Author's response to reviews

Title: Risk factors for latent tuberculosis infection in close contacts of active tuberculosis patients in South Korea: a prospective cohort study

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Version: 3
Date: 12 March 2014

Author's response to reviews: see over
Reviewer 1

Reviewer's report

In this paper, Lee and colleagues aimed to assess the prevalence and the predominant risk factors of contracting LTBI in close contacts of active pulmonary TB patients who visited the Gyeongsang National University Hospital, Jinju, in South Korea. Moreover, the study aimed to compare the efficiency of TST and QFT-G for LTBI surveillance. Prevalence of LTBI resulted high and Authors’ conclusions suggest that prior TB history and being a household contact were the predominant risk factors in the target population.

Major Compulsory Revisions

Some items addressed in the article need to be improved and some others have to be further clarified.

Comments) The first is to provide a clear definition of the inclusion/exclusion criteria for study entry. For example, those with a history of pulmonary TB were included in the study population: please, provide the reason for this choice. Moreover, give further information concerning both the duration of exposure (4 hours per week) and the method used for its measurement.

Responses) The impact of previous history of pulmonary TB on the latent tuberculosis infection (LTBI) had not been well studied. In South Korea, where the incidence of TB is intermediate, considerable number of people has a previous history of pulmonary TB (approximately 7 % of study population in this study). We aimed to assess the association between previous history of pulmonary TB and LTBI in close contact of active pulmonary TB patients. We discussed the reason in the text manuscript.

The definition of close contact is not clear-cut as far as we know. Household contact is considered to be a definitely close contact. Occasionally, a contact at work is close enough to be equivalent to a household contact (Thorax 2000;55:887–901). In a report of Centers for Disease Control and Prevention (CDC), it is written that for any specific setting, index patient, and contacts, the optimal cut-off duration is undetermined. Administratively determined
Durations derived from local experience are recommended, with frequent reassessments on the basis of results (MMWR, December 16, 2005 / Vol. 54 / No. RR-15). Actually, definition of close contact was decided by principal investigators of multi-center study. Household contact and contact over 4 hours per week was defined as close contact in this multi-center study. We measured the duration of exposure by self-reported questionnaire and added this content in the method of manuscript.

Comments) The second refers to the flow-chart for the screening and diagnosis of LTBI: more details need to be given concerning the Korean guidelines comparing them with other international guidelines. Moreover, no specific criteria were used for the screening of LTBI throughout the study population (someone was tested by TST, someone was evaluated using IGRA and some others underwent both the methods….).

Responses) TST and IGRA are complementary tests. Centers for Disease Control and Prevention (CDC) recommended that TST and IGRA should be used as aids in diagnosing infection with M. tuberculosis. CDC recommended that IGRA may be used in place of (but not in addition to) a TST. Meanwhile, National Institute for Health and Clinical Excellence (NHS) recommended that both tests should be offered and that depending on operational issues, the most appropriate should be used. In Korean guidelines, both single screening strategy using TST or IGRA and dual screening strategy using TST and subsequent IGRA were recommended. Therefore, we gave an option of choosing between TST and/or QFT-G to participants according to the Korean guidelines. We think that this is a limitation of the current study. We discussed more details regarding Korean guidelines in the discussion of text manuscript.

Comments) The third is to clarify why and how the data presented in this study were acquired from another multi-center research; were the objectives investigated in the present study foreseen in the original protocol approved by the local IRB?

Moreover, the study needs to be carefully reviewed through all the manuscript with respect to the proper use and choice of some references.

Responses) All participants in this study were close contacts who visited our institution as a
part of international multi-center study. IRB of our institution approved this study. We reviewed and changed some references as your recommendation.

**Minor Compulsory Revisions**

**ABSTRACT:**
Page 2 lines 38, there is an error in the calculation of the percentages, please verify it. The total of TST positive is incorrect, please correct in this way “Of 308 subjects, 38.0% (116/305) were TST positive”.

Responses) The error was corrected. Thank you for your comment.

**BACKGROUND:**
Page 3 lines 52-53: reference [1], please cite an update article in the reference and use more recent data in the sentence, according to Global Tuberculosis Report 2012. WHO.

Responses) Updated article (Global tuberculosis report 2013, WHO) was cited and the data was changed.

Page 3 lines 62 – 64: references [3,4], please provide other recent International references to support the correct statement in the text.


Page 3 lines 65 – 68: the sentence is not clear. Please rephrase it.

Responses) We rephrased that sentence.

**METHODS:**
Page 4 lines 80 – 81: please cite an appropriate reference to support the content of the text.
Responses) The multi-center study is still ongoing. We cannot cite the reference because the results were not published yet.

Page 4 line 87: please verify the period of exposure (4 hours per week) to AFB smear-positive and/or culture positive active pulmonary TB patient, according to international guidelines.
Responses) Please check our responses to your 1st comment.

Page 4 lines 91 – 92: please use the term “potential risk factors”.
Responses) The sentence was changed as your recommendation.

Page 5 line 101: please verify the dosage of intradermal injection.
Responses) 2 units in 0.1ml was used. The error was corrected.

Page 5 lines 102-103: please, give more details why you used 5 mm and not 10 mm as the induration cut off for positive TST cases.
Responses) The cut-off value for positive TST was 5mm because the cut-off value of multi-center study was 5mm. The multi-center study was designed in Canada where the cut-off value for TST is 5mm.

Page 5 lines 112-113: please use the term “potential risk factors”.
Responses) The sentence was changed as your recommendation.

RESULTS:
Page 6 line 124: please give more details about definition of “close contacts”.
Responses) Close contact was defined as exposure to AFB smear-positive and/or culture-positive active pulmonary TB patient during their infectious period for at least 4 hours per week. As previously discussed, the definition of close contact is unclear except for household contact and 4 hours per week was a definition used in the multi-center study.

Page 6 line 127: the results are different from those reported in the abstract. Please verify it.
Responses) Error in the abstract was revised.
Page 7 lines 150-159: Please rephrase this paragraph with less details; the numbers have been already outlined in Table 3.
Responses) We eliminated detailed numbers in the manuscript.

Page 7 lines 161-166: Please explain in more details the flow-chart used for the screening and diagnosis of LTBI.
Responses) We presented number of participants in total and who performed TST and QFT respectively. Close contacts who visited our institution were screened for LTBI. Screening of close contact is national policy project in South Korea. Close contacts are recommended to visit hospital for screening of LTBI. Method of diagnosing LTBI was presented in the method of manuscript.

Page 7 line 164: In this study, 11 subjects resulted QFT-G positive and TST negative. Please, give a possible explanation for this result in the discussion.
Responses) We think that result of QFT-G testing might be false positive. To clarify this issue, we need baseline QFT result before close contact and follow-up QFT test. But, it is not available at present.

DISCUSSION:
Page 7-8 lines 170-172: the patients with a history of TB had to be excluded from the study. Lack of a basal TST and/or QFT-G has to be considered in subjects with household contact.
Responses) As discussed earlier, the impact of previous history of pulmonary TB on the latent tuberculosis infection (LTBI) had not been well studied. We wanted to assess the association between previous history of pulmonary TB and LTBI in close contact of active pulmonary TB patients. We totally agree with you regarding lack of a basal TST and/or QFT-G.

Page 8 line 179: Please verify the percentage reported in the sentence.
Responses) We are sorry for our mistake. 36% is correct. Error was corrected.

Page 8 lines 180-182: Please check reference [11], maybe it is not appropriated.
Responses) That reference is meta-analysis regarding tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis. Positive rate of TST for LTBI diagnosis was presented in Table 2. We changed percentage.

Page 8 lines 183-187: this sentence refers to a study with a very small number of subjects. Please change reference [14] with a more appropriate.
Responses) We changed reference to the multi-center study performed in South Korea in health care workers. The percentage of positive rate of both tests is similar to the previous one.

Page 8 lines 192-197: please rephrase this paragraph.
Responses) We rephrased that paragraph.

Page 9 lines 198-205: the gender differences in subjects with LTBI were not relevant in this study. Please rephrase this paragraph with less details on this issue.
Responses) We revised that paragraph according to your recommendation.

Page 9 lines 209-210: please, comment this sentence in more details: IGRA is a gold standard test in the diagnosis of TB infection in individuals with TB history.
Responses) We added comment regarding importance of IGRA in the manuscript.

Page 9 lines 212-215: reference [21] is not appropriate, please change it.
Responses) We changed it.
We truly appreciate for your exact and excellent comments.

Reviewer 2
1. Comment: These culture positive pulmonary TB patients are L-J culture positive or MEGIT 960 culture positive? How many are smear positive?
Responses)

2. 每周4小时为密切接触，有依据吗？
Responses) Unfortunately, we cannot understand this sentence.
I guess that you are asking the duration of exposure (4hr per week).

The definition of close contact is not clear-cut as far as we know. Household contact is considered to be a definitely close contact. Occasionally, a contact at work is close enough to be equivalent to a household contact (*Thorax* 2000;55:887–901). In a report of Centers for Disease Control and Prevention (CDC), it is written that for any specific setting, index patient, and contacts, the optimal cut-off duration is undetermined. Administratively determined durations derived from local experience are recommended, with frequent reassessments on the basis of results (MMWR, December 16, 2005 / Vol. 54 / No. RR-15). Actually, definition of close contact was decided by principal investigators of multi-center study. Household contact and contact over 4 hours per week was defined as close contact in this multi-center study.

3. only X-ray?
Responses) Chest X-ray was performed in all subjects to identify active pulmonary TB. If active pulmonary TB is clinically suspected, additional tests including sputum AFB stain, culture, TB-PCR etc. were performed.

4. to avoid TST boost effect, TST should be done second?
Responses) We totally agree with you. That is a limitation of this study.

**Reviewer 3**

**Reviewer's report:**

This work was done to investigate the risk factors of contracting latent TB infection in contacts of active TB patients. The authors claimed they prospectively collected the contacts of active TB patients and did the TST and/or QFT-G to detect latent TB infection. The quality of data is not compatible with a prospective study. As mentioned by the authors, there are limitations of the study so that the data are not sound enough to make more contribution to the field.

Specific comments are listed as follows:

Discretionary Revisions
1. In the method section of this manuscript, the authors did not mention how to collect the subjects who had contact with active TB patients. It is better to define the target subjects who would be investigated. Therefore, the completeness of collection of the target subjects can be assessed. There are also some points can be done better in a prospective study: 1) only part of the investigated subjects received both tests; 2) both tests were not done according to a standard protocol to exclude test interaction, though reason not interfering the result proposed.

Responses) Close contacts who visited our institution were screened for LTBI. Screening of close contact is national policy project in South Korea. Close contacts are recommended to visit hospital for screening of LTBI. We presented more details regarding subjects collection.

1) In Korean guidelines, both single screening strategy using TST or IGRA and dual screening strategy using TST and subsequent IGRA were recommended. Therefore, we gave an option of choosing between TST and/or QFT-G to participants according to the Korean guidelines. We think that this is a limitation of the current study. We discussed more details regarding Korean guidelines in the discussion of text manuscript.

2) This issue is also a limitation of this study.

2. In a previous large-scale study (JAMA. 2001 Oct 10;286(14):1740-7), the multivariate analysis revealed that the odds of having a positive TST result but negative IFN-gamma assay result were 7 times higher for BCG-vaccinated persons compared with unvaccinated persons. The report concluded the IFN-gamma assay was less affected by BCG vaccination compared to TST. However, in your multivariate analysis BCG vaccination did not seem to predict a positive TST. The reason as mentioned in your discussion is that most close contacts (94%) of TB infection patients were BCG-vaccinated so the test power is weak. Other risk factors of interest analyzed in the study such as sputum smear status of source case and cough of source case were not shown to predict a test result (TST and IFN-gamma assay). Again, the weak statistical power of the study is supposed to be responsible.
Responses) We agree with that this study has several limitations. Even if those limitations exist, this study showed that a prevalence of LTBI among close contacts of active pulmonary TB patients was high, and prior TB history and being a household contact were risk factors of LTBI.

Thank you for your exact comments.