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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Comments from Jérôme Robert (Reviewer 3)

Comment 1: First, although we fully understand that the authors would like to save data for further publications, it is not acceptable to remove all important data from the current submission. It is of major importance to have information regarding the rifampicin co-resistance of the INH-R isolates; indeed, the increase of INH resistance in 2015 is likely to be related to the increase in MDR. Hence, the change in molecular characteristics may be linked to the switch from INH resistance without rifampicin resistance towards more MDR. This should be brought to the readers.

Answer: Thanks for your constructive comments. We totally agree that the rifampicin resistance is an important issue for this study. We used the same set of MTB isolates, the in vitro drug susceptibility profiles of which has been described in our previous study. Of these isolates, the
significant increase in prevalence of drug-resistant tuberculosis was noted in rifampicin, isoniazid, and levofloxacin. For MDR, although the proportion in 2015 (31.2%) seemed higher than that in 2005 (24.2%), the statistical difference was not significant (P=0.067). According to your suggestion, we have cited the data in the result section. (Page 8, Line 170-175)

Comment 2: Second, it is difficult to understand how comparisons between groups were done and because the method for paired comparisons is not straightforward. The authors should make it clearer for the readers.

For instance, we do not understand the comparison between 2005 and 2015 in inhA prevalence and prior treatment history.

Answer: Thanks a lot for your constructive suggestion. The previous description regarding statistical analysis was not clear. We used Pearson’s chi-square or Fisher’s exact test rather than paired comparison to assess the proportions of variables between 2005 and 2015. According to your suggestion, we have supplemented it in the method section to make it clear. (Page 8, Line 159-160)

Comment 3: Third, the authors should be more cautious about the so-called trend. Indeed, assessing a trend with only two time points is not reasonable. Second, although there is an increase in INH MIC in 2015, with more isolates with MIC ≥ 16, the MIC distribution is clearly similar and the increase is mainly observed for the MIC level of 32 mg/L which is right on the chosen breakpoint for the definition of high-level resistance.

Answer: Thanks for constructive comments. We agree that the word “trend” is not suitable herein in view of only two time points compared in this study. According to your suggestion, we have revised the “trend” and “from…to…” in the manuscript as you mentioned. In addition, three gradient concentrations were both included in the definitions of low-level (0.5, 1, 2 mg/L) and moderate-level resistance (4, 8, 16 mg/L), and the MTB isolates with MIC values higher than 16 (32 and >32 mg/L) were defined as high-level resistant. Hence, we feel that the current definitions may be suitable to classify the MTB isolates with different drug-resistant levels. (Page 5, Line 102; Page 11, Line 228; Page 13, Line 267)

Comment 4: Finally, the authors elaborate on the link between PTH use and the increase in inhA resistance mechanisms. Although this is plausible, the lack information regarding resistance to rifampicin, MDR resistance, prior history of treatment is frustrating facilitate the adherence to this hypothesis. Moreover, it is likely that a majority of readers do not know standard and pretreatment regimens used in the observed population from China and thus could not understand the frequency of use of PTH in China.

Answer: Thanks a lot for your constructive suggestion. We totally agree that the standard and pretreatment regimens used in the observed population from China is important to conclude our results on the association between PTH use and the increase in inhA resistance mechanisms.
However, a high proportion of TB patients did not receive the standard regimens in China. In other words, the personalized and empirical regimens were widely used regardless of drug resistance pattern in China. As a consequence, the prior exposure history to various drugs are more important for our analysis, which has been compared in our results. In addition, a recent study on the anti-TB drug prescribing for patients in China indicates that there was a significant increasing trend for prothionamide prescribing in China between 2011 and 2015. We feel that it may serve as a supporting evidence for the increasing PTH usage, thus resulting in the potential effect on the inhA resistance mechanism. According to your suggestion, we have supplemented in the discussion part. (Page 13, Line 272-274; new Reference 33)