Reviewer's report

Title: The timing of death in patients with tuberculosis who die during anti-tuberculosis treatment in Andhra Pradesh, South India

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Reviewer: Dennis Falzon

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The authors describe the results of treatment in over 8000 TB patients reported between 2005 and 2009 in selected sites in southern India, in order to assess timing of death and to analyze factors associated with a fatal outcome.

The writing style is good and the research questions were well posed and the materials and methods are well described. The data appear to be fairly sound as they were collected from standard TB records in health centres supported by one agency and were reportedly cross-checked with monitoring registers of the national control programme. Reporting of outcomes also appears to be complete with very little “transfer outs”.

It is recommended to publish subject to Minor Essential Revisions. The following observations are made in this respect:

Abstract: The abstract starts with a statement that appears incoherent, which later also recurs in the text. If case fatality was truly 4-5% among the 2 million incident TB cases then this would “translate” into about 100,000 deaths and not 280,000. The case-fatality which is cited by the authors appears to have been averaged from the % deaths reported by India to WHO among cohorts of new and retreated smear positive cases. The mortality figure of 280,000 is derived from indirect estimates which also factor in case-fatality among non-notified TB cases. The authors may wish not to refer to or draw inferences from the case-fatality in the abstract and to highlight in the Introduction the problems in trying to reconcile observed deaths in cohorts and TB mortality estimates.

The conclusion also evokes the situation in sub-Saharan Africa which is not mentioned previously in the abstract. It is suggested to replace this sentence with one on concrete actions which can be usefully adopted by programmes to reduce early mortality in TB patients (in addition to “More research”).

Methods

- were the 16 selected sites included the only ones supported by LEPRA? If not how do they compare with others? The reader would be interested to know about the external validity of findings so this part should try to address this

- information on drug-susceptibility was not available. Given that this could be an important risk factor for death in patients on first line drug treatment it is important to state why this was not included.

- among the data collected there must have been smear status which was
reported upon later. Was it possible to distinguish the bacterial load in sputum and use this as a proxy of severity? Was type of previous treatment (beyond a Cat 2 treatment) available to be able to discern relapses from treatment failures for instance?

- in the analysis, apart from bivariate analysis, was a regression attempted in order to adjust for co-variates?

Results

- Table 2: I suggest that you show this as a survival curve with separate lines for new and retreated patients.

- The association with age could hardly be described as incremental (Table 3). I would suggest to state that odds were higher in individuals older than 50 years. Or else rerun the analysis with finer age-brackets.

- It may be useful to express the OR of cases with “HIV-status unknown” as well to see if this is comparable with the patients with known status.

- What is the hypothesis behind the association with manual labour? These three occupational categories are ordinal but the distance between them does not obey a numerical value, which is required in the assumption for Chi-square test for trend. Suggest to express ORs separately with skilled labour as a reference.

Discussion

- early death in the elderly may also be associated with delayed diagnosis in a group of patients in which non-specific chest syndromes may often be wrongly attributed to chronic bronchitis, smoking or lung cancer.

- The limitations of the work need to be more clearly stated, as they are now reserved to a brief mention in the penultimate paragraph of the Discussion. A more objective stance should be taken and a longer discussion devoted as a second paragraph of Discussion, evoking sources of potential bias, particularly any possible selection of patients which were included, and how this may have affected the generalizability of findings.

- In conclusion it would be helpful to identify some logical measures to take for the benefit of managers reading this faced with a similar scenario. For instance, how would you address default before start of treatment? Will carrying out a representative drug-resistance survey in the State or the whole country be expected to help? Should doctors keep an index of suspicion for early death in the elderly? You could cite some published work as well in this respect.

**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