Author’s response to reviews

Title: Risk factors for non-cure among new sputum smear positive tuberculosis patients treated in tuberculosis dispensaries in Yunnan, China

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Author’s response to reviews: see over
Comments
This study attempts to identify factors leading to TB treatment failure in rural China. Its strengths are prospective data involving a sizeable patient population. The main new information provided is that family members, and other lay people in the community can act effectively as treatment observers instead of health care workers. However, there are major concerns regarding this report:

As this study looks only at DOTS, I suggest changing the title to ‘Risk factors for unsuccessful directly observed treatment short-course regimen among new sputum smear positive tuberculosis patients in Yunnan, China’.

As was evident from our results, not all patients were indeed treated under direct observation. As suggested by the other reviewer, we changed the analysis to assess risk factors for non-cure instead of unsuccessful treatment outcomes. Therefore we have changed the title to ‘Risk factors for non-cure among new sputum smear positive tuberculosis patients treated in tuberculosis dispensaries in Yunnan, China’.

The authors describe unsuccessful treatment as treatment failure, death or default. Treatment failure can be a) immediate failure with persistence of smear positivity, and b) relapse of TB after apparently successful treatment within a finite period (usually 5 years). It is not clear from this study as to how many patients had lack of response with persistence of smear positivity and how many had a subsequent relapse. Did the patients go through a period of follow-up after completing course of treatment?

In this study only outcomes as registered directly at the end of treatment were included, so relapse cases were not included. We have clarified this in the background and methods section.

The authors state that there is no data available on drug-resistance. This could explain a proportion of treatment failure cases. Some of these cases would fall under the category of relapsed TB with retreatment. This is unclear in this report. The study targets 26 counties with known high treatment failure rates. Although this is a reasonable approach, there may also be significant differences between these counties and the larger number of other counties showing better outcomes, in terms of levels of education, earnings, health care resources, and public awareness of the services available for diagnosis and management of TB. A comparison, therefore, of failing counties and successful counties could give more valuable insight into factors leading to treatment failure.

The information that we could collect per county that was relevant for a comparison was on the gross domestic product (GDP) and number of health care workers. Both the average GDP and number of health care workers per population was lower in the 26 counties included in this study than in the other counties in Yunnan province. We have included this information in the discussion section of the manuscript.
The outcome of fewer treatment failures among those who missed doses of <2 weeks as compared to those who did not miss a single dose is unexpected. The authors speculate that this could be due to those who died during the treatment period. To support this statement, the compliance with therapy for those who died should be compared with those who survived. Although there are 2 tables attached to the manuscript, there are no references to these tables given in the text. Thank you for this suggestion. We compared the proportion of patients that had not missed any doses among those who had died or failed treatment and among those that were cured (92% versus 95%) and added this information to the text.

There are several errors in the list of references and refs 10 and 31 are the same. We corrected the errors in the references and deleted reference 31.

Table 1 is very large and some of the comparisons given do not add much to the results, such as:
a) breakdown of age into 4 bands, b) income divided into high, medium and low, c) delay in seeking health care broken into <30, 30-59, and >60 days, and d) family attitude categorised as supportive, indifferent and less supportive. The breakdown of these parameters should be simplified as:
- age: <30 vs >30 yrs
- income: low vs medium or high
- delay in health seeking: <30 vs >30 days
- family attitude: supportive vs not supportive
The category for each parameter which is used as control for estimating RR should be given on top preferably in bold, and clarified by a statement beneath the table. This will make the table more meaningful and easier to follow. The obvious controls for different parameters are:
Age < 30 yrs
Secondary school or higher education
Medical insurance – yes
Income – high
Co-morbidity – no
Patient delay < 30 days
DOT – by healthcare staff
Baseline sputum smear status <2
Sputum smear at 2 months – negative
Side effects – no
 Interruption of treatment – no
Number of missed doses – none
Drugs taken as per guidance – yes
Patient aware of attending CDC for check-ups – yes
Patient aware of duration of therapy – yes
Patient realises the need for DOT – yes
Family attitude – supportive
Each given p value should follow the parameter and its category in question. We redid the analyses with the suggested categorization and reference groups. We only kept the categorization of income in three groups considering the fact that there was a trend towards lower proportions of non-cure in the group with high income only compared to those with medium and low income.
To make reading of the tables easier, we wrote all variable descriptions in bold.
We show the overall p-value for the variable, not the p-value per category, as the overall p-value is used to select variables included in the multivariate analysis. As described in the methods section, all variables with a p-value <=0.2 are included in the initial multivariate model. The final multivariate model is determined by backward selection of the model.

