Reviewer's report

Title: Risk factors associated with default from tuberculosis treatment, South Africa, 2002: a case-control study

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Reviewer: Hans L Rieder

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This is a nice and important study, rather comprehensively covering almost all of South Africa. While the authors are rightly a bit self-critical about the low response proportion, it is rather in the nature of things that this is so, and I would not dare making a critique of problems with representativeness. It is how it is, and obviously great efforts were made to trace as many patients as possible.

I have thus only a few minor comments to make, some are related to phrasing and the like. Of substance is, if anything, only the weighing in the interpretation of different associations: some are solid - age, sex, income, transfer, etc, others are important like attitude of health care workers, but they are not solid. Some factors have direct impact on services (communication when it comes to "transfers" which are not transfers, but actual default) while others are less influenced by the services (imbibe or don't). Perhaps, such differences could be worked out a bit more in the discussions. My comments thus may be taken with a grain of salt, and one or the other might prove useful in the revision.

Certain questions may beg for an association: for instance, putting the blame of default on a health care worker's attitude by a defaulter is almost certainly more associated with default than with non-default even if in fact there would be no association.

The authors state (Introduction, para 2): "Persons under treatment for TB who default from treatment are at risk for clinical deterioration and complications, death, worsening drug resistance, and they may continue to be infectious to others" quoting Pablos-Méndez A, Knirsch C A, Barr R G, Lerner B H, Frieden T R. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med 1997;102:164-70. In the latter study, non-adherence is not quite the same as "default" as it is used in this study. These were patients on and off treatment. Abandoning treatment and not to return to again on treatment (default) is unlikely to lead to acquisition of drug resistance as resistance can develop only as a result of pressure by the presence of drugs. A person stopping taking the drugs at any point in time will have a strain with the susceptibility at the point of default, and if the disease recurs, that will be the strain's susceptibility pattern. Thus default in that sense will never be the cause of resistance. It is different, if patients are on and off treatment, irregular in intake and dosage, something that will give a selection advantage to resistant mutants (Mitchison D A. How drug resistance emerges as a result of poor compliance during short
course chemotherapy of tuberculosis. Int J Tuberc Lung Dis 1998;2:10-5.) as there is selection pressure.

Methods, page 8, last para: "Data were entered into an EpiData ..." (note correct spelling of the software, and note that the citation is not quite correct: "BM" probably stands for Michael Bruus but it would be unusual to cite the second author only with his initials). There is nothing mentioned about data validation, ie, quality assurance of electronically captured data through double entry, comparison, and correction. It should be stated whether or not this was done so that the reader can make up his / her own mind of whether sophisticated analysis was done on quality-assured data or whether potentially erroneous data were analyzed.

Results, page 10, first para: How can such a large proportion of control patients who were presumably cured have died after cure from tuberculosis? Is information on cause of death worth anything or do they just scribble "tuberculosis" on the death certificate because the person once had tuberculosis? Certification of cause of death is extraordinarily complex and physicians often do not know the difference between "underlying cause" and "immediate cause" and if HIV comes into play it is likely to get even trickier to correctly codify the chain of events. Unless the authors have a clear explanation why cured patients died from tuberculosis, it might be better to just drop the entire thing of trying to figure out "cause".

Results: "Social and economic factors" appear to be rather solidly based on objective factors, and it is appropriate that this paragraph is separated from the "Patient-related factors" and particularly "Health care team and system-related factors", the latter of which is (see above) a bit of questionable in many ways, but admittedly important to report, but it should be clearly taken with a grain of salt and that might be critically assessed in the discussion.

**Level of interest:** An article of importance in its field

**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