Author's response to reviews

Title: Risk factors of latent tuberculosis among asylum seekers in Switzerland: A cross-sectional study in Vaud County.

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Author's response to reviews: see over
About: Cover Letter of the revised manuscript

Dear Editor,

We thank you and the reviewers for having revised our manuscript. We have studied the comments and prepared detailed answers for each of them. Please find in attachment:

1. A point-by-point answer to the comments by the reviewers.

2. The manuscript in a revised form, with all changes highlighted in color.

We hope that the text in the current form will be accepted for publication and await your decision.

With our best regards

On behalf of the authors

Dr. A. Sarivalasis
We thank the reviewers for their considered and pertinent comments. Please find below how we have addressed each reviewer's comments.

**Reviewer N°1 Dr. Ingun Harstad**

**Major revisions**

1.1: The phrase “risk factor” is used throughout the manuscript where a better phrase would be “factors associated with”. Particularly to call “cough” a risk factor for LTBI is not correct. Rewrite/rethink the phrasing throughout the manuscript.

- We agree that “factors associated with” it’s a better phrase than “risk factor” and describes better the nature of the study findings. We therefore rephrased the term throughout the whole manuscript. The variant cough as factor associated with LTBI was examined in the answer to reviewer n°3, point 7

Methods, page 7: “all asylum seekers with positive T.SPOT.TB without symptoms—“but asylum seekers with cough are included and they are not without symptoms. This must be changed.

- We would like to thank the reviewer for highlighting this potential confusion. We changed the phrase as follows: “All asylum seekers with positive T.SPOT.TB without signs suspect of active tuberculosis or abnormal x-ray were considered as carriers of LTBI”.

1.2: Methods/results: the study group was volunteers, thus only 393 of 639 (61%) were screened. Generalization of the results could therefore be a problem. I suggest adding some information about the 39% that were not included in the study, at least information about country of origin, sex and age to see if they are comparable to the study group.

- We acknowledge that since the screened population was of volunteers some limitation can apply to the generalization of the results. We need though to consider that this limitation couldn’t be avoided since the ethic
comity wouldn’t accept a compulsory screening protocol with a preventive treatment for LTBI.

- Although our survey had included more than 60% of the targeted collective, we integrated the suggestion by adding the demographic information about the 38.5% that were not included after the results for the eligible population in fig.4. There was no obvious difference in the demographic characteristics of the screened versus non-screened population and the staff of the refugee Center did not allow for any discrimination or selection of the participants.

- The median age of the eligible population was 29.26 years, the sex distribution in the eligible sample was 25% of women and 75% men (concordant with the demography of the AS population in Switzerland). As for the region of origin, 8% came from FSU, 17% from the Balkans, 28% from Asia and 47% from Africa.

**Minor revisions**

2.1: Background p4: “not influenced by—contact with non-tuberculous mycobacteria”, IGRAS are influenced but to a lower degree than TSTs by some non-tuberculous mycobacteria. This must be rewritten.

- We agree with the correction and we have rewritten the text as follows: “IGRAs are highly specific, not influenced by prior BCG vaccination or contact with most non-tuberculous mycobacteria.”

2.2: Limitations of the study: Some discussion about the low number studied and that only 61% were included should be added and whether the results can apply to other groups of asylum seekers. There were some selection done because only volunteers were included, they might have higher education/social status than the others?

- We thank the reviewer in pointing out the limitations of our study. Although there could be a selection bias due difference in educational/social status we do not have data on education level of the non-screened population for comparison but in general AS belong to poorly educated population groups so that this should not be a source of significant selection bias. Please refer to point 1.2 answer for further details.
Discretionary revisions

3.1: Background, p3: “asymptomatic are transferred in a local center”, in changed to “to”

We changed “in” to “to”.

3.2: Methods p 6: “for those AS who did not understood”. Corrected to understand.

The correction was made in the manuscript.

3.3: Discussion p 10; last paragraph: if this is describing the study population it would be better to say:“Switzerland border and who coughed, were mostly”, but if it is a general statement then the present tense is OK.

This is a general statement.

3.4: Discussion: married individuals and risk for infection, there are some studied that have shown that unmarried individuals have higher risk of TB disease, maybe because of other problems and association that are higher among unmarried individuals. (Int J Epidemiology 2005; 34:914-23), but most studies do not study infection but disease.

- The data of our study do not support this finding. In our study, using the multivariate analysis, married individuals are at higher risk for LTBI than single ones. We agree with the reviewer comment that most studies reporting a positive relation between unmarried marital status and disease do not assess the infected individuals.

Reviewer N°2 Prof. Albert Nienhaus

Major Changes

1) The five cases with active TB should be better described: When was TB diagnosed, how the IGRA result, age was and gender, marital status etc. should be described. Would all 5 cases have been identified when the new score would have been used?

