Author’s response to reviews

Title: Characterization of extensively drug-resistant Mycobacterium tuberculosis isolates circulating in Siberia

Authors:

Maya A. Dymova (maya.a.rot@gmail.com)
Andrey G. Cherednichenko (bact.nniit@gmail.com)
Olga I. Alkhovik (olgaalkhovik@mail.ru)
Eugeniy A. Khrapov (Khrap_off@ngs.ru)
Tatjana I. Petrenko (tipetrenko@gmail.com)
Maxim L. Filipenko (max@niboch.nsc.ru)

Version: 6 Date: 25 July 2014

Author’s response to reviews: see over
We thank once again all reviewers for a thorough revision of our manuscript. Please find below our response to their comments.

24th June 2014. Review of responses by Harriet Mayanja

Author's response to reviews
Title: Characterization of extensively drug-resistant Mycobacterium tuberculosis isolates circulating in Siberia
Authors: Maya A. Dymova (maya.a.rot@gmail.com), Version: 6, Date: 18 June 2014

Author's response to review: Harriet Mayanja

3. Isolates were randomly selected, with 29 XDR out of 30 MDR samples selected. Authors could say more about this - How was randomization done. With 29 of 30 isolates XDR, is a true reflection of the population isolates.

Response: Corrected. We replaced the sentences: "Thirty MDR (or pre-XDR) M. tuberculosis clinical isolates were randomly selected from a collection of TB isolates at the Novosibirsk Research Institute of Tuberculosis (NRIT), Russia. Each isolate was recovered from individual patients with pulmonary TB who were treated at NRIT from January 2011 to February 2012." to "All MDR+XDR TB MTB which recovered from individual patients with pulmonary TB who were treated at NRIT from January 2011 to February 2012 were included in study." THIS CHANGE WAS NOT EFFECTED IN THE REVISED MANUSCRIPT IN LINES 73-75

Response: We removed the sentences: “Thirty MDR (or pre-XDR) M. tuberculosis clinical isolates were randomly selected from a collection of TB isolates at the Novosibirsk Research Institute of Tuberculosis (NRIT), Russia. All MDR+XDR TB MTB which recovered from individual patients with pulmonary TB who were treated at NRIT from January 2011 to February 2012 were included in study”. To “This was a cross-sectional study, examining the drug susceptibility and molecular-genetic features of XDR isolates in Siberia and Far East of Russia. The Novosibirsk Research Institute of Tuberculosis (NRIT) acts as the national referral center for TB in Far East and Siberia region of Russia. Under the National Tuberculosis Control program, randomly selected patients with the MDR and relapse tuberculosis are referred to the NRIT for evaluation and treatment. 372 MDR isolates (31 XDR) were recovered from January 2011 to February 2012. We analyzed 30 consecutive XDR-TB clinical isolates correspond to 1.6% of all the XDR-TB ones isolated in Far East and Siberia region of Russia. All analysed MTB were recovered from individual patients with pulmonary TB who were treated at NRIT from January 2011 to February 2012 were included in study. Despite small size of tested sample set percentage of XDR among MDR isolates (8%) did not showed statistically significant differences (p-value= 0.76) with total one in supervised region (1858 XDR/24400 MDR during the same period of time)” (Line 72-82).

Reviewer: Duncan Chanda

Major
1. What is the study design? Observational prospective cohort or retrospective cohort study? Was it a clinical study with clinical and laboratory data prospectively collected? The authors should clearly state the kind of study design in order to put the findings in context.

Response: Refer to further minor observations below on the same subject

THIS MAJOR COMMENT HAS NOT BEEN ADDRESSED WITH THE MINOR COMMENTS BELOW AS INDICATED BY THE AUTHORS

Response: This was a cross-sectional study. And it was a clinical study with only laboratory data collected. Some clinical data was available but not included in the work due to the luck of an approval.

Minor essential observations

1. Line 137 to 154 describe clinical events whereas the methodology suggest “samples randomly selected”...earlier on line 79-80 makes reference to consent being obtained. Is this a prospective or retrospective study? From whom was the “consent obtained”?

Response: As we deal with MT isolated from patients so the consents obtained from these patients.

WHAT IS MT? RESPONSE ON CONSENT UNCLEAR

Response: Please, you can find the answer above. And as we deal with M. tuberculosis isolates, extracted from patients so the consents were obtained from these patients.

4. Some sentences need revision or recasting and some are ambiguous or not clear:

4.1. In the Abstract line 20-21: “The purpose of this study was to identify mutations in drug resistance genes and conduct drug susceptibility testing on clinical isolates of M.tuberculosis from TB patients from Siberian”. I suggest the sentence to be recast as “The aim of this study was to conduct drug susceptibility testing and identify mutations in drug resistance genes in clinical isolates of M.tuberculosis from some TB patients presenting for treatment in Siberia”...This is because the aim is to identify MDR/XDR TB and THEN find associated genes.

Response: Corrected. We replaced the sentence: “The purpose of this study was to identify mutations in drug resistance genes and conduct drug susceptibility testing on clinical isolates of M.tuberculosis from TB patients from Siberian” to “The aim of this study was to conduct drug susceptibility testing and identify mutations in drug resistance genes in clinical isolates of M.tuberculosis from some TB patients presenting for treatment in Siberia”. THIS IS NOT SEEN IN REVISED MANUSCRIPT. PLEASE INDICATE LINE WHERE CHANGES WERE MADE

Response: Corrected. Line 19-21. We replaced the sentence: “The purpose of this study was to identify mutations in drug resistance genes and conduct drug susceptibility testing on clinical isolates of M.tuberculosis from TB patients from Siberian” to “The aim of this study was to conduct drug susceptibility testing and identify mutations in drug resistance genes in clinical isolates of M.tuberculosis from some TB patients presenting for treatment in Siberia”.

Also we added affiliation - Novosibirsk State University (NSU), Novosibirsk, Russian Federation (Line 7). Because on the latest requirements we have to indicate all the places of our work. And we pointed out to the center (SB RAS Genomics Core Facility) where we sequenced genes (pncA, rpoB, etc.)

We highlight (green highlighted text) all changes made when revising this version of manuscript to make it easier for the Editors to give a prompt decision on manuscript.

Yours faithfully, Dymova Maya.