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: 1 Date: 2 April 2009

Reviewer: Frank Cobelens

Reviewer's report:

This paper provides data on TB drug resistance levels under program in an urban area in India. It is well generally written (although with a tendency for very long sentences) and the laboratory and statistical methods are largely appropriate.

Its main conclusions are that levels of MDR in new patients are much higher than those reported from sentinel surveillance in the country, and that these sentinel data underestimate the existence of MDR “hot zones”. This is a relevant finding given the large contribution of India to the global TB burden, and its potential consequences for the need for second-line treatment.

Major compulsory revisions

It is obvious from these data that there is a problem of MDR-TB in Mumbai. The question is however whether its magnitude has been adequately estimated, in particular since the authors make quite a point of the validity of their data compared to sentinel surveillance and other resistance data in India. There are a number of reasons to suspect a huge potential for selection bias in this study.

First, the sample of patients is not representative for Mumbai but based on a convenience sample of wards in the city, selected for their low cure rates.

Second, half of the eligible patients were excluded from testing and analyses for a variety of reasons.

Third, and most importantly: apparently not all patients in these wards were eligible during the enrolment period. Only 1454 patients were screened over a period of 42 months, i.e. 436 per year. With the stated population of 3 million this translates into a notification rate of 15 per 100,000, whereas India’s notification for smear-positive TB is around 50/100,000 and that in these wards presumably higher. In other words, at most one-quarter of registered patients were screened. I expect this is because there was a fixed sample size. It is then conceivable that, since DST is not routinely available, doctors preferably included those patients whom they suspected of MDR-TB, e.g. because of their treatment history (as suggested by the high proportion of new patients who turned out to be previously treated), of delayed treatment response (as suggested by the 41% exclusions for being screened after start of treatment), or contact history.
Thus, in total not more than 10-15% of a population at increased risk of MDR-TB were included in the study, and it is not at all inconceivable that these were selected for having an increased risk of MDRTB. This could have introduced bias of similar magnitude to that of studies done in tertiary hospitals from which this study is claimed to be different.

In order for this paper to be in any way scientifically meaningful and justifiable, the authors must at least:

1. provide the total number of smear-positive patients who were registered for treatment in the participating TB units during the study period, i.e. provide a denominator for the participation rate, separately for new and cat1 failure patients.
2. explain the eligibility criteria for screening.
3. acknowledge the strong potential for selection bias in the discussion and abstract and discuss its repercussions for the interpretation of their data.
4. remove from abstract and manuscript body any claims about the validity of their patients selection.
5. consider adding the data on second-line resistance testing among the MDR patients, since this would really add to the body of data and the XDR estimate among the MDR patients would be less affected by selection bias.

Minor essential revisions

Abstract: the term “stringently selected” is misleading. Although not a scientifically defined term, it suggests representativeness, which is in my view not at all guaranteed.

Introduction:
1st sentence: neither reference identified India as a MDR hot spot. Blower end Chau may have suggested that India could develop as such based on their model, but that is a different issue.
Reference 3: I prefer reference to the WHO Global Drug Resistance reports for this rather than a secondary review that is unavailable to me (and most readers) and probably reviews data based on this report.
P. 6, 2nd para: “relatively small”. The last sentence of this paragraph should be split up.

Methods:
Round off percentages.
P10. Third sentence from bottom of page (“If deltaG.I. was less…”) is unclear.
P11, final paragraph: The use of concordance and kappa values here is highly questionable because they may inflate the validity of the ST results in the field. It should instead be a comparison with a reference standard (i.e. the results at the reference lab), and sensitivity and specificity estimates should be provided.
Results:
Round off P-values to 3 decimals. Chi-square values are not really needed.
P13, 1st para, 2nd sentence: “than that of resistance…”
P13, 3rd para, 2nd sentence: “significantly higher proportion of…”
Idem, final sentence: “trend for monoresistance” incorrect terminology.

Discussion:
P5, 2nd para. I do not think that the sample size is that relevant. What should have been done is a representative selection. See above.
P16, 2nd para. The discussion about the proportion MDR among cat1 failures is somewhat irrelevant if the cat1 failure rate is unknown. In fact, a high proportion MDR with a low failure rate indicates good treatment adherence if the pretreatment MDR prevalence is not too low (because then most failures would not have been cured with a first-line regimen anyway). So authors should provide this statistic for the population and period under study.
P17, 1st para. “..the noncomputation of …” unclear.

Table 1.
Provide data by drugs, ideally using standard WHO reporting format (for purpose of comparison) as done in most DR papers. Especially the proportion of PZA resistance is interesting because few data are available.

Table 2. see above. Also provide numbers.

Figure 1.
Whence the addition “urban”? I understood that all data are from urban clinics.
>5 doses. Of what? When?
Defaulting. How was this defined?
Whence the addition Chest radiography? This is not mentioned in the text.

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

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

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