Author’s response to reviews

Title: Tuberculosis recurrence and mortality rates in successfully treated tuberculosis patients in southern Ethiopia: retrospective cohort study

Authors:

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Author’s response to reviews: see over
Reviewer #1

Reviewer Name: Kalappan Pillai

The reviewer’s comment: Major Compulsory Revision

1. Cases included in this study are cured and completed cases. These cases are appropriate for studying recurrence rate only. But not appropriate for mortality rate because these groups of cases have the least mortality rates. The findings from this study may not be comparable with studies reporting TB mortality rates for all types of cases. For studying mortality rate, all cases should be included because defaulters and failures have highest mortality rates. This study has selectively excluded defaulters and failures, which will result in, under estimation of mortality rate among TB cases.

I respond to the reviewer’s comment as follows:

The aim of the study was to measure the long-term efficacy of DOTS in successfully treated patients. Thus patients that did not adhere to treatment could not indicate the efficacy of DOTS on the long-term. Failure cases that were successfully treated were also enrolled if they did not default from treatment. The importance of understanding the recurrence and mortality among patients who did not adhere to treatment (defaulters) is important nevertheless the scope of the study did not include them. Yet, the fact that excluding these patients underestimates overall mortality is valid point.

The reviewer’s comment: Major Compulsory Revision

2. The calculation of Recurrence rate and mortality rate (The authors describe them as IR for recurrence and death), which are the outcome measures, are not correct. Even though they were correctly defined in the text (page 6, para 3, line 5) as number of deaths or
recurrences per 100PYO, in the results section and in tables 2 and 3 they have calculated them as recurrence or death PYO/ Total PYO. For example, the mortality rate was reported as (148/2602 in page 8) 5.7/100 PYO. But the actual mortality rate is (64/2602) 2.46/100 PYO. The entire paper has to be thoroughly revised as all the findings and discussions based on them have to be suitably modified.

I respond to the reviewer’s comment as follows:

I have recalculated the recurrence and mortality rates in table 2 and 3, and revised the results and discussions related to it. *The revised tables appear as follows*

Table 2 factors predicting rate of recurrence in successfully treated smear-positive tuberculosis patients in southern Ethiopia from 1998 - 2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>Recurrence</th>
<th>PYO*</th>
<th>Recurrence rate per 100PYO</th>
<th>Crude HR (95% CI) †</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (in yrs)</td>
<td>14</td>
<td>411</td>
<td>1495.3</td>
<td>0.94</td>
<td>1.0 (0.9 - 1.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>201</td>
<td>727.8</td>
<td>0.69</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>211</td>
<td>777.0</td>
<td>1.29</td>
<td>1.8 (0.6 - 5.2)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>5</td>
<td>176</td>
<td>661.4</td>
<td>0.76</td>
<td>1.0</td>
</tr>
<tr>
<td>Literate</td>
<td>9</td>
<td>205</td>
<td>734.0</td>
<td>1.23</td>
<td>1.7 (0.6 - 5.1)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>1</td>
<td>99</td>
<td>336.9</td>
<td>0.29</td>
<td>1.0</td>
</tr>
<tr>
<td>Married</td>
<td>14</td>
<td>298</td>
<td>1123.3</td>
<td>1.25</td>
<td>4.0 (0.5 - 30.6)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>12</td>
<td>273</td>
<td>1016.5</td>
<td>1.18</td>
<td>1.0</td>
</tr>
<tr>
<td>Non farmers</td>
<td>3</td>
<td>139</td>
<td>488.4</td>
<td>0.61</td>
<td>0.5 (0.2 - 1.9)</td>
</tr>
</tbody>
</table>

* PYO - person-year observation
† HR - hazard ratio, 95% CI - 95% confidence interval
Table 3 factors predicting mortality in successfully treated tuberculosis patients in southern Ethiopia from 1998 - 2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>Death</th>
<th>PYO*</th>
<th>Mortality rate per 100 PYO</th>
<th>Crude HR (95%CI)</th>
<th>P-value</th>
<th>Adjusted HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>321</td>
<td>1270.8</td>
<td>1.89</td>
<td>1.0</td>
<td>1.6 (0.9 - 2.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Male</td>
<td>40</td>
<td>337</td>
<td>1320.5</td>
<td>3.03</td>
<td>1.24</td>
<td>2.2 (1.3 - 3.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>15</td>
<td>284</td>
<td>1118.5</td>
<td>1.34</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literate</td>
<td>11</td>
<td>350</td>
<td>1289.9</td>
<td>0.85</td>
<td>0.6 (0.3 - 1.4)</td>
<td>0.3</td>
<td></td>
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<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>5</td>
<td>179</td>
<td>632.3</td>
<td>0.79</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>23</td>
<td>476</td>
<td>1861.3</td>
<td>1.24</td>
<td>1.6 (0.6 - 4.1)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>19</td>
<td>479</td>
<td>1838.4</td>
<td>1.03</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non farmers</td>
<td>45</td>
<td>180</td>
<td>757.2</td>
<td>5.94</td>
<td>5.7 (3.3 - 9.7)</td>
<td>&lt; 0.01</td>
<td>6.3 (3.6 - 11.1)</td>
</tr>
<tr>
<td>TB classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear positive PTB*</td>
<td>33</td>
<td>394</td>
<td>1504.8</td>
<td>2.19</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear negative PTB</td>
<td>22</td>
<td>142</td>
<td>606.9</td>
<td>3.62</td>
<td>1.7 (0.9 - 2.9)</td>
<td>0.1</td>
<td>1.1 (0.6 - 1.9)</td>
</tr>
<tr>
<td>EPTB‡‡</td>
<td>9</td>
<td>122</td>
<td>481.1</td>
<td>1.87</td>
<td>0.9 (0.4 - 1.8)</td>
<td>0.7</td>
<td>1.1 (0.5 - 2.2)</td>
</tr>
</tbody>
</table>

PYO - person year observation
† IR - incidence rate
‡ HR - hazard ratio, 95%CI - 95% confidence interval
§ PTB - pulmonary tuberculosis
‡‡ EPTB - extrapulmonary tuberculosis

The revised part of the results on page 9 paragraph 2 line 1 now reads:

The average observation was 3.59 person years and the total was 2602 person years. The recurrence rate was 0.77% per annum (20/2602.06) [0.99 (15/1506.3) for smear-positive, 0.65 (4/611.82) for smear-negative and 0.21(1/481.13) for EPTB cases]. The mortality rate was 2.46% per annum (64/2602.06) [2.19(33/1504.8) for smear-positive, 3.62 (22/606.9) for smear-negative and 1.87 (9/481.13) for EPTB cases] as shown in table 2 and 3.
The reviewer’s comment: Major Compulsory Revision

3. The smear positive case is not clearly defined.

I respond to the reviewer’s comment as follows:

The diagnosis of smear-positive cases based on the sputum smear result and x-ray for there was no laboratory facility to conduct culture.

The revised part of the method on page 5 paragraph 2 line 1 now reads:

PTB suspects who had productive cough for two weeks or more with at least two positive sputum smears or one positive smear and x-ray findings consistent with active PTB were classified as smear-positive PTB cases.

The reviewer’s comment: Major Compulsory Revision

It has to be clearly defined, whether it includes only new smear positives or both new and retreatment smear positive cases. It is desirable to bifurcate smear positive cases into new cases and retreatment cases, as the mortality rate is more among retreatment cases than new cases.

I respond to the reviewer’s comment as follows:

The study participants included smear-positive cases new and retreatment cases. We have compared the mortality rate among new and retreatment cases. However, there was no difference between new and retreatment cases (log rank p = 0.139). This could be due to the few number of retreatment cases to detect the difference in mortality.

The revised part of the methods under study design on page 4 paragraph 3 line 2 now read:
We enrolled new and retreatment cases that either were cured or completed their treatment under DOTS programme from 1998 to 2006 by conducting house-to-house visit.

The revised part of the results on page 9 paragraph 2 line 6 now reads:

There was no difference between new and retreatment cases (log rank p = 0.139).

The reviewer’s comment: Major Compulsory Revision

4. The smear negative cases also are not defined clearly. How was the diagnosis of smear negative cases made? Does this group include only radiological cases or smear negative culture positive cases or clinically suspect cases.

I respond to the reviewer’s comment as follows:

The diagnosis of smear-negative patients was based on clinical examination, sputum microscopy and radiological evidences. Sputum cultures were not done because the facilities were not available in the study area.

The revised part of the methods on page 5 paragraph 2 line 3 now reads:

Patients presenting with cough of two weeks or more with initial three negative smears and no clinical response to a course of broad-spectrum antibiotics, three negative smear results after a course of broad-spectrum antibiotics, x-ray findings consistent with active PTB and decided by a clinician to be treated with anti-TB chemotherapy were classified as smear-negative PTB cases.

The reviewer’s comment: Major Compulsory Revision
5. The study population is a cohort of TB cases registered from 1998 to 2006. When was this retrospective cohort study started? When was the data collection completed? This has to be clearly stated in the methods section.

**I respond to the reviewer’s comment as follows:**

I have added one sentence indicating that data collection was started in September 2007 and ended in February 2008.

*The revised part of the methods on page 6 paragraph 2 line 6 now reads:*

The data collection was done from September 2007 to February 2008.

**The reviewer’s comment: Major Compulsory Revision**

6. The methods section must include details of DOTS programme in the study area like number of health institutions in the TU, the type of DOTS providers, quality of recording and reporting in the programme, estimated case load in the study area, performance indicators such as case detection rates, conversion rates, cure rates and completion rates during the study period.

**I respond to the reviewer’s comment as follows:**

I have added more sentences stating the implementation of DOTS in the study area.

*The revised part of the methods under study area and population section on page 4 paragraph 2 line 1 now reads:*

We did this study in Dale and Wonsho districts of Sidama zone in the southern Ethiopia (Figure 1). It is a densely populated area (with a population of 296,811) and agriculture is the backbone of the economy. The farmers also cultivate cash crops (coffee and ‘khat’) that non-farmers depend on for commercial activities. In this district, DOTS started in
There were six health facilities providing TB service in the study area. Trained general health workers administer DOT. Standard recording and reporting formats were used in health facilities and the districts. District TB programme coordinators regularly checked the completeness and accuracy of the recording of TB cases in the unit TB register. The estimated prevalence of TB in the study area was 643 per 10^5 population; and the incidence of smear-positive cases was 168 per 10^5 population for 2006. The case detection, cure and treatment success rates were 41%, 58% and 76% respectively. The sputum conversion rate at second month of follow-up was 83% (unpublished report from the study area).

**The reviewer’s comment: Minor essential revision**

1. The duration of treatment and mandatory sputum examinations during treatment have to be clearly stated.

**I respond to the reviewer’s comment as follows:**

I have added a sentence stating the duration of treatment and follow-up.

*The revised part of the methods on page 5 paragraph 3 line 1 now reads:*

TB patients received two months intensive phase treatment and 6 months continuation phase treatment. Follow-up sputum examination was done at the end of 2\textsuperscript{nd}, 5\textsuperscript{th} and 7\textsuperscript{th} months of treatment.

**The reviewer’s comment: Minor essential revision**

2. Explain how the recurrent cases were diagnosed especially for smear negative
and extra pulmonary TB.

**I respond to the reviewer’s comment as follows:**

TB diagnosis whether it was new or recurrent was based on the case definition according to the National TB and Leprosy Control Programme. There was no especial way to make the diagnosis. *Therefore, we have restated the case definitions under methods on page 5 paragraph 2 line 3 as follows.*

Patients presenting with cough of two weeks or more with initial three negative smears and no clinical response to a course of broad-spectrum antibiotics, three negative smear results after a course of broad-spectrum antibiotics, x-ray findings consistent with active PTB and decided by a clinician to be treated with anti-TB chemotherapy were classified as smear-negative PTB cases. Patients presenting with symptoms suggestive of TB other than the lungs, which did not respond to a course of broad-spectrum antibiotics and decided by a clinician to be treated with anti-TB chemotherapy were classified as EPTB cases.

**The reviewer’s comment: Minor essential revision**

3. The authors say that the reference population and the study population have similar socioeconomic development and have same altitudes. Comparison of the health care services in the two populations will be more relevant.

**I respond to the reviewer’s comment as follows:**

The two populations were from the same administrative region - southern Ethiopia and similar health policy applies to them. They have similar socioeconomic status and altitude, about 50% of the population has access to health service and DOTS was
implemented in all health centers. The two areas were among the places where DOTS was first piloted.

*The revised part of the methods under data analysis on page 7 paragraph 1 line 7 now reads:*

In addition, about 50% of the population has access to health service and DOTS was started about the same year and provided in all health centers of the two population.

**The reviewer’s comment: Minor essential revision**

4. Table 4 is not clear. The SMR is calculated as follows:

Observed number of deaths O, PYO for this group n P-Ys, Standard rate y/1000 P-Ys

Expected number of deaths E (calculated as n* y/1000), SMR O/E. Rewrite the table 4 as shown.

**I respond to the reviewer’s comment as follows:**

I have rewritten table 4 as suggested.

*Table 4 is shown on next pages:*
## Table 4 Excess mortality in successfully treated tuberculosis patients in southern Ethiopia from 1998 - 2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>Deaths</th>
<th>Total</th>
<th>PYO*</th>
<th>Deaths per year</th>
<th>Standard population†</th>
<th>Expected deaths per year</th>
<th>SMR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 9</td>
<td>0</td>
<td>17</td>
<td>3.06</td>
<td>0.00</td>
<td>14.33</td>
<td>0.24</td>
<td>0.00 (0.00 - 0.00)</td>
</tr>
<tr>
<td>10 - 19</td>
<td>4</td>
<td>117</td>
<td>3.47</td>
<td>1.15</td>
<td>1.75</td>
<td>0.20</td>
<td>5.63 (0.38 - 10.87)</td>
</tr>
<tr>
<td>20 - 29</td>
<td>12</td>
<td>263</td>
<td>3.68</td>
<td>3.26</td>
<td>2.72</td>
<td>0.71</td>
<td>4.56 (2.04 - 7.09)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>10</td>
<td>158</td>
<td>3.70</td>
<td>2.71</td>
<td>4.92</td>
<td>9.78</td>
<td>3.48 (1.36 - 5.60)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>13</td>
<td>88</td>
<td>3.44</td>
<td>3.78</td>
<td>6.61</td>
<td>0.58</td>
<td>6.50 (3.15 - 9.84)</td>
</tr>
<tr>
<td>50 - 59</td>
<td>11</td>
<td>46</td>
<td>3.85</td>
<td>2.86</td>
<td>12.57</td>
<td>0.58</td>
<td>4.95 (2.02 - 7.87)</td>
</tr>
<tr>
<td>60 - 69</td>
<td>12</td>
<td>24</td>
<td>2.86</td>
<td>4.20</td>
<td>23.78</td>
<td>0.57</td>
<td>7.35 (3.76 - 10.94)</td>
</tr>
<tr>
<td>70 - 79</td>
<td>1</td>
<td>5</td>
<td>4.86</td>
<td>0.21</td>
<td>35.46</td>
<td>0.18</td>
<td>1.16 (-1.40 - 3.72)</td>
</tr>
<tr>
<td>80 - 89</td>
<td>0</td>
<td>1</td>
<td>2.94</td>
<td>0.00</td>
<td>45.36</td>
<td>0.05</td>
<td>0.00 (0.00 - 0.00)</td>
</tr>
<tr>
<td>Total</td>
<td>63§</td>
<td>719</td>
<td>3.60</td>
<td>17.51</td>
<td>5.41</td>
<td>3.89</td>
<td>4.50 (3.42 - 5.57)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>19</td>
<td>497</td>
<td>3.70</td>
<td>5.14</td>
<td>5.25</td>
<td>2.61</td>
<td>1.97 (1.10 - 2.84)</td>
</tr>
<tr>
<td>Non farmers</td>
<td>44</td>
<td>222</td>
<td>3.44</td>
<td>12.79</td>
<td>5.79</td>
<td>1.29</td>
<td>9.95 (7.17 - 12.73)</td>
</tr>
</tbody>
</table>

* PYO - person year observation
† Mortality in standard population from 2000 - 2004, Butajira population in southern Ethiopia
‡ SMR - standardized mortality ratio (95% confidence interval)
§ One patient was 90 years

### The reviewer's comment: Major Compulsory Revision

…Thoroughly revised as all the findings…

Our results suggest that more deaths than expected occurred during the follow up of the TB patients. The SMR was 4.12 (95%CI: 3.09 - 5.12) for all patients. However, as the risk of dying in was higher among non-farmers, we calculated their SMR as 9.73 (95%CI: 6.98 - 12.49). The SMR for farmers was less (1.73; 95% CI (0.92 - 2.55), and not significantly different from our reference population.

I respond to the reviewer’s comment as follows:

In reference to the revision done in table 4, the results related to it were revised.

The revised part of the results on page 9 paragraph 3 line 1 now reads:
Our results suggest that more deaths than expected occurred during the follow-up of the TB patients. The SMR was 4.50 (95%CI: 3.42 - 5.57) for all patients. The SMR was higher in non-farmers (9.95, 95%CI: 7.17 - 12.73) than in farmers (1.97, 95%CI: 1.10 - 2.84).

The reviewer’s comment: Minor essential revision

5. Discussion is very shallow. Needs to be completely revised; Comparison with findings of similar studies. Discuss possible reasons for the difference. References to HIV prevalence and MDR TB should be substantiated with appropriate figures. If the authors have information on HIV prevalence and MDR TB in this study population, it should be reported and used in the discussion. Difference in the Mortality rates between farmers and non-farmers should be discussed in more detail.

I respond to the reviewer’s comment as follows:

I have added more details to the discussion and added available reference to HIV prevalence and MDR TB as shown in brackets.

The revised discussion on page 10 paragraph 1 line 1 now reads:

Our study shows that eleven percent of successfully treated TB patients either had recurrence or died. More deaths occurred in TB patients after treatment than the general population. The mortality rate was higher in non-farmers compared to farmers.

The estimated recurrence rate in our setting was 3.5%. This could be due to HIV infection, MDR TB, reinfection due to high TB burden and inadequate treatment supervision and patient follow-up. HIV infection increases the risk of infection,
reinfection, recurrence and death. It also increased the workload by fuelling TB epidemic and affected the performance of TB programme [6]. In southern Ethiopia, the prevalence of HIV infection in the general population and TB patients was 3.8% and 17.5% in southern Ethiopia explains the role of HIV infection [17]. Though the prevalence of MDR TB in Ethiopia was believed to be low (1.6% in new and 12% in previously treated TB cases), 50% resistance to one or more drugs in re-treatment cases in Ethiopia) [18]. Similarly 7.7% resistance to at least one TB drug was reported from our study area [19]. Higher recurrence rates reported elsewhere, 8.6% in Vietnam after 19 months, 11% in India after two and half years and 36% in Kazakhstan after 22 months of follow-up [20 - 22] were attributed to MDR TB, poor treatment supervision and inadequate patient follow-up [8,9,11,12].

The mortality rate was 2.46% per annum (2.46 per 100 PYO) lower than report from Malawi (23.7 per 100 PYO) where the prevalence of HIV and TB HIV coinfection was higher [10]. In our study, the mortality rate was higher in males and non-farmers (merchant, x-soldiers and employees of government or private sector). This could be explained by the high mobility among these group of people, increased risk and high prevalence of HIV infection. They were the main routes for the transmission of HIV infection from urban to rural areas [23]. In addition, mortality rate was more in males and increased with age. This could be explained by the increased risk of HIV infection in males in rural areas compared with females, and other medical condition that increase the risk of developing active disease and death as age increases [24,25]. As expected
mortality rate was similar in smear-positive, smear-negative and EPTB cases possibly due to similar rates of HIV infection [17].

Similar to the study report from India [25], our study showed the excess mortality rate in TB patients (SMR = 4.50) over the general population. This could be due to TB or other co-morbidities. The mortality rate was more in non-farmers. The plausible explanation could be the high rate of recurrence and mortality due to increased risk and prevalence of HIV infection. MDR TB is the unlikely explanation however this should be cautiously interpreted in presence of high resistance to at least one anti-TB drugs.

Moreover, factors that affect the performance of TB programme (poor treatment supervision and failure to do follow-up sputum examination) and the patients’ general condition could increase the mortality and recurrence rate. Inadequate treatment supervision, more pronounced during continuation phase when patients receive unsupervised treatment, reduces treatment adherence and increases the risk of treatment failure and MDR TB. This is worsened when the importance of treatment adherence is not well addressed during health education sessions [26]. Additionally, failure to conduct follow-up sputum examination reduces the chance of detecting failure cases (smear-positive at 5th or 7th month) without affecting the number of patients that complete treatment.

Using sputum microscopy for the diagnosis of recurrence in smear-positive patients, shortage of health workers to diagnose recurrence in smear-negative and EPTB cases and
lack of information for about ten percent of the cases might have underestimated the rates of recurrence. Using standard general population might have underestimated the mortality rate in TB patients. Failure to ascertain the causes of death could also have included other causes of death to TB patients that improves the underestimation due to using standard population in the estimation.

The significance of this study is more in settings with high TB and HIV prevalence. The performance of TB programme could be improved by addressing factors that affect treatment adherence and increase the risk of MDR TB. TB patients could also benefit from the access to HIV prevention and control measures in high-risk patients to reduce recurrence and improve their long-term survival.

**The reviewer’s comment: Minor essential revision**

6. Three different terms are used for mortality. Mortality rate, IR for death and death rate. Mortality rate is an incidence rate. I would suggest using the term mortality rate only.

*I respond to the reviewer’s comment as follows:*

I have replaced IR for death and death rate by mortality rate as suggested.

**The reviewer’s comment: Discretionary Revision**

1. Under discussion in Para 2 the authors compare recurrence rate of 3.5% with studies reporting similar rates for different follow up periods but this study has not mentioned any period of follow up. Not possible to compare. But this study reports recurrence rate
as cases/100PYO. (2.8/100PYO reported in table 2 is not correct . The correct recurrence rate is 0.94/100PYO). This rate can be expressed as 0.94% per annum.

**I respond to the reviewer’s comment as follows:**

The 3.5% mentioned was the result of our study we are reporting. I have corrected the recurrence rate in the results section and also used the % per annum in the results and discussion as needed.

*The revised part of the results section page 9 paragraph 2 line 2 now reads:*

The recurrence rate was 0.77% per annum (20/2602.06) [0.99 (15/1506.3) for smear-positive, 0.65 (4/611.82) for smear-negative and 0.21(1/481.13) for EPTB cases]. The mortality rate was 2.46% per annum (64/2602.06) [2.19(33/1504.8) for smear-positive, 3.62 (22/606.9) for smear-negative and 1.87 (9/481.13) for EPTB cases] as shown in table 2 and 3.

*The revised part of the discussion on page 10 paragraph 3 line 1 now reads:*

The mortality rate was 2.46% per annum (2.46 per 100 PYO) lower than report from Malawi (23.7 per 100 PYO) where the prevalence of HIV and TB HIV coinfection was higher.

**The reviewer’s comment: Discretionary Revision**

2. Page 9, para 1 line 4 states ‘gaps’ in the programme. Explain the ‘gaps’

**I respond to the reviewer’s comment as follows:**

The main gaps in the implementation of TB programme were explained in the discussion.

*The revised part of the discussion on page 11 paragraph 3 line 1 now reads:*

The main gaps in the implementation of TB programme were explained in the discussion.
Moreover, factors that affect the performance of TB programme (poor treatment supervision and failure to do follow-up sputum examination) and the patients’ general condition could increase the mortality and recurrence rate. Inadequate treatment supervision, more pronounced during continuation phase when patients receive unsupervised treatment, reduces treatment adherence and increases the risk of treatment failure and MDR TB. This is worsened when the importance of treatment adherence is not well addressed during health education sessions [26]. Additionally, failure to conduct follow-up sputum examination reduces the chance of detecting failure cases (smear-positive at 5th or 7th month) without affecting the number of patients that complete treatment.

The reviewer’s comment: Discretionary Revision

3. Page 9, para 2line 2mentions mortality rate as 7.7%. How this figure was obtained? Table 3 shows 5.7/100pyo as mortality rate. But as mentioned above this is not correct. The correct mortality rate is 2.5/100PYO or 2.5% per annum.

I respond to the reviewer’s comment as follows:

The figure was calculated as the proportion of deaths among the smear positive patients followed as shown on page 8 paragraph 4 line 2 reads as follows: Thirty three of 428 patients (7.7 %, 95%CI: 5.2% - 10.2) with smear-positive patients. I have changed the mortality rates in the texts according to the rates calculated in table 2.

The revised part of the results on page 9 paragraph 2 line 3 now reads:

The mortality rate was 2.46% per annum (64/2602.06)....
The reviewer’s comment: Discretionary Revision

4. Same page, Para 3, line 1 says IR of death as 5.7/100PYO. To be corrected as 2.5/100pyo.

I respond to the reviewer’s comment as follows:

IR of death was changed to mortality rate and 5.7/100PYO was changed to 2.46/100PYO as shown in table 3.

The reviewer’s comment: Discretionary Revision

5. Page 9, para 4, line 1 says similar study report from India but the study is not referred. Which study is being referred? Give reference.

I respond to the reviewer’s comment as follows:


The reviewer’s comment: Discretionary Revision

6. Page 10, para 2, limitations should include exclusion of cases with other treatment outcomes for the study.

I respond to the reviewer’s comment as follows:

The fact that exclusion of TB cases with other outcomes on mortality is valid. However, the scope of the study was to measure the long term efficacy of DOTS in TB patients
successfully treated. Thus, I did not include the limitation as it does not indicate the long-term efficacy of DOTS.

The reviewer’s comment: Discretionary Revision

7. The study findings have to be discussed rather than comparing with other study results.

I respond to the reviewer’s comment as follows:

I have added more details to the general discussion of the study as shown above under essential revisions.

The reviewer’s comment: Discretionary Revision

8. Conclusion should relate to this study objectives and findings. It mentions that Tb treatment has improved the survival of patients. Show evidence. The authors refer to patients occupationally associated with HIV. What are the occupations? Conclusion has nothing to do with the study findings. Completely rewrite relevant conclusions for this study.

I respond to the reviewer’s comment as follows:

The occupation described as non-farmers was explained in the methods and also discussed under discussion. It includes merchants, x-soldiers and employees of government or private sectors. The conclusion was rewritten as follows

The revised part of the discussion on page 12 paragraph 4 line 1 now reads:

Eleven percent of successfully treated TB patients either had recurrence or died. The morality rate was high in TB patients compared to the general population. High mortality
in non-farmers indicates that these patients could benefit from improving performance of TB programme and HIV prevention and control measures.

**The reviewer’s comment: Discretionary Revision**

9. Table 2: different variables have different totals. Should have same totals. Recurrence PYO column not required. IR of recurrence to be replaced by Recurrence Rate per 100 PYO. Age variable has only one row and no reference group.

**I respond to the reviewer’s comment as follows:**

The difference in the totals was due to study participants censored at different periods of follow up and few missing variables. IR of recurrence was replaced by Recurrence rate per 100PYO as suggested. Age was analyzed as a continuous variable that was why it appeared without reference group (valid option for continuous variables).

**The reviewer’s comment: Discretionary Revision**

10. Table 3: The comments for table 2 applies to Table 3 also.

**I respond to the reviewer’s comment as follows:**

The difference in the totals was due to study participants censored at different periods of follow up and few missing variables. IR of death was replaced by mortality rate per 100PYO as suggested. Age was analyzed as a continuous variable that was why it appeared without reference group (valid option for continuous variables).
11. Table 4: Age category can be grouped into two or three groups. Table should be rewritten as mentioned in the comment on calculation of SMR.

**I respond to the reviewer’s comment as follows:**

I have rewritten the table as per the comment of recalculating the SMR. However, I kept the age-group for better understanding in each age group.

**The reviewer’s comment: Discretionary Revision**

12. Figure 3: The curve shows follow-up up to 8 years. The text says average follow-up period was 3.59 person years. How many patients were followed up in each group and how long? Show the numbers followed up for each group in the figure. The text and the figure do not match.

**I respond to the reviewer’s comment as follows:**

The perceived mismatch was explained as follows. The mean and total PYO refer to different values. The actual follow up period was nine person-years (1998 to 2006, including patients from 1998 that were treated in 1997). Thus, the follow-up of 9 person-years indicates the longest period of follow-up.

*The number of patients followed-up was added below figure 3 as it appeared below.*

<table>
<thead>
<tr>
<th>PYO</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (died or recurrence)</td>
<td>27</td>
<td>11</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>percent</td>
<td>3.7%</td>
<td>1.7%</td>
<td>1.5%</td>
<td>2.8%</td>
<td>3.0%</td>
<td>3.6%</td>
<td>2.2%</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>Withdraw</td>
<td>40</td>
<td>112</td>
<td>105</td>
<td>104</td>
<td>93</td>
<td>96</td>
<td>59</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Patients followed</td>
<td>723</td>
<td>656</td>
<td>533</td>
<td>413</td>
<td>297</td>
<td>195</td>
<td>92</td>
<td>31</td>
<td>5</td>
</tr>
</tbody>
</table>
Reviewer #2

Reviewer Name: Donald A Enarson

The reviewer’s comment: Major compulsory revisions

1. It would appear from peripheral comments that the treatment given was 8-months’ duration. However, the actually treatment applied is never specified.

I respond to the reviewer’s comment as follows:

I have added one sentence describing the duration of TB treatment.

_The revised part of the methods on page 5 paragraph 3 line 1 reads now:_

TB patients received two months intensive phase and six months continuation phase treatment.

The reviewer’s comment: Major compulsory revisions

2. Clearly a major co-variate in this setting is HIV infection but this was not measured in the patients.

I respond to the reviewer’s comment as follows:

HIV testing was not offered to TB patients because of unavailability of HIV testing in the study area at the time the study was conducted.

The reviewer’s comment: Minor essential revisions

1. Introduction, para 2: The authors state that ‘DOTS has improved treatment success’. However, Cochrane reviews indicate that there is not sufficient evidence to attribute this improvement to DOTS per se.
I respond to the reviewer’s comment as follows:

Decentralization of DOTS has improved access to patients and improved treatment adherence. The sentence was edited as follows.

*The revised part of the introduction page 3 paragraph 2 line 1 now reads:*

Decentralization of DOTS service has increased the number of successfully treated TB patients.

The reviewer’s comment: Minor essential revisions

2. Introduction, para 3: The authors state that ‘there are only a few follow up study’. There are, indeed, more than those quoted, not even taking into account clinical trials that always have follow up.

I respond to the reviewer’s comment as follows:

I have replaced the phrase ‘there are only few follow up studies’.

*The revised part of the introduction on page 3 paragraph 3 line 1 now read:*

…Post-treatment studies conducted on treated TB patients reported high mortality (24 %) and recurrence rate (36 %) after 22 months of follow up…

The reviewer’s comment: Minor essential revisions

3. Study Design: It is not stated if this study included only patients who had previously not been treated (so-called ‘new’ cases) or if it included all cases (including retreatment cases).

I respond to the reviewer’s comment as follows:
The study participants were TB patients that were successfully treated both new and retreatment cases.

*The revised part of the methods under study design on page 4 paragraph 3 line 2 now read:*

We enrolled new and retreatment cases that either were cured or completed their treatment under DOTS programme from 1998 to 2006 by conducting house-to-house visit.