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 (olgaialkhovik@mail.ru)
Eugeni A. Khrapov (Khrap_off@ngs.ru)
Tatjana I. Petrenko (tipetrenko@gmail.com)
Maxim L. Filipenko (max@niboch.nsc.ru)

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

1. Reviewer's report №1

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

Version: 4
Date: 6 May 2014
Reviewer: Harriet Mayanja

Reviewer's report:
This paper aims at delineating new molecular techniques for the detection of MDR and XDR by looking for mutations in drug resistant genes that can be used for quicker diagnosis of drug resistance.

It’s a generally well written paper which despite the technical details is understandable in the TB care field, and of potential benefit to future patient care. The message and outcome has potential practical long term potential.

Minor revisions.

1. Lines 77-79 for the international community, the region names are not very informative. I suggest indicating where these regions are in Siberia; are they in any particular area e.g. north, east etc. Are they in high or low TB endemic regions? Are they urban or rural. Are they distributed throughout the region? A map would have been ideal, but to cut down on figures, some description would probably suffice as suggested above.

Response: Corrected. We added the sentences: “This clinical isolates were collected from different regions of West and East Siberia, this regions related to high TB endemic regions. In general, involved in this study TB patients were rural people.”

2. It’s unclear what percentages of samples were from HIV infected participants.

Response: Corrected. We replaced the sentence: “…while two had HIV..” to “…while two participants (6,6% of total) had HIV..”

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.”

4. Line 26 - Abstract, results - 29 isolates XDR. While line 164 in results - 28 isolates were XDR.

Response: Corrected.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: 'I declare that I have no competing interests'
2. **Reviewer's report №2**

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

**Version:** 4

**Date:** 8 January 2014

**Reviewer:** Duncan Chanda

**Reviewer's report:** BMC Review Dymova et al

A potentially good piece of work that adds to understanding of MDR/XDR epidemiology in the region and the comparative use of two molecular epidemiological tools I propose minor essential revisions is line with the following observations:

**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

**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.

2. Sentence from 157 to 161 needs revision. What is the relevance of mentioning the death? This is not an outcomes study. Is this the only death that occurred

**Response:** Corrected. We removed these sentences.

3. Description of TB, I would recommend “tuberculous pneumonia” instead of cheesy pneumonia which is not standard English. (Line 141) This can be confused with caseous granuloma or cheesy granulomatous lesions-found at post mortem. My understanding of “cheesy pneumonia “ in this context is pulmonary tuberculosis. Is this what the authors are trying to portray? Then they should state so or use one of the standard word.

**Response:** Corrected. We replaced “tuberculous pneumonia” to “caseous pneumonia”.

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”.

4.2. Under Introduction line 55 the sentence “The cause of XDR TB isolates...” the term “isolates” should be dropped from the sentence

Response: Corrected.

4.3. Under Sample Description in line 149, there is reference to “Destructive changes in lungs.....were detected radiologically”. Since these changes are radiological the term “lesions” to cover opacities, cavitations etc would be more appropriate than “Destructive changes...” AND line 150 make reference to “Tuberculous decay was not detected in one patient...” What does the term “Tuberculous decay ..” mean in this context.

Response: Corrected. We replaced “Destructive changes...” to “Lesions”.

In line 152, there is reference to “Bacterial excretion...” being microbiologically confirmed. This sentence is ambiguous. Normally excretion is a physiological process implying expelling of toxic products from the body through the GIT? Is this the meaning? This needs clarification.

Response: Corrected. We replaced the sentence “Bacterial excretion was confirmed by microbiological methods in all of the patients.” to “All patients had smear-positive tuberculosis”.

5. Line 157-161 make reference to ..”continuous flow of recurrent tuberculosis” ..The sentence is ambiguous and must be revised

Response: Corrected. We removed all sentences (Line 157-161).

Level of interest:
An article of importance in its field

Quality of written English:
Needs some language corrections before being published

Statistical review:
Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests

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

Yours faithfully, Dymova Maya.