**Author's response to reviews**

**Title:** High levels of Multidrug Resistant Tuberculosis in new and treatment-failure patients from the Revised National Tuberculosis Control Programme in an Urban metropolis (Mumbai) in Western India.

**Authors:**

Desiree T B Dsouza (desireetb_dsouza@yahoo.co.in)
Nerges F Mistry (fmr@fmrindia.org)
Tina S Vira (tina_vira2002@yahoo.com)
Yatin Dholakia (yatindholakia@gmail.com)
Sven Hoffner (sven.hoffner@smi.se)
Geoffrey Pasvol (g.pasvol@imperial.ac.uk)
Mark Nicol (Mark.Nicol@uct.ac.za)
Robert J Wilkinson (r.j.wilkinson@imperial.ac.uk)

**Version:** 4  **Date:** 9 June 2009

**Author's response to reviews:** see over
Reviewer's report

Title: High levels of Multidrug Resistant Tuberculosis in new and treatment-failure patients from the Revised National Tuberculosis Control Programme in an Urban metropolis (Mumbai) in Western India.

Version: 3 Date: 19 May 2009

Reviewer: Frank Cobelens

Reviewer's report:

I thank the authors for their extensive response to my comments. Their revisions and additions have taken away many of my concerns. I do however think that two related issues need to be properly addressed before this paper can be published.

Major compulsory revisions

In my view the issue of selection bias towards preferential inclusion of patients at increased risk of MDRTB has not been adequately addressed. Selection bias in itself is not a major problem – after all, epidemiology is “the art of making sense of imperfect data”. This does however require that potential biases are identified, quantified wherever possible, and above all, acknowledged. The statement in the discussion on selection bias now reads: “The fact that only 52% of the cases registered with the RNTCP were screened is an operational limitation of the study and not a recruitment strategy. Acknowledging the bias the generated in the incorporation of such vulnerable wards, the emphasis on...”. This is not an acknowledgement of the major risk of selection bias inherent in the way the study was done. That risk is in my view substantial because (repeating my previous comments, hopefully now clear to authors):

1. Only 52% of eligible patients were screened. It is customary in epidemiology to regard any exclusion of eligible patients of >20% as a source of selection bias unless a strong case can be made to the contrary. The authors have yet not been able to make such a case: exclusions were for “logistical reasons”, whatever that may be.

The inadvertent bias that may have arisen from a) a high degree of prescreening exclusion, b) a high degree of post screening exclusion and c) the inadvertent inclusion of previously treated cases has been acknowledged prominently in the second paragraph of the discussion and linked with under- or overestimation of MDRTB.

The major logistical reasons which were contributory to bias a have been identified in the first section of the Results and referred to in the Discussion.

The bias in a may be minimal since the inclusion of patients for screening was based solely on availability and contact of patients with the field workers at the health posts.

The field workers selected the patients strictly on the stipulated inclusion criteria.
2. Of the 1136 screened patients registered as new cases, 57% had to be excluded, mainly because they had some sort of history of TB treatment. Although I am convinced that the investigators managed to exclude most if not all patients among these 1136 who had previous exposure to TB drugs, it does suggest that there was a preference among doctors to include patients whom they suspected to have MDRTB, the consequence being that there may have been other “selection pressures” at work that the authors were unable to capture in their exclusion algorithm. An important example would be a history of contact to a patient with increased MDR risk (e.g. a failure patient). It is this potential for selection bias that I would like to see acknowledged, with a serious discussion of how the authors think this might have affected their estimates. Interestingly, the revision of the discussion section offers yet another reason to doubt the validity of the MDR estimate among new patients. The authors state that “(observations) in a subgroup of patients whose MDRTB status at diagnosis and post treatment was tested in our laboratory and whose treatment outcomes were recorded, revealed that 13% (21/162) of the failures were MDR at onset.” This means that 87% of failure cases were not, i.e. that the number of failure cases should be around 6.5 times that of the proportion of initial MDR patients that failed treatment. Now making the reasonable assumption that failure rates among patients who are MDR at onset of cat1 treatment are between 25 and 50%, one would thus expect that if the selection of patients tested was unbiased with regard to the risk of MDR, the failure rate in the unselected cohort of eligible new patients would be between 40% (0.25x0.24x6.5) and 80% (0.5x0.24x6.5). Authors are reluctant to give failure rates in their patient cohort because these may be biased, but I would be much surprised if they were indeed in this range. So somehow the data do not add up. Either their proportion initial MDR out of the failure cases is grossly underestimated, or the true MDR prevalence in the full cohort of eligible new patients is substantially lower that the 24% reported (as I suspect it is). In other words, they have to come up with a plausible explanation either way.