- The five cases of active TB demonstrate the possible occurrence of active TB shortly after arrival associated with reactivation of LTBI and
comfort the rational of this study, but this was not the objective of this paper. For clarification, we added a table with some indications about the five cases. As the score was designed for screening to identify LTBI but not active TB, we do not consider that the score could replace due attention to clinical symptoms.

2) Please distinguish between statistically significant tests and those that are not significant.

- We acknowledge the confusion made by the use of 95% C.I. repartition as indicator of the power of the association. We therefore added the p-score (<0.005) next to the 95% C.I. on the tables.

3) Please describe the development of the score in the method section.

- We acknowledge the wrong placement of the description of the score development. We therefore placed it in the method section.

4) I’m not convinced that the score is useful. At least you should discuss simple approaches like screening all those from countries with a high incidence rate of TB or combining fewer variables like provenance and type of travel. To take marital status as a risk factor is somehow surprising.

- We thank the reviewer for his comment. The value of the score is that it summarizes the factors associated with LTBI. Screening all migrants from countries with an incidence above a predetermined rate (as recommended for instance by the NICE Guidelines) is one option but does not seem to be selective and cost-effective enough (see the current controversy: Klinkenberg E, ERJ 2009;34:1180 and Pareek M, ERJ 2011;37:1175). If the cut-off is low, most migrants will have to be screened and the costs are high. If the cut-off is high, some or many cases may be missed. As there is currently no official policy for screening for LTBI in Switzerland, this pilot study was designed as a test to assess if a combination of factors could possibly detect the majority of cases at a reasonable cost. We consider that this was achieved and allowed to define the most important factors associated with the presence of LTBI. The marital status was found to be related to LTBI in the multivariate analysis and was therefore considered as a factor associated with in the elaboration of the score, although we do not have a clear explanation for this association.

5) The methods used in figure 3 and 4 should be explained in the method section.

- Explanation of the ROC curve was added to the method section according to reviewer’s proposal.
6) It is surprising that cough is a risk factor for a positive IGRA. Please discuss whether this might have been caused by selection bias. Migrants with cough might be more likely to accept TB screening.

- We thank the reviewer for his pertinent comment. The statistical analysis yielded a positive association of cough and LTBI. The issue was discussed on reviewer n°1 point 1.1 and reviewer n°3 point 7 since all reviewers were concerned on this issue. Therefore, we replaced “risk factor” by factor “associated with”. The cough pattern was important since chronic cough was treated differently than cough of acute onset. We believe that the congregated living conditions resulting in high prevalence of passive smoking and upper airways infections were the reason for this association. We have no indication that migrants with acute cough would be more willing to accept the screening, but we cannot exclude this.

7) Please provide the distribution of the quantitative results of the t.spot.tb. Are they high or close to the cutoff?

- We thank the reviewer for letting us add additional information on IGRA spots distribution. We added the following sentence to the “Results”. Ten AS had a T-SPOT.TB result between 6 and 9 spots, 71 between 10 and 50 spots and 17 over 50 spots. Following the current recommendations of the Swiss Guidelines, the cases with 6-9 points were counted as positive (knowing that, according to the recent recommendations of CDC, these cases would be considered as borderline and retested). Cases with an active TB had all more than 10 points.

8) The detection rate is quite high 5 out of 393. This would be about 1200 per 100,000. With such a high detection rate the program would be very successful and a score which reduces the number of migrants to be screened is unwanted. Please discuss this issue.

- We thank the reviewer for his point of view. We consider that this score is pertinent as a screening tool for LTBI at the border where only active TB screening is currently performed. We would like to highlight the fact that the high number of active TB cases detected at screening after the border control is confirming the high risk of reactivation among young immigrants with undetected LTBI. In practice, screening for LTBI was an occasion to examine some AS with recent or mild symptoms who turned out to have active TB. Finally we would like the reviewer to consider that, although repeated screening may be successful, the financial burden of a generalized screening would be high, considering that some
20'000 migrants either each year in Switzerland, many of them from
countries with a low or median risk of TB. Therefore, our aim was to
assess if a more targeted use of IGRA screening could be implemented
at reasonable costs.

9) It would be niche to discuss whether a short term preventive therapy
would be useful.

- We thank the reviewer for his comment. The indication for preventive
therapy and the choice of the treatment options are a matter of
controversy and goes beyond the aims of this paper. The choice of
treatment, the follow up and completion rate will be discussed in a
separate paper (under submission).

**Minor Changes**

10) Please use Former Soviet Republics: EX-URSS or Former Soviet
Union FSU but not both.

The correction was made in the manuscript.

11) Please control the literature list. Some citations seem to be
incomplete. See reference one and six.

The correction was made in the manuscript.

12) Page 3 first line second paragraph: consists of and not consist on
Sixth line: county instead of County
Last line: suspended instead of suppressed

The corrections were made in the manuscript.

13) Page 7: once it is x-ray and another time X-ray

The correction was made in the manuscript.

14) Page 8, second line: period,,

The correction was made in the manuscript.

15) In the section Author’s contribution in the second line the “of”
should be deleted.

The correction was made in the manuscript.
Reviewer N°3 Prof. Jean-Paul Janssens

Changes:

1. The score devised is based on migration patterns at a given time in a given country. Going through statistics of origins of asylum seekers coming to Switzerland over the past 10 years, it is easy to see that dominant nationalities change overtime, sometimes very rapidly, and thus that the score is "site specific" and "time specific"; this should be acknowledged by the authors.

Although the areas included in the model cover most of the high incidence countries in the world, the model's validity may change with changes in representation of different nationalities within these areas.

- We acknowledge that the score is site and time specific and it was designed with that purpose. To be broadly generalized the score should, after the process of internal / external validation, integrate the particularities of each country, the distribution of origin of migrants and its evolution overtime.

2. It is unclear why coming from Asia is integrated in the model since this variable is no significant with a CI which includes 1.

- The variant “Asia” is a sub-variant of the supra-variant “origin” that is significantly related to LTBI. The 95% C.I. includes 1 when internal stratification and comparison to the reference group “balkan” is made. We therefore cannot dissociate “asia” from the significant results and the model elaboration.

3. Why pregnancy tests in patients with a positive LTBI? Pregnancy is not a contraindication for treating LTBI

- We agree with the reviewer. There is a misunderstanding: The pregnancy test is a standard test performed on request to female AS by the nurse of health center (CSI) and is not associated with this study. We therefore deleted the end of the sentence.

4. The fact that immunosuppression is not associated with LTBI may be related to the lower sensitivity of IGRAs in this group: a specific strategy for these patients should be evoked (of course this is not the topic of your paper, but it is a limitation of the score)

- We thank the reviewer for pointing out this important feature. Indeed the tuberculin skin tests (TST) screening is subject to severe alteration by
immunosuppression. The IGRA sensitivity is less altered by immune deficiency. Furthermore, in our collective there were not AS with known major immune deficiency to influence the results.

5. I am not very convinced by the rationale for married persons being at higher risk of LTBI: the statement that "Being married is an indicator of a social network with increased risk of inter-humane transmission" is very speculative; the opposite could easily be considered. The authors should see if there is any kind of epidemiological observation to explain this finding.

- The identification of married marital status as a factor associated with LTBI was clearly established by the statistical analysis but we actually have no solid explanation for it. The statement that a married condition is risk factor for LTBI is a source of concern for all reviewers. We therefore integrated in the text dr Harstad's proposition and replaced the term “risk factor” by “factor associated with” for all the finding of our study.

6. When you mention the NICE guidelines, I suppose you refer to a threshold of 50 and not 500 per 100,000 inhabitants

- We thank the reviewer for his comment. Indeed the 2011 NICE guidelines threshold is of 50 not 500. We corrected this typing error.

7. It would be interesting, if data collection allows this, to see if "coughing" can be replaced by "active smoker" with similar results: it is indeed confusing to integrate in a score for LTBI a potential symptom of active disease

- We thank the reviewer for his comment. The “active smoker” factor was integrated to “addiction” and “coughing” was found an independent factor associated with LTBI. There may be some confusion with coughing as a variant. Chronic cough, defined as cough for more than 3 weeks, is suspect for active disease while cough of recent onset (less than 3 weeks), that could be the result of a congregated way of living resulting in upper airways virus infection and intensive passive smoking, was reported but is not an alarming feature during clinical evaluation. Although confusing, the integration of cough in the present setting would be helpful and act as gate keeper feature to diagnose recently activated TB from LTBI as shown by this study.

8. Finally but importantly, and in order to propose a score which may be less "site and time specific" it would be interesting to look at incidence of TB in the countries of origin of the 393 subjects screened and
determine if this specific item, associated or not with the other items identified in the multivariate analysis (age, married status, ground transition, cough, previous TB exposure) gives an interesting result. This would open the possibility of a wider testing of such a score.

- We thank the reviewer for his interesting proposition for upgrading the screening coverage of the proposed score. The number of the screened subjects being limited to 393 a more detailed stratification by country was not feasible since the sample is insufficient. Nevertheless the sample is representative of the flux of AS origins for the studied period (2009-2010) and could be updated according to future immigration evolutions.