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.

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.

**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