Table 2: The parameter of patient delay should be reduced to 2 categories of <30 days and >30 days as there is no difference between the effect of delay of 31-59 days and >60 days. A third column of ‘p value’ should be added, as some of the parameters seem statistically more significant than others.

In the results on the multivariate analysis, we had given 95% CI only as from these it can be deduced whether the OR is significantly different from 1. In the revised version, we added p-values.

Other minor points:
Title page
Change ‘the Netherlands’ to ‘The Netherlands’ Done

Abstract
Results, line 4 – change ‘health care seeking delay to ‘delay in seeking health care’ Done
Background
para 1, line 4 – add a reference to the statement, ‘The targets for case detection and treatment success are 70% and 85% respectively’ Done
para 3, last sentence – rephrase as ‘The influence of this approach on treatment outcomes in not known’ Done

Methods
Page 4, para 1, line 1 – change ‘Out of the total’ to ‘Out of a total’ We removed this sentence altogether due to duplication of information.
Page 4, para 2, last line – change ‘required’ to ‘taken’ Done
Page 4, para 4, line 8 – change ‘knowledge on TB treatment’ to ‘knowledge of TB treatment’ Done
Page 5, para 1, line 1 – change ‘Information on chest X-ray’ to ‘Information on chest radiograph’ Done
Page 5, para 4, last line – change ‘Yuan equalled’ to ‘Yuan equaled’ Done
Page 5, para 6, last line – change ‘during intensive and continuation phase’ to ‘during both phases’ Done
Page 5, last para – give the name of manufacturer, country and year for the two softwares used. Done
Page 6, line 4 – change ‘participants and non-participants’ to ‘participants and non-participants registered and treated by the TB dispensaries at the local CDCs’. We changed this to ‘participants and non-participants registered and treated by the TB dispensaries at the local CDCs’.

Results
Page 6, last 2 lines – add the actual numbers to the percentage figures The numbers are in Table 1. To avoid duplication we did not add the numbers but referred more clearly to the Table where the numbers can be found.
Page 7, 1st para – add the actual figures to all the percentage figures given Idem.
Page 7, 2nd para, line 2 – change ‘health seeking’ to ‘seeking health care’ Done
Page 7, para 2, line 3 – I presume the figure of >2+ refers to the average number
of bacilli seen under a high power field. If so, this should be added. *We added this information to the definitions in the methods section.*

**Discussion**

Page 8, para 1, line 3 – change ‘did know’ to ‘knew’ *Done*

Page 8, para 1, line 6 – add a ref to the statement ending in ‘18% for Yunnan province in 2007’ *These are unpublished results but retrieved from the registration system. We made clear that these are unpublished data.*

Page 8, para 3, last line – change ‘compared for those’ to ‘compared to those’ *Done*

Page 9, para 1, last sentence – extend this sentence to ‘A prerequisite is that they are trained well, and they remain motivated and committed to the programme’ *Done*

Page 9, para 3, last sentence – change ‘have’ to ‘has’ and remove the word ‘before’ *Done*

Page 9, para 4, first sentence – rephrase as ‘Our study has a number of limitations’ *Done*

Page 9, para 4, last sentence – re-write as ‘non-participation in this study will have biased our findings significantly’ *Done*

