Author's response to reviews

Title: Screening for Latent Tuberculosis Infection among Undocumented Migrants in Swiss Healthcare Centres; a Descriptive Exploratory Study

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Author's response to reviews: see over
Dear Dr Ling, dear Dr Zwerling, and dear Editor,

Thank you for having taken the time to review our article and giving us your feedback. We are very grateful for your critical appraisal and your advices and have done our best to respond to your preoccupations.

Below, you will find the personalised responses to your comments.

**Reviewer 1: Daphne Ling**

**Minor essential revisions**

1. **Suspected false negative result**
   
   **Reviewer's comment:** In the last paragraph of the Results section, the third sentence should read "Among the 18 immigrants..."

   **Our response:** From all the negative assays, only one was believed to be falsely negative. The denominator far all the negative test was 101 and not 18. We however have changed the sentence to prevent any confusion.

   **Changes:** "One patient was suspected to falsely have a negative interferon-γ assays as he had been treated for a sputum confirmed active tuberculosis two years previously."

2. **Proximity**

   **Reviewer's comment:** In Table 1, the item “Proximity with other people” appears irrelevant to the objectives of the study for LTBI. It does not add much information given that most people have participated in these activities in their lifetime. It is unclear what point the authors are trying to make with this item.

   **Our response:** Patients were questioned on their “close” contacts during at least one hour during the last three months. This question is relevant to give an idea of the risk of contamination had each patient developed an active tuberculosis. To prevent any confusion, the heading in the table was modified.

   **Changes:** "Proximity of at least one hour with someone during previous 3 months"

3. **Number of refusals**

   **Reviewer's comment:** In Figure 1, the number of refusals adds to 31. Either the number in the first box or the second box is incorrect.

   **Our response:** One patient initially refused to enter the study without giving any reason and then was finally enrolled as he changed his mind. This patient was falsely considered as not having been included. The flow-chart was corrected.
Discretionary Revisions

4. Vaccine policy

**Reviewer’s comment:** The study would benefit from information on the BCG vaccination status of the immigrants and the association, if any, of the vaccine with the TSPOT results. Given that the authors have data on the countries represented, a reasonable inference can be made on the BCG status.

**Our response:** Including the country of origin vaccination policies to describe the population seems to be a good idea. This is however partially described through the countries’ incidence rate of active tuberculosis. Herd protection could protect unvaccinated patients. Patients from countries which have recently changed their vaccine policy could therefore be more likely to have been infected before the vaccine policy was put into place. It is however very difficult for us to use this information appropriately as the risk of exposition also depends of the age of the patient and the time spent in a country with high rates of tuberculosis. The aim of this study is not to model the risk of latent tuberculosis for which we are largely underpowered. We have therefore decided not to infer the patients’ vaccine profile from their origin.

5. Validity of the TSPOT

**Reviewer’s comment:** Was the TSPOT test ever validated by the authors? There was no serial testing performed. Given that conversions and reversions have been an issue with the Quantiferon test, another interferon-gamma based assay, and TST was not done, it is uncertain whether the TSPOT results represent true or false positives.

**Our response:** A recent meta-analysis has shown the TSPOT to be more sensitive than the Quantiferon test for detecting latent tuberculosis. In the method section, the sensitivity and specificity of the TSPOT was added (Pai et al., Ann Int Med; 2008; doi 0000605-200808050-200800241).

**Changes:** "Within the next 24h, an enzyme-linked immunospot γ-interferon assay (T-Spot.TB™, Oxford Immunotec) was performed to assess the previous tuberculosis infection status. This test has been shown to have a sensitivity of 90% and a specificity of 93% to detect latent tuberculosis."

We thank you for the time you have spent revising and checking our draft. Thank you for spotting-out our error in the flow-chart.

**Reviewer 2:** Alice Zwerling

Major Compulsory Revisions

**Generalisability to all undocumented migrants and limitations to the interpretation of the IGRA**

**Reviewer’s comment:** It is difficult to assess the potential presence of selection bias with the information provided currently. By using the health clinics as a recruitment point, all participants are assumed to have some reason for visiting medical services.

What were typical reasons participants were seeking health care initially? Would these individuals be less healthy than average undocumented immigrants? What
about immune suppression conditions or prescription medications? Are these undocumented immigrants similar in other demographic characteristics to other undocumented immigrants in Switzerland (ie: age, SES, etc)?

Given the study limitations stated above coupled with holes in our ability to interpret IGRA, and understand their predictive abilities, more emphasis should be placed on the limitation that IGRA positivity may not equate perfectly with latent TB infection. As such additionally data using another IGRA or the TST would be helpful. In addition, I would challenge their statement on p7 that “our observations suggest that a reported contact with someone that had TB might not be a valid measure for detecting the infectious state.”; at the very least this statement requires additional justification.

Authors should be careful regarding conclusions such as “the number of patients that need preventative treatment has been largely reduced.,” and temper their statements with caution.

Our response: This study attempts to test the prevalence of latent tuberculosis in a setting which makes it possible to consider targeted screening and prevention programs to take place. Our design therefore limits the interpretation to other settings. As suggested by the reviewer, we added the following limitations to our study.

Changes: “The setting of our study could limit the generalisability of our results to rural migrants attending a healthcare centre. Patients who do not attend a healthcare centre could be younger and less deprived than those included in the study. Our population could be more at risk to have been in contact with tuberculosis. Our results are therefore limited to quantifying the prevalence of latent tuberculosis in a setting in which it is possible to consider targeted screening and prevention programs to take place. Finally, interferon-γ positivity may not equate perfectly with latent TB infection. As such additionally data using another interferon-γ or the tuberculosis skin test would have been helpful.”

As suggested, we revised our conclusions in consequence. The statement from page 7 was suppressed, and the one from page 9 adapted.

Changes: “Furthermore, compared to tuberculosis skin tests, the introduction of interferon-γ assays has largely improved the specificity of LTBI detection; thus, the number of patients that would receive preventative treatment without needing it can be reduced.”

Discretionary Revisions

Reviewer’s comment: It would be very interesting to compare the IGRA results with TST results. Even if the authors did not want to subject the individuals to both TST and IGRA, perhaps they have information on previous TST results (which are known to remain fairly constant over time).

Our response: Undocumented patients are very difficult to follow-up and medical files are difficult to recover. There is therefore little hope in been able to access to data on previous TST. We had decided not to do the TST as it is difficult to make patients come back to the healthcare centre (which is essential to measure the skin reaction). No data was collected on previous TST and caregivers did not inspect patients for scares from this assay. Using such methods could be worthwhile in other studies and we thank you for suggesting it to us.
We also thank you for your thoughtful comments and for helping us improve our paper.

Regards,

Paul Vaucher,
Patrick Bodemann,
Jean-Pierre Zellweger