Author’s response to reviews

Title: Change in prevalence and molecular characteristics of isoniazid-resistant tuberculosis over a 10-year period in China

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Author’s response to reviews:

Comments from Reviewer #1

Comment 1: Line 118: Sub-culture should be incubated until 4-6 weeks at 37 C.

Answer: Thanks a lot! We have changed it according to your suggestion. (Page 6, Line 118)

Comment 2: Line 123-131: Drug susceptibility testing was done for first and second line anti-TB drugs. It would be better to mention first and second line drugs. in the manuscript only INH is used for the subsequent analysis and other drugs are not used. this section should revise.

Answer: Thanks a lot for your constructive comments. As you mentioned, several other drugs rather than isoniazid were included in this study. It would be better to mention the primary
results for their drugs, while our manuscript is focused on investigating the dynamic of INH resistance among MTB isolates, and other findings will be summarized in other reports. Hence, according to your suggestion, we have deleted the description on other drugs in method section. (Page 6, Line 124-126)

Comment 3: Line 123-131: It does not clearly mention the resistance or sensitive formula for the used method.

Answer: Thanks for your constructive comments. The previous description was not clear enough. We have supplemented the formula used for the interpretation of resistance or susceptibility in the method section accordingly. (Page 6, Line 124-126 & Line 129-130)

Comment 4: Results: 1. Line 144-146: This statement is not clearly mentioned regarding the level of INH-resistance, Ref 21, it was not mentioned the level of resistance.

Answer: Thanks a lot for your constructive suggestion. The reference previously cited was used to interpret the INH susceptibility of MTB isolates tested. Hence, we have revised the description in this part. In addition, we have supplemented the detailed description on cut-off values for distinguish different resistant levels. (Page 7, Line 143-147)

Comment 5: Line 149: replace "exacted" with "extracted"

Answer: Agreed! We have revised it according to your comments. Thanks a lot. (Page 7, Line 151)

Comment 6: Table 3: replace "PTO" with "PTH".

Answer: Agreed! We have replaced it according to your suggestion. Thanks a lot for your comments. (new Table 3)

Comment 7: Line 183-184: Rephrase the statement..

Answer: Thanks for your constructive comments. (Page 9, Line 185-186)

Comment 8: Line 191: KatG mutation in 2015 would be "58" instead of "57".

Answer: Thanks a lot for your suggestion. We have changed it according to your suggestion. (Page 9, Line 193)
Comment 9: Discussion: in the discussion section, describe PTH and INH correlation treatment management and developing of resistant.

Answer: Thanks for your constructive suggestion. We have supplemented the description how PTH and INH correlate treatment management and development of resistance in the discussion section. (Page 13, Line 269-277)

Comments from Reviewer #2

Comment 1: In this manuscript the authors show the variations of isoniazid behave in two sets of clinical isolates from China. The information is interesting and could be published, however some questions emerging from the review of the document.

Answer: We appreciate the general positive comments from review. Thanks a lot!

Comment 2: In the Bacterial strains section could the authors clarify with more detail how was selected the populations of isolates in both periods of time, how was the collecting and selection process. Considering that in both periods they have almost the same number of isolates from each year. This is important considering that the rest of the comparisons were made considering these isolates.

Answer: Thanks for your constructive comments. The previous description was not clear enough. We have described it in detail in the method section according to your suggestion. (Page 6, Line 112-115)

Comment 3: How was made the storage and further recovery and processing of the strains from 2005.

Answer: Thanks for your constructive suggestion. The previous description was not clear enough. On the basis of your comments, we have supplemented it in the method section. (Page 6, Line 115-116)

Comment 4: Why the results were totally concentrated in the description of isoniazid resistance, why was not included data from other resistances, at least a general description of them could be very informative. This was mentioned as work done in the methods section, but no more data was included. By example, which was the percentage of isolates with MDR, or the characteristics of resistance against second line drugs in the isolates from both periods of times, at least a table summarizing these data is necessary.

Answer: Thanks for your constructive comments. As you mentioned, several other drugs rather than isoniazid were included in this study. It would be better to mention the primary results for their drugs, while our manuscript is focused on investigating the dynamic of INH resistance
among MTB isolates, and other findings will be summarized in other reports. Hence, according to your suggestion, we have deleted the description on other drugs in method section. (Page 6, Line 124-126)

Comment 5: Could the authors mention which is the behave of the isolates bearing inhA mutations in relation to the other resistances, this could important in terms of see the bias of the mutations or the possibility of compensatory mutations.

Answer: Thanks for your constructive comments. Although there is strong evidence on the correlation between these mutations and PTH resistance, the isolates with inhA mutations may be the compensatory mutations due to the absence of experimental data in the present study. According to your suggestion, we have discussed it as a limitation of this study in the revised manuscript. (Page 13, Line 273-277)