Author's response to reviews

Title: Deaths among tuberculosis cases in Shanghai, China: Who is at risk?

Authors:

Xin Shen (shenxin1977@hotmail.com)
Kathryn DeRiemer (kderiemer@ucdavis.edu)
Zheng’an Yuan (zayuan@scdc.sh.cn)
Mei Shen (mshen@scdc.sh.cn)
Zhen Xia (zhen.xia@live.cn)
Xiaohong Gui (jiehe3@scdc.sh.cn)
Lili Wang (laura6699@hotmail.com)
Jian Mei (jiehe2@scdc.sh.cn)

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Author's response to reviews: see over
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Authors:

Xin Shen: shenxin1977@hotmail.com

Kathryn DeRiemer: kderiemer@ucdavis.edu

Zheng’an Yuan: zayuan@scdc.sh.cn

Mei Shen: nshen@scdc.sh.cn

Zhen Xia: xia.zhen@live.cn

Xiaohong Gui: jiehe3@scdc.sh.cn

Lilli Wang: laura6699@hotmail.com

Jian Mei: jiehe2@scdc.sh.cn

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Author’s response to reviews: see over
Title: Deaths among tuberculosis cases in Shanghai, China: Who is at risk?

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Dear Editor,

Thank you very much for the comments from the reviewers and the editorial office on our manuscript. We are now submitting our revised manuscript for your consideration to be published in the *BMC Infectious Diseases*. We have revised our manuscript in accordance with the reviewers’ suggestion. In the accompanying pages, we provide a point-to-point response to the concerns of the reviewers.

Yours sincerely,

Jian Mei, MD, PhD
Department of Tuberculosis Control
Shanghai Municipal Center for Disease Control and Prevention
1380 West Zhongshan Road
Shanghai 200336, China
Telephone: + 86(21)6278-1851
Fax: + 86(21)6278-1851
Email: jiehe2@scdc.sh.cn
Reviewer: Christie Jeon

Version: 1 Date: 10 January 2009

Reviewer’s report:

I have had the pleasure of reviewing the article by Shen et al, titled “Deaths among TB cases in Shanghai, China: Who is at risk?” submitted to BMC Infectious Diseases.

TB remains a major source of morbidity and mortality in the world and China ranks second in the burden of TB in the world. As little is known about causes of mortality among TB patients in China, this article takes a valuable step forward in elucidating the relationship between major risk factors and TB mortality in Shanghai, China. The study was well-powered to be able to detect weaker associations that smaller studies wouldn’t be able to capture.

The study however was limited in that several specific risk factors of interest were missing or otherwise combined into a larger category. For example, HIV/AIDS, malnutrition, diabetes have all previously been considered to be predictors of poor treatment outcome but to different degree. Further, MDR TB status was missing in a high proportion of the cases. Furthermore, the study could have employed a method of analysis that take person-time into account by either proportional hazards analysis or Poisson regression. The discussion could have explained the results and the apparent discrepancies with existing literature more thoroughly.

Response: As described in detail below, the study performed retrospectively and we were not able to collect detailed information about specific potential risk factors such as HIV/AIDS, diabetes, and malnutrition among the TB patients. We did perform proportional hazards analysis as well as multivariate logistic regression, and chose to present the results of the logistic regression models.

Major compulsory revisions:

Introduction:

1. It is interesting to read that TB mortality in Shanghai is markedly higher than in the rest of China. Does your finding agree with this figure? What would be the reason for the difference and how does it compare to other countries? Perhaps you could comment on this in the
Discussion.

Response: Yes, the case fatality rate of total new smear-positive cases in China was 1.7% (WHO TB Report, 2008), which was lower than that of our study population (5.5%). We explained the high TB case fatality rate as the result of an aging population. In Shanghai, 11.5% of the population was ≥ 65 years old in 2000, a much higher percentage than the national average (6.9%). We thank the reviewer for their comment, and added to the Discussion section, “A larger aging population and longer lifespan could be one of the reasons why the case fatality rate of TB cases was higher in Shanghai.”

Methods

2. If possible, it would be very informative to the reader to have a finer group of comorbidity, such as: HIV/AIDS, diabetes, cardiovascular disease, cancer, COPD, other infectious diseases.

Response: We thank the reviewer for this suggestion. Since this is a retrospective study, we were not able to collect precise information about the exact comorbidities. However, one of our ongoing studies shows that the prevalence of HIV among TB patients in Shanghai is very low (<0.1%). We assumed that HIV was not significantly associated with death among TB patients in Shanghai. We discussed the limitations of the data in the revised manuscript.

3. What was the treatment regimen for the MDR TB patients? Were these then followed-up for a longer period of time (as their regimen would have been longer)?

Response: Individualized therapies were given to MDR TB patients based on the patient’s physical and financial situation, the drug-susceptibility pattern of the infecting strain of *M. tuberculosis*, and the clinicians’ experience. The following drugs were used, in different combinations: two injectable second-line drugs, including capreomycin and amikacin; fluoroquinolones, including ofloxacin, levofloxacin, gatifloxacin, moxifloxacin and ciprofloxacin; and 4-aminosalicylic acid. In Shanghai, all TB patients are followed after they initiated anti-TB treatment until they stopped treatment for any reason. The duration of follow-up depended on the prescribed treatment regimen and the patient’s response. For example, new patients infected with drug susceptible *M. tuberculosis* received 6 months of a
standardized regimen and were followed for just 6 months, but MDR TB patients were followed for a longer period because they received a longer treatment regimen.

4. Were the retreatment cases followed up for a longer period of time? If so, I think it’s important to state average time of follow-up by previous treatment, as with longer follow-up you may find more non-TB associated deaths.

Response: Yes, the follow up period for each TB patient depended on the treatment regimen. Retreatment patients required a longer treatment regimen and were followed for a longer period of time than new patients. In our study, the mean follow up period was 212 days for new cases, and 259 days for retreatment cases. However, we did not detect a significant difference between the proportions of non-TB deaths between new cases and retreatment cases. Among new cases, 49.8% of all deaths were attributable to causes other than TB, while among retreatment TB cases, 46.7% of all deaths were attributable to causes other than TB (p = 0.4410). We did not present this information in the Results Section of the manuscript.

5. You could also do a stratified analysis and investigate if the predictors of TB-associated deaths are different from that of non-TB associated deaths.

Response: We performed the stratified analysis, as recommended by the reviewer; the results are given below. The predictors of TB deaths are different from the predictors of non-TB deaths, with the exception of age > 52 and male sex. We would like to analyze and compare the differences between TB associated deaths and non-TB associated deaths in a separate manuscript.

Table. Results of the multivariate analysis of the characteristics of tuberculosis patients associated with TB death and non-TB death

<table>
<thead>
<tr>
<th>Variables</th>
<th>TB death vs alive</th>
<th>non-TB death vs alive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age &gt;52</td>
<td>9.3</td>
<td>5.9-14.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.6</td>
<td>1.1-2.4</td>
</tr>
</tbody>
</table>
Presence of cavity on initial chest radiograph  NS  0.7  0.5-0.9  0.011
Sputum smear positive  2.8  1.7-4.8  <0.001  NS
Presence of comorbidity  NS  1.8  1.4-2.4  <0.001
MDR  2.5  1.4-4.6  0.003  NS

*AOR = Adjust odds ratio, CI = confidence interval; NS = Not significant; MDR = multidrug-resistance.

Discussion
6. Perhaps you could include a discussion of why cavitation was inversely associated with mortality, while a smear positivity was positively associated with mortality.

**Response:** In univariate analysis, cavitation was inversely associated with mortality, but in the multivariate analysis cavitation was not independently associated with mortality. This finding could be due to bias. In contrast, sputum smear positivity was associated with mortality in both the univariate analysis and multivariate analysis. We discussed sputum smear positivity in the Discussion Section.

Minor essential revision
7. I think “case fatality” or “case fatality proportion” is a more appropriate term than “case fatality ratio.” It would be helpful to know the time frame, during anti-TB treatment? For how many months?

**Response:** We agree with the reviewer’s suggestion, and are using “case fatality rate” in the revised manuscript. “Case fatality rate” was widely used in previous papers.

Discretionary revisions:

Introduction
8. It is helpful to know how densely populated Shanghai is, perhaps you could give a comparison, say New York, Paris, or Hong Kong.

**Response:** We thank the reviewer’s comment, and provided the population density in the Methods Section, under the sub-heading “Study area.”
Methods

9. It’s great that you’ve looked into interactions. Which two-way or three-way interaction did you investigate?

**Response:** As we described in the “Statistical analysis” section: We tested the interaction between those variables that had a \( p \) value < 0.05 in the multivariate model, and kept the interaction terms in the multivariate model if they were significant (\( p < 0.05 \)). We tested the interaction of age*male, age*sputum smear, age*comorbidity, male*sputum, male*comorbidity, and sputum*comorbidity. But none of the two-way interaction terms were significant, independent predictors of TB deaths in the multivariate model. Therefore, we didn’t test any three-way interaction terms.

10. I think age categorization could be finer than \( \leq 52 \) and \( > 52 \). It would also be interesting to know if further increase in age is associated with mortality among the elderly (\( > 60 \)). It may be helpful to describe the relationship between age and mortality with spline regression and try to see if there is a non-linear relationship.