I also suggest a concluding sentence at the end saying ‘More resources and effort are needed to educate the general public to enable them to act effectively as community-based observers of DOT.’ *Done*

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**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.
Reviewer's report

Title: Risk factors for unsuccessful treatment among new sputum smear positive tuberculosis patients in Yunnan, China

Version: 1 Date: 28 October 2010
Reviewer: Andrew Wilson

Reviewer's report:
General comments by section

Abstract

Use of terms 'treatment success rate' and 'cure rate' is ambiguous (P2 para 1). The initial impression is that they are interchangeable. Treatment success is later defined (p5 para 3) as 'cure and treatment completion', with a WHO target of 85% (p3 para1). P3 para 2 states 24/129 counties with a success rate lower than this target but counties with cure rate <85% (26/129) are used for data collection. It would be better to examine “cure” not “success”.

We agree and redid the analyses with ‘non-cure’ as outcome instead of ‘unsuccessful treatment outcome’, hereby excluding the 5 patients who completed treatment but did not have bacteriological proof of cure. According to the internationally accepted definition, patients who completed treatment but did not have a smear examination result registered, and did have no signs of failure are considered to be treated successfully. Therefore, we excluded these patients from the analyses. We did mention in the results section that inclusion of these patients in the group with successful outcomes did not affect the results.

The background should describe what is already known about the research question (as discussed in the introduction of the main paper). The research aim is mentioned in the background not the methods section. There is duplication in the background and method section. The study type is appropriate for the research question. The finding that interrupted treatment is associated with better outcome is not mentioned in the abstract.

We adjusted the abstract taking into account these comments. We removed duplication in the background and methods section. The author guidelines dictate that the purpose of the research should be mentioned in the background section so we kept it there. We did not mention the finding that interruption for less than two weeks was associated with cure as we feel that there are explanations to explain this; however, there is not sufficient space to detail these explanations in the abstract.

Background

P3 para 2: It would have been interesting to contrast with other regions in China/national figures to set the study in context and provide an indication of generalisability. It is not clear why this province was chosen in preference to others. The staff of the provincial CDC of Yunnan perceived the observed number of counties with a relatively low cure (treatment success) rate as a problem and instigated a study to look into reasons for this low cure (treatment success) rate. We tried to clarify this in the text. Unfortunately we were not able to collect data on the proportion of counties per province with a cure rate <85%, to compare those with Yunnan.

Literature review – found over various sections, may be better organised into this
We rearranged the background according to this suggestion.

Methods
Sample size calculation seems adequate. I suggest that “cure” is used rather than “successful treatment” as the later does not include many more patients. Patient who completed the treatment but are not cured cannot be considered to have a successful outcome. Sticking to “cure” would be less confusing and would probably not change the results.

We agree and redid the analyses as described above.

Results
P7 para 3 line 4 – ‘….refusal of direct observation of taking drugs (table 2).’
Presented in table 2 as ‘Patient not seeing the need for treatment observation’ does not equate to refusing observation.

We corrected this.

Discussion
P9 para 2 first sentence. Poor readability + introduces new information which may have been better in the ‘background’ section. (p8 para 3 last sentence) It seems a major issue that interruptions in treatment increase the chance of successful treatment. Do those with interruptions received DOT? I am not sure what new information this study brings.

We rewrote this paragraph and moved the information on drug resistance being a risk factor for failure to the background section. Those with a health care worker as DOT observer (the preferred situation) less often interrupted than those without DOT observer: 92% versus 78%.

Major compulsory revisions
Assessment of “cure” rather than treatment. Done
Remove duplication of data in results and in table. Done
First paragraph of discussion to state the new information that this paper provides. Done
We rewrote the first paragraph based on this suggestion.

Minor essential revisions
Modification of abstract layout. Done.
There are several typographical errors. We aimed to correct all errors.

Discretionary Revisions
None

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests