Author’s response to reviews

Title: Frequency and Patterns of Second-line Resistance Conferring Mutations among MDR-TB isolates resistant to a Second-line drug from eSwatini, Somalia and Uganda (2014-2016)

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Author’s response to reviews:

April 12, 2019
The Editor,
BMC Pulmonary Medicine
Dear Sir/Madam,


We thank you once again for allowing us to revise our manuscript in light of the reviewer’s suggestions, and finding it potentially acceptable for publication in BMC Pulmonary Medicine. We are glad to inform you that we have made all the necessary changes/corrections and our revised manuscript conforms to the journal style. Below, please find our point-by-point response to the reviewer’s concerns, which we have also uploaded as a supplementary file “point-by-point-response”. We look forward to hearing from you soon.

Yours sincerely,

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POINT-BY-POINT RESPONSE TO REVIEWERS COMMENTS

REVIEWER 1

Comment:

One of the main concerns regards the interpretation of mutations as markers for resistance (line 259-260). In particular, authors miss to identify the gyrB mutations Asp500His and Asn538Asp that are in the QRDR as mutations conferring resistance to fluoroquinolones, and that MTB strains with these mutations have MIC for fluoroquinolones that are above the critical concentration (Malik, S., et al. PLoS One 7, e39754 (2012). Technical Report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.5). Licence: CC BY-NC-SA 3.0 IGO.

Response:
We are indebted to you for your pointing out this error. We have now described and discussed the gyrB mutations Asp500His and Asn538Asp detected in this study (please lines 250-262; 304-325), and this has greatly improved the manuscript.

Comment:

Authors should specify the gyrB numbering systems used (ref. to Maruri et al. J Antimicrob Chemother. 2012 Apr; 67(4): 819-831).

Response:

We specified the gyrB numbering system used i.e. the codons “500-538” gyrB numbering system (1998) that most studies have used, lines 200-202.

Comment:

Line 261: The number of LFX/MXF resistant isolates lacking known drug resistance conferring mutations in the QRDR should be modified (N=5, not 6).

Results/discussion/conclusion and Table 1 should be modified accordingly.

Response:

The number of LFX/MXF resistant isolates lacking known drug resistance conferring mutations in the QRDR has been adjusted to 5 (see line 261-262). Results/discussion/conclusion and Tables 1 & S1 have also been modified accordingly.

Comment:

Authors should define "high level resistance" (used in lines 61-62, 64, 262, 272) as opposed to resistance mutations. The gyrA mutations in position 88, 90, 91 and the gyrB mutation Asp500His and Asn538Asp are not associated with a high-level increase in MIC for fluoroquinolones (World Health Organization, Technical Report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.5). Licence: CC BY-NC-SA 3.0 IGO), so it is not clear why authors refer to them as high level resistance mutations.

Response:
Indeed our use of “high level resistance” was inappropriate as we meant “drug resistance mutation”. We have corrected this anomaly throughout the text. We thank you.

Comment:

According to Supplementary Table1, sample TC54005 is susceptible to both OFX and MXF but resistant to LFX. This is a very unlikely situation suggesting that this is possibly a case of false resistance to LFX. Phenotypic DST for LFX should be repeated for this sample.

Response:

Sample TC54005 was indeed susceptible to OFX, MXF and LFX. The error has been corrected (was a typo during our updating of the results table upon repeat DST for second-line anti-TB drugs). We thank you.

Comment:

References should be revised. Line 87: Ref 5. Malik S, et al. PloS one 2012, 7(6):e39754, is not the appropriate reference for the sentence "MDR-TB and XDR-TB are very difficult to treat as the drug regimens are lengthy, toxic, and expensive" [5].


Response:

Appropriate references have been provided, please see Seung et al (doi: 10.1101/cshperspect.a017863) & Manjelievskaiia et al (doi: 10.1093/trstmh/trw006) references 6 and 5, respectively. The above references have been corrected as advised (now references 22, 23, 24, 25, and 26).

Minor comment:

Line 63: Asp94Gly is repeated twice, replace one of them with Asp94Asn.

Response:

The repetition has been removed. Thank you.