Author's response to reviews

Title: Patient- and provider-level risk factors associated with default from tuberculosis treatment, South Africa, 2002: a case-control study

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Author's response to reviews:

Dear BMC Public Health Editor,

Please find below our Response to Reviewers.

Reviewer #1

1. Low response proportion, but great efforts were made to trace as many patients as possible.

Response: Yes, great efforts were made, obviously we would have liked a higher rate but it was difficult to find the ones we did. Thank you.

2. Some factors are solid, some are important but not solid, some have direct impact on services, while others are less influenced by the services. Perhaps, such differences could be worked out a bit more in the discussion. Putting the blame of default on a HCWs attitude by a defaulter is almost certainly more associated with default...

Response: We agree there are differences in the reliability of the variables, and perhaps how “hard” versus “soft” they are (not clear what the reviewer means by “solid”), but these various influences all contribute a spectrum of attribution to the ultimate causes of default, and while some are measurable measurements like age and sex, others are more difficult to define. There are inherent difficulties in collecting subjective data between such disparate subjects as social factors, economic factors, health care team characteristics, and patient-level factors all reported through one mechanism, the patient self-report. The patient self-report refers to experience, rather than to reality. It is the experience (of reality and not reality itself) that informs future decisions by people about adherence and retention. Hence if we are interested in understanding the relationship between satisfaction and adherence, we need to know the subjective experiences. The same applies to experiences that are quantifiable and can actually be verified.
from institutional data, such as the number of doctors, waiting times, etc. Also here the subjective experience is the overarching factor when it comes to making decisions by patients. Some of these factors we measured have direct impact on health care services, and others have indirect but equally large impacts on services. However, this should not make us want to separate them out, as in many other epidemiologic studies we study factors the best way we know how, with some being more accurate measures of what we are trying to measure than others. Unfortunately it was also not possible to include the provider perspective (health care workers and treatment supporters) on default and non-adherence in this study. The limitation is now noted in the discussion.

3. Default is unlikely to lead to acquisition of drug resistance as resistance can develop only as a result of [selective] pressure by the presence of drugs.

Response: We agree, and we have taken out the mention of development of drug resistance from the introduction. We agree that we were studying default, not non-adherence.

4. Citation of Epi Data is not correct.

Response: We have fixed the citation.

5. There is nothing noted about data validation.

Response: We had several checks on data validation in the data analysis protocol. The first ascertained that only expected characters were present in field entry. We also had cross-system consistency checks, e.g. new patients being given streptomycin were flagged and reviewed, and if retreatment patients were not given streptomycin this also triggered a flag. We also had data checks: scroll down menus given at closed questions allowed only a range of codes. Lastly, we had a uniqueness check a unique study number was given and duplication was not allowed. These were reviewed as batch totals, i.e. each province had a unique number from 0 -1 as the first digit of the study number.

6. How can such a large proportion of control patients who were presumably cured have died after cure from tuberculosis? It might be better to just drop the entire thing of trying to figure out “cause.”

Response: Agreed, we have no explanation. We have dropped this attribution and data from the results.

7. Some factors are solid, some are a bit questionable in many ways, but admittedly important to report, but it should be taken with a grain of salt and added to the discussion.

Response: As we stated above, we have added a short discussion of the differences in factors to the limitations section.

Reviewer #2
We would like to thank the reviewer for some very excellent comments, and
allowing us to improve this paper.

1. Retrospective study performed a long time after the episode. These are important limitations as the authors recognize.

   Response: We feel we have recognized these limitations.

2. Definition [of controls] showed in abstract is more correct than the definition on page 3.

   Response: We apologize for this error, the definition in the abstract is correct and we have corrected the paper.

3. The study design was 1:2 case:controls, but the authors analyze 1:4.

   Response: Correct, the study was designed as 1:2, but there were far more controls found than cases (by definition, cases were hard to find!!). Thus, our final ratio was closer to 1:4, which has no relation to the measure of association that we find, but only strengthens our CIs.

4. Large proportion of patients who have died.

   Response: Correct, this is also something we expected but it was more common than even we expected. During the early 2000s, TB/HIV became an explosive problem and the mortality rate in the country was astronomical. This is something out of our control and I don't feel there is any revision in the study analysis that can change this. In addition, ARVs were not available during our study period.

5. Page 10, about cause of death – the number of deaths is similar to the number of cases studied.

   Response: Correct, and again, this is something out of our control. But Reviewer #1 noted the same, and we have removed the section about cause of death since it is likely not reliable data.

6. Authors describe 33 patients who died 2 months after stopping treatment and assume these patients were misclassified…. I do not understand, at what time of the treatment do they stop the treatment?

   Response: Yes, they abandoned treatment before the 6/8 months were over. We have no data about when during treatment they stopped (defaulted) because data sources were not consistent across all data points, but we do know that it was not after properly completing treatment. We included have included the lack of data in the results.

7. Cases interviewed defaulted later in the treatment course, this can also be another limitation.

   Response: This is a limitation and is noted in the conclusion. The temporal association, however, is unknown.

8. Results on page 13 are not cited in the abstract.
Response: We apologize for the omission, they have been added to the abstract. However, this is a word limit on the abstract.

9. I do not find any result in the article about the issue [supervision] that support the affirmation.

Response: It was omitted in error, but we have added it to the text. Exactly half of both cases and controls reported no supervision during treatment. However, we recognize that what they reported and what was recorded were not necessarily the same.

10. Abstract: there is an error in new OR.

Response: We have noted the typographic error and corrected.

11. This is a discordance between abstract and Table 5, because they did not feel better, or because they did not feel better. This should be clarified.

Response: In our final study report, both new and retreatment defaulters reported that they stopped treatment because “they felt better.” This was left off the table inadvertently and has been added back in.

12. The population is people enrolled in treatment DOTS (add).

Response: We agree with this addition to the abstract.

13. Treatment regimen of new and retreatment should be described in methods.

Response: We agree with this addition. All new patients would have received the FDC called Rifafour (INH, RIF, PZA, ETHAM) and if any patient was a retreatment case would have received Rifafour plus Streptomycin.

14. The definition of default should be incorporated into the abstract.

Response: We have added the definition to the abstract.

15. They do not have data about the HIV status.

Response: This is correct. At the time the patients went through treatment, HIV testing was not common nor mandatory. The South African IRB thus felt that inquiring about HIV status was not ethical, and therefore we had no data to include.

16. Travel time to clinic is not in Table 3.

Response: We have removed the last line of the second paragraph page 11 and replaced the factors with factors that are significant from Table 3.

17. Add in the title and objectives a word or short phrase about these factors.

Response: We agree to add into the title the words “patient level and provider level”.
18. Tables 2/3 have too much data and they are difficult to understand.

Response: We have much more data to present, but have limited it to the factors listed in the tables due to space constraints. We feel we have presented the data in clearly defined columnar form.

19. Page 11: you repeat cases were more likely than controls to be male.

Response: This is noted, and the first sentence has been removed.