Reviewer's report

Title: QuantiFERON-TB-Gold In-Tube test conversions and reversions among Tuberculosis patients and their household contacts in Addis Ababa: a one year follow-up study

Version: 2 Date: 1 October 2014

Reviewer: Lisa Pascopella

Reviewer's report:

The manuscript describes a study of QFT-GIT test results in a sample of TB patients and their household contacts at baseline, and at one year after baseline. The authors report the test results as positive or negative or indeterminate at each timepoint, and note reversions and conversions from baseline to one year. The article is of general interest to TB clinicians and researchers because there are few longitudinal studies of QFT-GIT in this specific population (HIV-negative, high TB incidence), and the findings contribute to the knowledge base for improving utilization and interpretation of QFT-GIT.

However, I have a few questions that need to be resolved before determining whether the discussion and conclusions were well balanced and adequately supported by the data. A recent publication (“Reproducibility of interferon gamma release assays: a systematic review,” Tagmouti, S. et al, ANNALSATS Articles in Press. Published on 04-September-2014 as 10.1513/AnnalsATS.201405-188OC) summarizes sources and estimates of variability with repeat IGRA testing, and concludes that reversions and conversions around the existing cut-point should be interpreted with caution.

Major compulsory revisions:

• Can the authors provide the numeric test results (i.e. IU/ml of interferon gamma) for each study subject that demonstrated QFT-GIT conversion or reversion? Although these are presented in Figures 1, 2 in aggregate, it is important to see how each value changed from baseline to the one year followup timepoint. (Figure 3 shows these in graph form for only the subset of subjects with negative QFT-GIT at baseline. This figure could be improved by labeling each point (because it is difficult to differentiate values between 0 and 1, e.g. around the 0.35 cutpoint), or, could be replaced with a table that provides values for each subject at baseline and at one year.

• If many of the conversions are around the 0.35 cutpoint, how would this finding impact the authors’ interpretation of these conversions?

• Can the authors provide further methodological detail, specifically related to potential sources of known variability of the QFT-GIT test? (e.g. how was the process from phlebotomy to readout quality-controlled? Was blood volume standardized or could it have differed by at least 0.2 ml from subject to subject and/or time to time?)
• If the authors can address above-mentioned questions and points, the conclusions need a bit of softening, because the study findings are suggestive, but not definitive. For example, line 52, “repeated screening of QFT negative contacts may be (rather than is) needed to diagnose TB infection in a TB endemic setting.”

Minor Essential Revisions:
• Grammar and spelling need to be reviewed and corrected/made consistent throughout the document.
• Further detail is needed to describe the timing of QFT-GIT testing in relation to TB diagnosis and assessment of contacts (e.g. rule-out of active TB disease). How was active TB disease confirmed (with culture or only with smear and clinical signs/symptoms?), How were contacts assessed for exposure- was it self-reported exposure to the index case living within same household? Did the contact report sleeping in same room as index case? Were number of hours of exposure to the index case within the home determined? Were all study subjects tested for HIV infection, or, was HIV-negative status based on self-report?
• Please provide further detail about what occurred during the one year followup (in addition to blood draw for QFT-GIT test). Were subjects assessed for TB/TB medication side effects during the interim? Was one year actually 12 months, or, was it 12 months plus or minus 2 weeks, or a month or ?
• Line 149. The data in Table 1 shows that 10 contacts had conversions, but the sentence says “11.” Which number is correct?
• Consider summarizing the findings with numerical data (e.g. lines 156 and 157, add percentages of reversions and conversions in parentheses)
• Line 159 -160. Consider providing the range of prevalences/percentages of latent TB from similar studies.
• Lines 175-178. Consider adding the estimate of the TB rate in Ethiopia to further bolster the point that multiple exposures to TB were expected during the study timeframe.
• Lines 182-183. But the specific antigens in QFT-GIT exclude most environmental mycobacteria. Are there data that suggest that M. marinum, which cross-reacts, is the main environmental bacterium to which Ethiopians would be exposed?
• Line 188. Suggest caution when using term “immunity.” QFT-GIT measures one component of the immune response; interferon gamma’s role in “protective immunity” is not clear.
• Lines 205-212. Study limitations will need to be expanded to include how the known sources of variability in QFT-GIT may impact the study findings (see above).

**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

**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.