Author's response to reviews

Title: Transmission of Specific Genotype Streptomycin Resistant Strains of Mycobacterium tuberculosis in the Tokyo Metropolitan Area in Japan

Authors:

Akihiro Ohkado (ohkadoa@jata.or.jp)
Yoshiro Murase (ymurase@jata.or.jp)
Masaaki Mori (hltctryj@yahoo.co.jp)
Naoki Hasegawa (hasegawn@sc.itc.keio.ac.jp)
Goro Otsuka (ootsuka-g@city.kawasaki.jp)
Michiko Nagamine (Michiko_Nagamine@member.metro.tokyo.jp)
Hideo Maeda (Hideo_Maeda@member.metro.tokyo.jp)
Kazuhiko Uchimura (uchimura@jata.or.jp)
Masako Ohmori (ohmori@jata.or.jp)
Norio Yamada (nyamada@jata.or.jp)
Shinji Maeda (maeda@jata.or.jp)
Seiya Kato (kato@jata.or.jp)
Toru Mori (tmori-rit@jata.or.jp)
Nobukatsu Ishikawa (ishikawa@jata.or.jp)

Version: 2 Date: 13 July 2009

Author's response to reviews:

Response to the editors:

The ethical consideration part was further expanded as below in the methods section to elaborate our standpoint on obtaining the informed consent from research subjects with regards to the present observational epidemiological study only using anonymous and unlinked data of TB patients. The ethical committee board permission number was also indicated.

"According to the Ethical Guidelines for Epidemiological Research by the government of Japan, informed consent does not necessarily need to be obtained from research subjects to conduct an observational study using the existing epidemiological data if the study does not use any human biological specimens. Therefore informed consent was not obtained retrospectively for this study because the present study was an observational study using anonymous and unlinked data of TB patients, whose data sources were existing three databases which had already collected and analyzed. The informed consent had been however routinely verbally obtained about the DNA fingerprinting surveillance of M.tuberculosis from each of the bacillary positive tuberculosis patients registered in the Shinjuku PHC by the PHC staff, and the documented consent forms were also routinely obtained from each of the TB patients by the hospital staff in Kawasaki City. The study protocol was approved by the Institutional Review Board Committee of the Research Institute of Tuberculosis
with the reference number 21-1.

Response to the reviewers' comments

To the reviewer 1

1. (minor essential revision)
I agree with the comments, so I inserted the sentence at the first part of the 6th paragraph of Discussion as below:

"The epidemiological investigation in the context of the present study has been limited to those whose strains sharing the closely related genotype caused the outbreak in a university campus, therefore this limits the ability to draw conclusions clearly as to the specific risk factors for acquisition of this strain."

2. (discretionary revision)
Thank you for your suggestions but the M-strains tended to be isolated from younger age group because many patients with this strain belonged to the outbreak incident of a university campus in Yokohama City. We have no data to support that being Beijing genotype strains tends to cause outbreaks and be associated with more rapid progression to disease than other types of strains in the present study. What with regards to Beijing genotype we can imply from the present study are 1) M-strains belong to Beijing genotype which is very common in Japan (around 79%, reference 1), 2), the M-strains (only 1.7% of M.tuberculosis isolated in Shinjuku City, 2nd paragraph on page 11) seem spread among young age group people, among general people as well as homeless people in the TMA.

To the reviewer 2

(Major essential revisions)

1.1 The databases of Kawasaki City and Shinjuku City were chosen to investigate how M-strains have spread in the TMA because these databases were the only ones for us to do so. So far unfortunately there has been no database covering the wide area across the TMA. A sentence below was inserted, in the 9th line of the 1st paragraph under the method part on page 6, to elaborate this point.

"These two databases, which were independent each other, were chosen because these were the only ones for us to investigate how these strains spread in the TMA. As of this study, there has been no database covering the wide area across the TMA."

1.2 As described in the manuscript, Kawasaki City is located just next (north) to Yokohama City (9th line of the 1st paragraph under Background, page 5) and the university where the TB outbreak happened was located in the site very close to the border between the two cities. Hence it might have been highly possible to have some link between the TB bacilli at the university in Yokohama City and
those in Kawasaki City. A sentence below was inserted, in the 12th line of the 1st paragraph under the method part on page 6 following the inserted sentence above, to elaborate this point.

“In addition, the database of Kawasaki City, although its coverage among bacillary positive TB patients registered in the City was relatively low, approximately 21% (unpublished data), was chosen because we suspected there existed some link between the M-strains isolated from TB patients at the university campus in Yokohama City and TB bacilli in the Kawasaki City database for the university campus was located very close to the border between the two cities.”

1.3 The Kawasaki City hospital-based database is independent of that of population-based database in Shinjuku City. A sentence below was inserted, in the 9th line of the 1st paragraph under the method part on page 6, to elaborate this point.

“which were independent each other”

2. The Table was fully revised according to the comment made.

3. The sentences both in abstract and in conclusion were rephrased not to be conclusive accordingly as below.

“Although firm conclusions could not be reached through the present study, it suggested that we have to take into consideration that TB could transmit in congregated facilities like internet-cafés where TB high-risk people and general people share common spaces for relatively long time.”

(Minor essential revisions)

1. The study period was set as it was because the outbreak incident at the university campus in Yokohama City, which prompted us to investigate the transmission situation of M-strains in the TMA, seemed to be subsided by the end of 2006. However, as you mentioned, matched strains have been identified sporadically through either of the DNA Fingerprinting surveillance in Shinjuku City or in Kawasaki City so far until this year. A sentence below was inserted, in the 13th line of the 1st paragraph on page 6, to elaborate this point.

“The study period was set from September 2002 through to January 2008 because the outbreak incident at the university campus in Yokohama City, which prompted us to investigate the transmission situation of the M-strains in the TMA, seemed to be subsided by the end of 2006.”

2. The tracking function of the Microsoft Word was completely deleted from the revised manuscript and the English was edited again by a native English user.

Thank you for your kind comments and suggestions.

Akihiro Ohkado