Author's response to reviews

Title: Epidemiology of Anti-tuberculosis Drug Resistance in a Chinese Population: Current Situation and Challenges Ahead

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Author's response to reviews: see over
Dear editors and reviewers,

We thank the reviewers for their thorough review and constructive comments regarding our manuscript titled “Epidemiology of Anti-tuberculosis Drug Resistance in a Chinese Population: Current Situation and Challenges Ahead”. We are appreciative that the reviewers found the study to be of potential interest and have carefully revised our manuscript according to the reviewers’ comments and suggestions. The following are the point-by-point responses to the reviewers’ questions:

Reviewer: DIMITRIOS Papaventsis

In their revised manuscript entitled "Epidemiology of Anti-tuberculosis Drug Resistance in a Chinese Population: Current Situation and Challenges Ahead", Shao et al. investigated the epidemiology of first-line anti-TB drugs resistance among sputum smear positive pulmonary TB patients from the Jiangsu Province, China. I found authors' responses to my previous comments satisfactory and I would like to congratulate them for their effort. I propose that this study should be accepted for publication after a discretionary revision regarding the role of migration in the transmission of MDR-TB. In my opinion, a short comment similar to the one included in the authors' response letter (3.g.), should be added.

Answer:

Thanks a lot for your suggestions. We added a short comment on the role of migration in the transmission of MDR-TB.

Reviewer: PENG WU

The authors have revised the manuscript based on the comments. However some important issues have to be solved before the manuscript is qualified to publish.

Major Compulsory Revisions

1. In the last reviewer’s report, it was mentioned that the interpretation of odds ratios (ORs) was problematic. Unfortunately I found that the problem remains in the current version. For example, Page 11, the authors wrote “We found that patients with previous treatment history had more than 6-fold increased risk of MDR-TB (adjusted OR: 6.14, 95% CI: 4.61-8.17)”. Apparently this sentence implies that the OR was incorrectly interpreted. There are two common ways to interpret ORs. In this case, the authors could say “The patients with previous treatment history had a more than
5-fold increased risk of MDR-TB (adjusted OR: 6.14, 95% CI: 4.61-8.17), compared with those previously not having been treated.”, or the result can also be interpreted as “The risk of MDR-TB for patients with previous treatment history is more than 6-times of that for those without a previous treatment history.” There are a few similar mistakes observed in Results and Abstract in the manuscript.

Answer:
Thanks a lot for pointing out the problematic interpretations of the ORs. We have corrected these mistakes occurring in the parts of both Abstract and Results.

Minor Essential Revisions
2. It is a bit difficult to understand the reason why the authors applied geographic presentation to indicate the difference in MDR-TB prevalence in different places. Although Figure 3 is geographically clear, the varied risks of MDR-TB represented by values in the figure with three colors seemed rather confusing.

Answer:
The reviewer Isabelle Devaux suggested us to add a small geographic resolution to map the estimated rate of cases.

3. The meaning of P values showed in Figure 4 was not defined although three P values have been presented in the figure. What do these P values mean?

Answer:
Figure 4 illustrated the percentage of MDR-TB by age group. Distribution of MDR-TB among different age groups was evaluated by the Chi-square test. We added a statement on the P value in the legend of Figure 4.

4. A number of problematic sentences with grammar errors remain (e.g. Page 13, Line 4-5) and a number of typos (e.g. Page 13, Line 9, “system review”) throughout the manuscript should also be corrected.

Answer:
These errors have been corrected. We also asked a language expert to edit this manuscript.

Reviewer: Isabelle devaux
The authors have carefully included the comments from the reviewers. Some minor
clarifications are still needed:

P6 Thirty counties (districts) from Jiangsu province were systematically selected and the sample size of study subjects was estimated based on the following parameters: (1) The annual reported new sputum smear positive (SS+) cases were 23603 and previously treated SS+ cases were 5524 (based on unpublished surveillance data in Jiangsu province); (2) The precision was set at 2% for new cases and 4% for previously treated cases; (3) The initial monodrug resistance rate was set at 6% among new cases and 16% among previously treated cases based on the proportion of rifampicin resistant isolates from the previous pilot study. Additionally, the sample size was amplified by taking into account the design effect of the cluster sampling method and potential no-response of study subjects. If (1) is based on surveillance data from Jiangsu Provincial Center for Disease Prevention and Control, are not these data published by the Chinese CDC? Could it be possible to describe briefly the “pilot study” to which the authors refer in (3)? Could the authors discuss the advantages/inconvenient of cluster sampling compared to random sampling and explain how it can impact the results of the survey?

Answer:
(1) The annual new sputum smear positive cases and previously treated sputum smear positive cases were estimated based on the previous surveillance data in Jiangsu province. These surveillance data were not published annually.
(2) Until now, no study has been conducted to investigate the situation and patterns of drug resistance among TB patients at the provincial level in Jiangsu. The initial drug resistance rate used for calculating the sample size in the present study were estimated based on one pilot study with small sample size (not published).
(3) There are two most useful sampling strategies for the surveillance of drug resistance. 1) 100% sampling of diagnostic centres. This sampling method is most suitable for small countries with relatively small numbers of TB diagnostic units, good infrastructure, and facilities to transport samples from all diagnostic centres to the Central Reference Laboratory. All eligible patients enrolling at each diagnostic centre within the same limited intake period are included. 2) Cluster sampling. Cluster sampling methods are best used in situations in which it is logistically difficult to cover the entire area of the country and where the number of TB diagnostic centres is high. With this design, centres are randomly selected. If the cluster sampling method is adopted, the cluster design effect needs to be taken into account.
version, we discussed the advantages/inconvenient of cluster sampling compared to random sampling and its impact on the results of the survey.

Once again, we thank all the reviewers for their time and effort in reviewing our manuscript and contributing thoughtful suggestions. We hope the new changes satisfactorily address all the pertinent issues raised by the reviewers, thereby improving the content and presentation of the manuscript for publication.

Sincerely,

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