**Response:** We did not use spline regression models. Table 1 shows the increasing proportion of deaths with increasing age, and the high proportion of elderly (\( \geq 60 \) years old) among all TB patients in the study.

11. In addition to logistic regression, I think it may also be useful to do Poisson regression or Cox regression which takes person-time into account. This makes more optimum use of data, as time to death (or censoring) matters and follow-up time may not have been even between the individuals. With this method you could also incorporate the individuals who defaulted or transferred, because at least until they became lost to follow-up you know that they were alive.

**Response:** Yes, we performed the Cox regression considering the variable duration of treatment for each TB patient. Similar risk factors were identified in the Cox regression model except comorbidity. However, the model didn’t satisfy the assumption of proportionality very well, the goodness of fit of the model was not good, and we opted to not
present the Cox regression results in the manuscript. Below are the results of our Cox regression modeling.

Table. Results of Cox regression of the characteristics of tuberculosis patients associated with death in Shanghai, 2000-2004

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted HR</th>
<th>(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;52 years</td>
<td>10.1</td>
<td>(6.6-15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.6</td>
<td>(1.1-2.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>Sputum smear positivity</td>
<td>2.5</td>
<td>(1.5-3.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HR = hazards ratio; CI = confidence interval
Reviewer: Jay K Varma
Version: 1 Date: 19 January 2009

Reviewer’s report:
Major Compulsory Revisions
Abstract/Background
1. “This study is sought to identify individuals who are at higher risk of death.” In fact, the study compared individuals that died to those that did not die. The sentence should be re-rewritten to say: “This study sought to identify characteristics associated with increased risk of death.”
Response: We agree with the reviewer’s comment, and changed the sentence accordingly.

Abstract/Results
2. Use the term “rate” not “ratio” for deaths, because you are comparing “number of persons that died” to the “number of persons that were enrolled.”
Response: We agree with the reviewer’s comment, and are now using the term “case fatality rate” in the revised manuscript.

Abstract/Conclusions
3. The conclusions are quite weak. These could have been written without any study being conducted. The authors should write conclusions that extend directly from the results. How can the study’s findings about advanced age or smear positivity or co-morbidities directly translate into interventions right now?
Response: We agree with the reviewer’s comment, and changed the text in the Abstract’s Conclusions and in the Discussion Section.

Methods
4. A brief justification should be added about why the authors chose to restrict their analysis to culture-positive cases and not study bacteriologically positive (smear or culture positive) cases.
Response: There are several reasons why we just selected culture positive cases in our
analysis: (1) Culture remains the “gold standard” for TB diagnosis, not sputum smear positivity because the latter can also be caused by other species of mycobacteria. (2) Because MDR was a strong predictor of TB deaths in other studies, we wanted to determine whether MDR was associated with death in our study population. Mycobacterial culture was essential to perform the traditional drug susceptibility tests that were used in our study. (3) During the study period, the concordance between sputum smear and culture in Shanghai was high (> 85%). We thank the reviewer for the suggestions, and added the sentence under the subheading “TB surveillance”: “As culture remains the “gold standard” for TB diagnosis, and is essential for traditional drug susceptibility testing, we used all culture-positive pulmonary TB patients among local residents reported in Shanghai during 2000-2004, as our study population.”

5. Is the sputum smear positive definition two of three smears positive or any smears positive? If using definitions identical to the WHO definitions, the authors can just say so and don’t need to explain the definition.

Response: Yes, we used the WHO definition of sputum smear positivity. In the manuscript, we refer to the WHO definitions (Reference #13).

6. I have some concerns about the definitions used for cause of death and the exact follow-up that occurred. The authors write: “The cause of death was determined based on the treatment outcome monitoring. TB death was defined as a TB case whose treatment outcome was recorded the cause of death as caused or contributed by TB. All remaining deaths were defined as non-TB deaths… In the present study, follow-up was censored at one year after treatment.” My concerns are:

(a) The WHO definition of a TB death is standardized and widely accepted: Any death that occurs during TB treatment is a TB death. Deviating from this definition is acceptable if there is highly reliable cause of death data (e.g., autopsies) or the cause of death was indisputably not TB related (e.g., traffic accident). For this study, what assurances exist that TB program staff at the local level can accurately adjudicate when a cause of death is TB related or not TB related? Death certificate data, if it was used, is highly unreliable in every setting in which it
has been evaluated. Do the results remain the same when the WHO definition is used (all deaths during TB treatment are TB deaths)?

Response: In this study, we determined the cause of death from death certificate data. We agree with the reviewer that death certificate data is, at least in part, unreliable. However, in Shanghai, a death registration system was established during the 1990s based on the International Classification of Disease (ICD) of the World Health Organization, to classify the causes of death. