Author's response to reviews

Title: Risk of Latent TB infection in individuals employed in the health care sector in Germany: a multi center prevalence study

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Version: 2 Date: 24 February 2010

Author's response to reviews: see over
Rebuttal letter

Dear editor,

We are thankful for the thoughtful comments of the reviewers and made chances accordingly as you can see by our step by step answers to the suggestions of the reviewers. Also, a native English speaker of an professional copyediting service had now copyedit the paper.

Best regards

Anja Schablon

Reviewer's report

Title: Risk of Latent TB infection in individuals employed in the health care sector in Germany: a multi center prevalence study

Version: 1  Date: 26 November 2009

Reviewer: Delia Goletti

Reviewer's report:

The authors evaluate the prevalence and putative risk factors of LTBI in the health care sector in the German hospitals. The found a positive IGRA in 9.9% of the health care workers (HCWs) and that the putative risk factors for LTBI were age, being foreign-born, TB in the individual’s own history and previous positive TST results. No statistically significant association with gender, BCG vaccination, workplace or profession was found. The information provided are important. However it would be important to have the manuscript being reviewed by an English mother tongue person. Moreover other issues to consider are:

MAJOR:
1) PAGE 2: Conclusions are not correct. In this HCW population, migration (OR:1.99) is not an important risk factor for LTBI and therefore should be removed from the conclusions.

Answer to the editor: We don’t agree with the Reviewer, because we think an OR of nearly two is a risk factor. But we deleted it from the conclusion in the abstract.

2) Page 3: please provide in the text the numbers of TB incidence in Germany

Answer to the editor: We made the changes accordingly and now we provide the numbers of TB incidence in Germany in the introduction.

3) Include an additional reference that describe HCW in Italy [Girardi et al,
Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among healthcare workers. Euro Surveill. 2009 Oct 29;14(43)] and comment on it in the discussion

**Answer to the editor:** We now add the additional reference and comment on it in the discussion.

4) Page 5: specify that “the test was considered positive if IFN-g in the tube containing the M. tuberculosis antigen was…”

**Answer to the editor:** We made the changes accordingly and specified this part.

5) Page 6: last 2 sentences must go in the result section, at the beginning. Moreover, please add a figure 1 with a flow chart of the study population.

**Answer to the editor:** We made the changes accordingly and add a figure with a added flow chart of the study population in the text.

6) Page 13: third row. Rewrite :"In a recent review”.

**Answer to the editor:** We made the changes accordingly.

MINOR

1) Page 2: spelling of OSH

**Answer to the editor:** We made the changes accordingly.

2) Once provided the abbreviation IGRA, use it when needed, i.e. at page 3

**Answer to the editor:** We made the changes accordingly.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.

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**Reviewer’s report**

**Title:** Risk of Latent TB infection in individuals employed in the health care sector in Germany: a multi center prevalence study

**Version:** 1  **Date:** 11 December 2009

**Reviewer:** Alice Zwerling

**Reviewer’s report:**
The use of IGRAs in HCWs is an active area of research. While some countries
have indicated these blood based tests can be used to replace the TST in screening and serial testing HCWs for LTBI, other nations have been more cautious, and continue to use the TST or use the two tests in a sequential manner. A major strength of this study is the sheer size, at over 2000 HCWs, it would be the largest study using IGRAs in HCWS in a low incidence setting. However, authors chose not to repeat the TST, at the time of QFT testing. As such, it is difficult to compare the TST and QFT results. Secindly, as the authors mention, the cross-sectional design limits the authors ability to speak to serial testing, and the conclusions that can be made from such an analysis. None the less, this study will be a useful addition to this field of research, and I commend the authors for achieving such a large study sample.

Major Compulsory Revisions
There are a number of findings that are not consistent with similar studies conducted in low incidence settings, and without TST results to in a sense validate these results to a gold standard (of a sort), I think it might be helpful for the reader if the authors elaborated further on these findings in particular. Ex: High rates in administrative staff? no occupational risk factors were significant? Higher rates in individuals from Western Europe than former Spviet Union? Has this been seen in German HCW studies before? Possible explanations?

**Answer to the editor:**
We adjusted the data but we found no explanation for the high rate of positive QFT-IT results in the subgroup of the administration staff. We examined potential risk factors, e.g. age, migration, reason for testing (contact investigation), but no association for these putative risk factors was evaluated. We described these results in the discussion.

We found no significant occupational risk factors as other studies did. But, on the other hand, other research also described no association. This is displayed in the discussion. Higher rates in individuals from Western Europe than former Soviet Union were not described in other German HCW studies before, because they don`t split up subgroups of foreign born participants. Indeed we observed higher rates of participants in Western Europe 26.7% (8/30) than from the former Soviet Union/Eastern Europe 15.9% (40/251), but in total the subgroup from Western Europe is smaller than the subgroup from the former Soviet Union/Eastern Europe and the differences are not statistically significant.

This might explain the higher rates, we add the total numbers in the result section.

-How many HCWs were approached, what percentage consented?

**Answer to the editor:** The study population is now displayed in a flow chart. The study population was acquired by occupational physicians following the German occupational safety and health legislation (OSH). We don`t have any information how many employees don`t wanted to participate in the study. Therefore we can not give an exact response rate. However the screening is obligatory by German law. Therefore the participants rate is assumed to be close to 100%.

p12. end of 2st paragraph: Last two sentences are difficult to understand, are the results contradictory or do they not indictae an increased risk for physicians.
Answer to the editor: We made changes and now the results do not indicate an increased infection risk for physicians.

