Author’s response to reviews

Title: Factors associated with the low cure rate of tuberculosis in the remote poor areas of ShaanXi Province, China :a case control study

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Version: 2 Date: 25 November 2009

Author’s response to reviews: see over
Dear Miss Colette Homan,

Thank you very much for your email of Nov. 6, 2009, with regard to my manuscript (Ms. Ref. No.: 1857418540305996) together with the comments from the reviewers. We were pleased by the positive evaluation that our manuscript received from the editor and the reviewers. We carefully read their comments and suggestions and have now completed a revision of the manuscript that addresses their concerns.

As you will see in the revised manuscript, the background section of abstract now includes additional context information. We have revised parts in the original manuscript according to the reviewers’ comments. We also responded point by point to each reviewer comment as listed below, along with a clear indication of the location of the revision. Revisions have been made throughout the manuscript by colleagues with good English languages skills to ensure correct grammar and improve the text.

We thank the reviewers for their constructive suggestions that have improved both the quality and the clarity of the manuscript and we hope that the revised manuscript is acceptable for publication.

Thank you very much for your continued attention.

Yours Sincerely,

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We acknowledge both reviewers’ comments and suggestions very much, which were valuable in improving the quality of our manuscript. Please find below our point-to-point response to the reviewers’ comments:

Replies to Reviewer Dr. M A Hamid Salim:

Comment:
Study period: Not clear. It seems from the text that the 30 counties selected based on the treatment outcome (<85%) of 2005 and patients included those who registered from 1st June 2006 to 31st March 2007. However, under the sampling it was stated that to increase the number of non cured patients all non cured patients from the period of 1st June 2006 to 31st March 2007 were additionally added. What is additionally added to whom? and what is the registration period of those cases? Need to clarify more clearly.
Reply: According to the original design of study, patients were randomly selected from 30 counties with cure rates below 85% in 2005. But during the study period, we observed an increased cure rate in the study population compared to 2005. To increase the power to detect risk factors for non-cure, we decided to additionally include all uncured patients from the same study period that were not in the original sample already. We have clarified this in the sampling paragraph within the methods section.

Comment (continued):
Methods: It is not clear how patients (639) interview were conducted. Did all patients attended in the CDC? If yes, what was the mechanism used to invite all these cases in the CDC for interview. It is neither clear whether home visit done to interview those cases. Another important concern: except death there are some other reasons like: migration, refusal for interview etc may also contribute to the number missing for the interview-need more clarification.
Reply: All of patients were interviewed at their homes after making an appointment. We included information on non-participation in the first paragraph of the results section.

Comment (continued):
Analysis of data: Several definitions used in the manuscript does not comply with the internationally accepted definitions. Results explain that 37 patients had completed treatment but did not submit end sputum; these patients were considered among the non cured group. As per WHO guidelines outcome of these cases are considered as part of treatment success along with cured cases.More over data shows 12.8% of those 133 defaulted and 48.9% refused treatment-it is not clear how differentiation is made from default and refusals. As per WHO definition both are defaulters.
Reply: Our case definitions are according to the WHO guidelines. Unsuccessful treatment includes patients uncured and those who completed
treatment but did not submit a sputum sample after treatment. According to the definition, they are not cured. Of course, some of them probably would have a negative sputum smear but we do not know which ones. We collected the information of treatment of TB patients through medical records and questionnaires. According to the WHO definitions, indeed default and refusal as we defined it fall within the default category. We combined these categories now, while still also making the distinction.

Comment (continued):
Other observations:
Almost half of the cases experienced side effects due to TB treatment but it is not clear what kind of regimen used and for how long?
Reply: According to Operational Guidelines for National Tuberculosis Control Programmes (OGNTCP), China (2006 version), which refers to WHO guidelines, all of new smear positive tuberculosis patients received standard treatment (2H3R3Z3E3/4H3R3) for six months.
As the reviewer suggested, we added this information in the first paragraph of the methods section of the manuscript.

