Reviewer’s report

Title: Fluoroquinolone resistance and mutational profile of gyrA in pulmonary MDR tuberculosis patients

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Reviewer: Emily Kendall

Reviewer's report:

The authors have described the fluoroquinolone resistance associated mutations in a large sample of clinical TB isolates. However, without more information about the patient population and the methods by which isolates were selected for testing, it does not appear that their sample is sufficiently representation to address their research question or support their conclusions. I would encourage the authors to explain in more detail their patient population and selection of isolates for testing, and to reconsider their findings in light of any biases introduced in that process. I would also encourage the authors to consider what research questions can be answered with the particular data they have, which relates more to the distribution of particular resistance mutations about FQ-resistant isolates, than to the distribution of drug resistance in the population.

Specific comments:

Background:
If the authors are seeking to determine the "potential utility" of fluoroquinolones, why is this the right population (patients who had been on therapy) and study design (identification of specific gyrA and gyrB mutations? More representative samples from Pakistan have already been surveyed for prevalence of fluoroquinolone resistance (e.g. Zignol et al Lancet Inf Dis 2016). Reconsider how the relevance of fluoroquinolone resistance is explained. The risk of progressing to XDR is not the main reason it is important, particularly as injectable-free TB regimens are increasingly recommended and used.

Methods:
More detail about the patient population is needed to judge its representativeness. How were they selected, and what selection bias may have been introduced? Were the 562 samples from 562 unique patients? How much anti-tb therapy had these patients received? Enough that some had become LPA negative -- in which case this sample would biased toward those who had not responded quickly to treatment? What treatment regimens were they receiving? How were RIF and INH susceptibility determined? How was phenotypic susceptibility to FQs assessed?

Results:
Were there any associations between patient characteristics and resistance (overall, or specific mutations)? Did each FQ resistant isolate have only a single mutation?
What were the RIF and INH susceptibilities of those with no FQ resistance mutation identified?

Discussion:
A number of claims in the first two paragraphs lack appropriate references. Some of the conclusions are not supported by the evidence presented. Details of the population and methods are lacking, but it appears likely that the approach taken selected for patients with FQ-R TB (because they had a history of previous treatment, and had persistent MTBDRsl positivity after some amount of treatment) and does not reflect the overall prevalence of FQ-R among clinical TB. It is also not clear what resistance would have been identified had these patients been tested at the time of initial diagnosis, as the authors recommend doing. (Perhaps less resistance would have been detected, if this is truly emergent resistance or mixed infections, or if other patients with a quicker bacteriologic response to therapy had also been included.)

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.

Unable to assess

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

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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