Minor Essential Revisions
- Intro 2nd paragraph, paragraph should not begin with "But"

Answer to the editor: We made the changes accordingly.

-p4. "those assumed for German HCWs so far" perhaps authors could include examples so that readers understand what is the expected rate in Germany

Answer to the editor: Now we included the expected rate in the text.

-Discussion, 2nd paragraph should read >5mm, not <5mm

Answer to the editor: We made the changes accordingly.

-Table 1, space between BCG and vaccination

Answer to the editor: We made the changes accordingly.

-Tables could be tightened up a bit

Answer to the editor: We made the changes accordingly and tightened up table 1.

Discretionary Revisions
I think it is unfortunate that serial testing of a subset of HCWs was not done over the 4 year span of the study. While there are now over 20 cross sectional HCW studies using IGRAs in low incidence countries, serial testing data is remarkably scarce. This data would also allow the authors to consider yearly risk of infection, and compare that among different occupations/occupational risk groups. Perhaps this could still be done?

Answer to the editor: Serial testing was not the aim of this study. At the moment we are working on another study which covers the serial testing.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I received a travel award from Cellestis to present at the 2nd Global Symposium on IGRAs in June 2009.

Reviewer's report
Title: Risk of Latent TB infection in individuals employed in the health care sector in Germany: a multi center prevalence study
Version: 1 Date: 4 December 2009
Reviewer: Young Ae Kang
Reviewer's report:
Major comments
1) The major issue addressed (latent TB infection in healthcare worker) is important one, but similar data on this issue have recently been reported from many settings.

Answer to the editor: Yes, but to our knowledge our study is the largest study among HCW in low incidence countries especially for German HCW. Therefore our data are important.

2) Introduction: What's the current guideline for screening latent TB or active TB for healthcare worker in Germany? The description of shortcomings of current guideline will be needed to explain the objective of current study.

Answer to the editor: We made the changes accordingly and described the current guideline for HCW screening in Germany in the introduction section. But the object of the current study was not to verify current guidelines but to analyse LTBI prevalence in the exposed HCW in Germany. Verified the guidelines would have warranted on other study designs.

3) Methods: The flow chart to explain the participants status for enrollment, results of IGRA and TST will be helpful for understanding.

Answer to the editor: Now a flow chart explain the participants status for enrollment and TST, IGRA results and BCG vaccination status. We are grateful for the comment because we think the flow chart substantially added to the understanding of the data.

4) Methods: For TST, the methods of TST and positive criterion will be needed.

Answer to the editor: We made the changes accordingly and described the methods of the TST and the criterion of positive TST according to the German guidelines in the methods section.

5) Methods: In my opinion, the participants who had previous TB history are excluded to estimate the prevalence of latent TB infection. The positive results of TST or IGRA could be affected by the previous TB history.

Answer to the editor: Thank you for your comment. But we decided that we did not exclude these participants with previous TB history, because the small group of participants with TB history of only 1.2% did not affect the prevalence of LTBI in this study population. But it is interesting to see that 58% of those with a positive TB history were actually negative in QFT and therefore should not be excluded from QFT screening.

6) Results: The additional table for explaining the major result (positive results TST and IGRA) will be helpful for understanding the results.

Answer to the editor: We add a flow chart which explain the positive TST and IGRA results.
7) Results: page 8, as mentioned above, I’m not sure whether the previous TB history could be considered the risk factor of latent TB infection.

**Answer to the editor:** As mentioned above we did not exclude these participants with previous TB history. Yes, we agree that a previous TB history could not be considered as a risk factor of LTBI, but it is a risk factor for a positive IGRA result. A positive result of the diagnostic tests is primarily a measure of an immunological response to stimulation by mycobacterial antigens that should not therefore be equated with the presence of live M. tuberculosis in the human host. Also it is uncertain how long adaptive immune responses towards mycobacterial antigens persist in the absence of live mycobacteria. We now stated this in the discussion section and we made changes (instead of LTBI, positive IGRA) in the results section.

8) Results: In 1497 participants who underwent both TST and IGRA, the analysis of discordant results and the comparison of risk factor for positive results for both tests would be informative to understand the differences and similarities of the two tests.

**Answer to the editor:** We add the flow chart with the discordant results of both test depending on which Test was used and the BCG vaccination status. In our opinion these information explain the differences and similarities of the two tests in this study population.

9) Discussion: page 10 first paragraph, what’s the previous prevalence of latent TB infection through the TST in Germany? What’s the cause of the discrepancy of prevalence of LTBI compared to previous study? Is there any relation of BCG vaccination strategy in Germany?

**Answer to the editor:** We now described the previous prevalence of LBTI with the TST. The reason of the discrepancy compared to previous studies is the use of the more specific IGRA. So most of the previous TST were affected by BCG vaccination in German HCW. The BGC-vaccination strategy didn’t change in the time period. See comment 2 from Reviewer Goletti.

Minor comments
1) Methods: The description for the participants who included previous study (Nienhaus et al, Schaboln et al) will be needed in methods section

**Answer to the editor:** We made the changes accordingly and described the number of participants who are included in previous studies in the methods section.

2) Results: page 7, second paragraph, 54.2% and 68.7% in head of sentence could be replaced by the characters.

**Answer to the editor:** We made the changes accordingly.

3) Discussion: page 11, second paragraph, the expression of age seems to have an error: under 25: < 25.

**Answer to the editor:** We made the changes accordingly.
4) Table 1 and 2: age: seems to have an error: under 25, < 25

**Answer to the editor:** We made the changes accordingly.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests'