Reviewer’s report

Title: Comparison of Two Interferon Gamma Release Assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia

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Reviewer: Andrew Vernon

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Review of “Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia”

By Adetifa IMO, Lugos MD, Hammon A, Jeffries D, Donkor S, Adegbola RA, Hill PC

General: This is a very nice study which is part of a long-term set of studies being done by the MRC labs in The Gambia. Dr. Hill, as senior author, has published a number of related articles, and this piece adds a new and important contribution. My comments are relatively modest. I believe the paper should be accepted with minor revision.

Title: Accurate

Abstract:
1. The statement that IGRA/TST discordance was “mostly from IGRA positive and TST negative combinations” seems a bit misleading, since every type of discordance occurred in significant numbers. I would remove this phrase.

2. The abstract might include a statement that significant discordance among the two IGRAst and the TST remain largely unexplained.

Introduction: no comment

Methods:
1. The reason for limiting contacts to those over 15 years of age is unclear. Why was this done?

2. Persons with TB diagnosed within one month of recruitment were excluded. How many were these? Were they included as TB cases?

3. IGRA testing was done one month after the TST. The discussion incorrectly states that IGRAst are not subject to boosting. The IGRA will not cause boosting, because no antigen is exhibited to the patient by the IGRA. However, an earlier TST might affect subsequent IGRA results, and the cited CDC guidelines state this as a possibility for which no conclusive data are yet available. There is at least one recent report on this issue (Naseer, Europ Resp J 2007; 29(6): 1282-3).
4. The Elispot is an in-house test. How do the peptides used compare to the commercial product of Oxford Immunotec? How does the spot counting criteria compare to what is done with the commercial product?

5. The QFT-GIT had no positive control. I believe that the manufacturer now includes a positive control with the test. This should be noted if correct.

6. How was household clustering taken into account in the analysis?

Results:
1. The percentages in the 2nd paragraph seem in error. They should be corrected or explained.

2. The different types of discordance among the contacts is of considerable interest. Tables should compare the results of each IGRA with the TST, and compare the results of the two IGRA. These could be provided as an appendix or an online data supplement for interested readers.

Discussion:
1. The senior author published in 2004 a paper with a figure very similar to Figure 2. However, the absolute values of % positive were in the 40’s rather than the 60’s. That study included children, I believe. The authors should explain why their results now differ in absolute value (although the trends are similar).

2. The authors comment on the absence of an association with BCG. They could note that the exclusion of children meant that no person had received BCG less than 15 years earlier. This time differential, and the lack of prior skin testing as an anamnestic, might be one explanation for the lack of association of discordance with BCG. Another reason might be that scar is not a robust differentiator between persons with and without response to or receipt of BCG.

References:
1. No comment

Tables and Figures:
1. Why does Figure 2 not show the TST results? These should be added.

MINOR:
1. Typo page 10, line 4: “may not BE as sensitive….”

2. Typo page 11, line 22: “…once AN individual is infected….”

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

Our office issues guidelines on the use of IGRAs in the United States.

I have no financial interests in any organization with financial interests in this area.

I hold no patents and receive no fees or reimbursements.

I have no other competing interests.

Andrew Vernon