Author's response to reviews

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

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Author's response to reviews: see over
Sabina Alam, Ph.D
Assistant Editor
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Re: Manuscript 2139425866222112 - T-SPOT.TB responses during treatment of pulmonary tuberculosis

To the Editor:

Thank you very much for consideration of our previously revised manuscript and additional reviewers’ comments. Attached (next page) for your consideration are our point-by-point responses to the reviewers’ additional comments, as well as a revised manuscript. In addition, we have revised the references to now include that a manuscript describing the parent TB treatment study is now “in press” at The Lancet. Thank you very much for your consideration. Please feel free to contact me should you have any questions.

Sincerely,

Susan E. Dorman MD
Associate Professor of Medicine
From Dr. Charles von Reyn:
Major compulsory revision
The authors have still not acknowledged a critical issue that may have influenced results. The earliest samples, baseline samples, were stored longest and might have had spuriously low results. A caveat is needed.

We have added the following information to the Discussion section on page 8, as suggested by the reviewer: “We cannot exclude the possibility that frozen samples that were stored longest before testing (i.e., baseline samples) could have been most affected by storage and might have given spuriously low results; this could have diminished our ability to detect a decrease in assay responses with treatment. The effects of prolonged freezing could be studied by dividing samples into two aliquots, with one aliquot tested immediately and the other frozen for later testing.”

From Dr. Cynthia Bin-Eng Chee
Major Essential Revisions
1. Abstract, Results, line 6: should read “The incidence rate ratios (IRRs)…” instead of “The incidence rate…”.

The sentence has been modified as suggested and now reads: “For the group that was culture positive at completion of 8 weeks of treatment compared to the culture negative group, the incidence rate ratio (IRR) of ESAT-6, CFP-10, and summed RD1 specific SFC counts were, respectively, 2.23 (p=0.048), 1.51 (p=0.20), and 1.83 (p=0.047).”

2. Discussion, page 8, last paragraph on study limitations: line 3: “…the slightly lower-than-expected baseline sensitivity…” The baseline T-SPOT sensitivity of 72% is more than slightly lower-than-expected. Suggest to omit “slightly”.

We agree and have omitted the word “slightly”. The sentence now reads: “Freeze-thaw processes may have diminished T cell reactivity, and this could account for the lower-than-expected baseline sensitivity of the T-SPOT.TB assay.”

From Dr. Edward Graviss:
Discretionary revisions
As the site of extrapulmonary disease has not been captured by the original CRF and data set, a short clarification in the methods section might be warranted.

Respectfully, and after careful consideration, we do not believe that this information (that site of extrapulmonary disease was not captured) is helpful in interpreting the study, its results, or its generalizability. This was fundamentally a study of pulmonary TB patients; we have not attempted to analyze the data based on site of disease, and patients with very severe disseminated forms of disease would have been excluded by virtue of Karnofsky performance status score (see Methods section).