in the standard arm.

Major comments
1. The study was therefore under powered to measure the primary endpoint of appropriate treatment.
We acknowledge that the study was underpowered and this is detailed in the methods where we supply our original power calculations as well as in the results and in the discussion. Nonetheless, because we do not know of a similar study that has been conducted, and because of the rigor of the methods despite the smaller than expected sample size (due to budget cuts), we believe that the study still merits publication. In addition, we have highlighted the finding of early mortality, which we feel underlines the need for more accurate AND more rapid results, which is important in an era where programs are making decisions regarding purchase of GeneXperts in lieu of or in addition to adding capacity for culture diagnosis.

2. It seems plausible to me that the authors have a very important finding of early high mortality among TB suspects regardless of HIV status. They also refer to high mortality in the conclusions section in the abstract, the results and conclusions. It appears that death occurred 7.8-26 days after enrolment to the study and would most likely have been the time people were being investigated for TB. To this end the study highlights an issue that is key to the TB programme. This to me is more interesting and can be stratified by arm without requiring the same sample size as was required for the impact evaluation. The title of the paper would also need to change in this case.

Thank you for this comment. Indeed we also believe that the early mortality noted in the study was a key finding, and this was the reason that in the first sentence of the discussion we state that the results were blunted by early mortality, and there is a full paragraph of results as well as a table dedicated to mortality. However, we also agree with the reviewer that this can be further emphasized especially in light of the small samples size for the overall study. We have added additional data related to mortality in the body of the text and also added it into the title. We have further discussed the reasons for and implications of early mortality in the discussion. We hope these changes will direct readers to the importance of this finding.

Minor comments
1. In the methods the authors mention that parent provided informed consent for participants <18 years of age. Because these are minors parents give assent for the minors to take part in the study.

This is not correct according to our understanding. Parents provide consent for all minors under the age of 18. Assent can be documented for participants aged 12 years or older in addition to parental consent. This was done in our study and this has been added to our methods section.

2. Under inclusion criteria - Adults are defined as any one 6 years and above for the purposes of the analysis. What is the justification of using this cutoff?

Children less than age 6 are particularly prone to develop TB after a contact exposure, and are also more prone to severe disease. In addition, children <6 are much less likely to be able to expectorate a sputum sample. These were the reasons to separate out this group. We have mentioned already in the manuscript that the cutoff was chosen due to the unique disease properties in this age group.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

*We believe the English is of standard/high quality but please point to any specific areas that are not clear.*

Statistical review: Yes, and I have assessed