Reviewer’s report

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

Version: 1 Date: 15 Apr 2019

Reviewer: Jérôme Robert

Reviewer’s report:

The manuscript is a revised version with modifications following the suggestions of two reviewers.

The paper is a second paper on INH resistance in China comparing two periods (2005-2015). In this paper, the authors sought to assess the trend in INH MIC and in molecular characteristics of resistant isolates.

The authors have adequately replied to the reviewers. However, we have additional suggestions regarding the revised manuscript.

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.

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.

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 $\geq$ 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.

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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Acceptable

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