Reviewer’s report

**Title:** Sub-clinical abnormalities detected by PET/MRI in household tuberculosis contacts

**Version:** 1  **Date:** 09 Feb 2018

**Reviewer:** Hanif Esmail

**Reviewer's report:**

I appreciate the opportunity to review the revised manuscript. The authors have addressed some of the concerns. However, I still do not feel the conclusions are justified by the data presented and I do not feel that the methodology of the study is adequate as it lacks the appropriate controls or benchmarking to hard endpoints.

The authors assert that the abnormalities they identify (lymph node of >1cm in short nodule >6mm and any SUV max >0.95) relate to subclinical TB disease and imply that they may be more likely to progress to clinical disease. Although it has previously been shown that HIV infected persons with infiltrates and scars within the lung parenchyma primarily within the upper lobes of the lungs are associated with clinical progression, there is no evidence (that I am aware of) that LN uptake >0.95 especially in the absence of lymphadenopathy is associated with disease progression. Even if these abnormalities are as a consequence of contact with TB is it not possible that the lymph node activity just relates to antigen presentation within the lymph node and is part of the natural response to infection (i.e. may result in subsequent control of infection rather than disease progression). Vaccination is well known to result in increased lymph node activity and in the smaller study by Ghesani et al 80% of IGRA positive contacts had lymph node activity which correlated with background subtracted antigen specific IFN gamma levels. It is possible that these abnormalities within the lymph node may improve over time rather than worsen (I appreciate that 3 of the participants had repeat PET/MRI). Hence I still feel that to be of value and infer that the variety of abnormalities on the PET/MRI are all related to subclinical disease, that they would need to be benchmarked to clinical endpoints. This is especially important if the imaging modality is to be used for biomarker discovery in the future.

The authors are essentially making the a priori assumption that all the PET/MRI abnormalities they describe in their household contacts relate TB. Even we assume that the abnormalities could relate to natural infection with Mtb or the subclinical disease process it is surprising that there is no relationship with IGRA, intensity of exposure to index case, frequency of exposure, estimated duration of exposure or smear status of index case. These are all well known risk factors for both infection and disease risk in household contacts. The authors do not really explore this in the discussion. It may be that some of the abnormalities they identify are associated with future TB risk but does not appear that the sample size is adequate to investigate this in detail. A control group would allow for a more accurate assessment of where the threshold for the abnormalities should be set.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
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No

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I am able to assess the statistics

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