There was no conscious preference by field workers to include patients who were suspected to have MDRTB. The selection of patients was not by doctors who could be swayed by selection pressures but by field workers who were unaware of such pressures and who stringently applied the inclusion and exclusion criteria. We did attempt in the screening to establish connections of new cases to TB patients (patients here would be unlikely to be able to articulate regarding MDRTB) in their family or vicinity. Whist no direct or household contact could be epidemiologically established, the extreme population densities in these areas and the squalid living conditions would facilitate transmission of TB / MDRTB strains depending on the fitness of the organism and the susceptibility of the host. This would be a characteristic feature of most vulnerable areas. Hence proximity to TB patients in hyperendemic areas is more of an environmental characteristic (geographical proximity) than a “bias” especially since new patients and treatment failures accessing the health post are drawn from the same defined geographical area which the health post is supposed to serve. This has been reflected in the inclusion criteria in the Materials and Methods section.

Furthermore in view of the calculations presented by the referee, the authors feel that it would be appropriate to communicate the treatment failure rates computed by the FMR in the follow up patients based on sputum smear microscopy (a technique for which FMR has received accreditation from the TRC, Chennai during an earlier “External Quality Assurance Scheme” study for sputum microscopy in the RNTCP in Mumbai).
Whilst we do not wish to mention this in the manuscript, the failure rates obtained by concentrated smear microscopy in a subset of these patients who could be followed up by FMR was 48% (169/350) as opposed to the rate of 10% (35/350) presented by the system for these same patients. This was not reflected in the RNTCP Annual Reports of Treatment Outcomes which cited a failure rate of 2-3% over the study period. Of 680 confirmed new TB patients presenting to the RNTCP during the period 2004 - 2007, the District TB registers at the end of the DOTS course recorded outcomes for only 499 cases. The largest fallout (27%) was contributed by patients who were not traceable or had defaulted during first line treatment. Such patients in all likelihood are dropped from the denominator when cure rates are computed.

So in net response in the manuscript we have modified the Materials and Methods, Results and Discussion to read as follows:

**Material and Methods (4th para, pg 9):**

During the study period from April 2004 to September 2007, two groups of sputum smear-positive pulmonary TB patients registered with the RNTCP DOTS (Directly Observed Therapy Short Course) Centers were identified for inclusion. These consisted of - i) newly diagnosed, previously untreated patients at onset of therapy and ii) first line treatment failures (viz. sputum positive at the fifth month after commencement of a 2(HERZ)₃ + 4(HR)₃ regimen) (Figure 1). Field workers scrutinized treatment cards and District TB registers. In keeping with the larger study objective of investigating MDRTB transmission, the selection of as many new cases as was logistically feasible at a DOTS center, was attempted subsequent to the confirmed presence of a first line treatment failure at the same Center. Furthermore screening was based solely on patient availability and contact at the health posts. Logistical feasibility was influenced by factors such as the low ratio of field workers to health posts, extreme climatic conditions compounding difficult transport logistics and delays in systemic documentation of new patients in registers.

**Results : (para1, pg14)**

*Patient selection:*

A total of 1,454 patients (1,136 previously untreated and 318 first line treatment failures) were screened at the health posts between April 2004 to September 2007. Of the 2,184 cases presenting to the RNTCP for diagnosis during the screening period; 1,136 (52%) were screened due to logistical reasons outlined previously.

**Discussion : (para 2, pgs 17-18)**

Inherent in the study design are three points at which bias could have been introduced thereby leading to potential under- or overestimate of the prevalence of MDRTB in previously untreated cases. Firstly, only 52% of the cases registered with the
RNTCP were screened due to reasons mentioned in the results. Of the 48% who did not enter the study, it is likely that a proportion would have been excluded on the evidence of previous treatment. However it is equally possible that the enlarged number may have resulted in a lower rate of MDRTB than that reported here. Thus the possibility of bias generated towards MDR by the reduced intake of screening remains open. Secondly despite our efforts at excluding previously treated patients during screening, it is possible that those included for DST may not have admitted to taking prior treatment. This is a likely cause for an overestimation of MDRTB in new cases. Thirdly, of the 1136 screened patients registered as new cases, 24% had to be excluded because they had some sort of history of TB treatment. An additional 41% were excluded since they had consumed more than 5 doses of anti tubercular therapy prior to sampling (Figure 1), to reduce bias towards MDRTB. Whilst this could tend towards an underestimate in the total MDRTB prevalence in the area, there could have been other selection pressures that we were unable to capture in the exclusion algorithm. An important example would be a history of contact with a patient at increased risk of MDR-TB (e.g. a treatment failure case). We did attempt in the screening to establish connections of new cases to TB patients especially since new patients and treatment failures accessing a health post are drawn from the same defined geographical area which it is supposed to serve. However patients would be unlikely to be able to articulate regarding MDRTB in their family or vicinity.

We also draw the reviewer’s attention to a pre-existing section of the discussion,

‘Observations from treatment registers for the same cohort revealed a 27% drop out rate of patients who were not traceable or who had defaulted during the course of their first line treatment (data not shown). Such patients are in all likelihood omitted from the denominator when cure rates are computed.’

Finally we are thankful to the referees for their extensive efforts to generate a great deal of clarity in the manuscript.