Reviewer's report

Title: T-SPOT.TB responses during treatment of pulmonary tuberculosis

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Reviewer: Keertan Dheda

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This is an important study as it was performed in a high burden setting and explores the utility of the T cell assays as proxy markers of disease burden and an adjunct to the evaluation of new immunotherapeutic interventions.

The discussion needs to be expanded and improved. Specifically, there is selective quotation of the literature (paragraph 1 of the literature). There are several studies which show that responses do not decline or even become more robust during the course of treatment. There may be several putative reasons. Firstly there seems to be a dichotomy between high and low burden countries (bacillary load, strain (see de Jong BC et al, J Infect Dis, 2006 and 2008), exposure to ESAT-6 producing homologues of NTMs e.g. M. marinum, HIV, malnutrition etc). There is also the issue of peptides vs proteins as stimulants and incubation times. I have found (Dheda et al; J Infection, 2007; also used the T SPOT assay) a useful reference that summarizes the relevant studies and associated factors; these need to be discussed in more detail here.

These data also support the notion that the ELISPOT assay is detecting ‘infection’ rather than ‘exposure’ i.e. TB infection rather that memory of exposure (important as there is no gold standard for the detection of LTBI and it is controversial what this assay is really detecting). So, the data are useful in this respect.

Frozen cells; a differential effect may have occurred with ‘low’ ESAT responders being more affected by freeze thaw. This should be stated; the viability of the recovered cells should be mentioned.

Excluded patient’s characteristics........... Where these similar to the cohort analysed e.g. more or less extensive disease?

HIV negative patients were evaluated and this may not be generalisable to high HIV prevalence settings.

70% were smear +, which is not reflective of clinical cohorts in high burden settings (40 to 50% smear + in Africa). How and who reported the cavitation on chest radiographs?

Did the investigators look at change in weight from o to 2 months and correlate this with the ELISPOT data?

It should probably be mentioned that only one biomarker was evaluated here (IFN-g). It is entirely possible that other biomarkers e.g. IP-10, or including a
combination, may be more useful in predicting response to treatment.
The culture + group and CFP-10 shows a transient increase and then decrease; could this be a compartmentalization effect? It is possible that the response 1st increase and then decrease but the timepoints used here cannot detect this change. This should be mentioned.

**Declaration of competing interests:**

I declare that I have no competing interests