Comment (continued):
Among the variables considered for non-cure in this study some other important variables like: accessibility to health centers in terms of distance and communication system plays very important roles; these are not considered in this analysis.
Reply: In fact, we investigated the accessibility to health centers in terms of distance and transport system, but unfortunately neglected to write it in paper. Distance to the health center was associated with non-cure in univariate analysis and was added to Table 1. Transport used to reach the health center was not associated and therefore not included in Table 1. We checked that not more variables had accidentally fallen out of Tables 1 and 2.

Comment (continued):
Overall text need to be more readers friendly.
Reply: Colleagues with good English skills have gone over the manuscript to ensure correct grammar and easiness of reading.

Replies to Reviewer Dr. Peng Wu
Comment:
1. Major compulsory revisions
   (1) Many previous studies mentioned alcohol is also a risk factor affecting the outcome of tuberculosis treatment. Drinking should be popular in northern China where the study was carried out. Have the authors ever considered it in the study? And why was it not included in the study? In addition to that, would
the clinical type of tuberculosis and/or the degree of relief in disease symptoms affect the outcome of treatment?

Reply: Because most of patients in our study were from poor and remote counties and according to our observation alcohol abuse were rare in these populations, we did not include alcohol dose measurement in our study. As all of patients in our study were diagnosed as new smear positive pulmonary tuberculosis, we expect that the clinical type of tuberculosis has little impact on the outcome of treatment in our study. It is possible that the degree of relief in disease symptoms affects the outcome of treatment. Our results indeed showed that the relief in disease symptoms was one of reasons on interruption of treatment.

Comment (continued):
(2) The authors mentioned in the “Methods (Sampling)”, “To increase the number if non-cured patients, we additionally included all uncured patients registered from June 1, 2006 to March 31, 2007”. Would they like to explain the reason to do this instead of choosing the exactly same time period for recruiting cases and controls? Would this extra recruitment of non-cured patients affect the whole study design and results?

Reply: The sampling period was the same for the original sample and those non-cured patients added later. We have clarified this in the sampling paragraph within the methods section. According to the original design of study, patients were randomly selected from 30 counties with cure rates below 85% in 2005. But during the study period, we observed an increased cure rate in the study population compared to 2005. To increase the power to detect risk factors for non-cure, we decided to additionally include all uncured patients from the same study period that were not in the original sample already.

Comment (continued):
(3) The authors suggested “to make it possible for family members performing supervision in remote areas where logistically it is difficult to have village doctors perform treatment supervision” in the conclusions, I believe, which was resulted from numbers in Table 4. However, it’s not appropriate to say “no difference in cure rates were observed for patients with village doctors or family member as a supervisor” based on the numbers in Table 4. Please reconsider the interpretation of the results.

Reply: Indeed, we drew the conclusion from Table 4. The non-cure rate was significantly better for those with a doctor as treatment observer than for those without treatment observer. The non-cure rate was borderline significantly better for those with a family member as treatment observer than for those without treatment observer (p=0.07). There was no significant difference between non-cure for those with a doctor or family member as treatment observer, as the confidence intervals overlap. We have adjusted the text to clarify and soften the conclusion.
Comment (continued):
2. Minor essential revisions

(1) There seems to be some mistakes or incorrect alignment of in Table 1, 2 and especially 4, particularly the columns for P values. Please check them up and try to make the tables readable and understandable.

Reply: As the reviewer suggested, we modified the contents in Table 1, 2 and 4 of the manuscript.

Comment (continued):
(2) For table 3, why did the authors only choose to test the relationship between co-morbidity and age and between side effects and age? And why the cut-off point for age grouping is different here from those in the table 1? Are there any special reasons for age group categorization?

Reply: Among all of the independent risk factors for the cure rate, interrupted treatment (OR=8.7) and co-morbidity (OR=5.8) played most important roles. As older age often is a confounding factor in studies on risk factors for disease, we want to know how these factors interacted in treatment of tuberculosis. To clarify and simplify analysis, we dichotomised age.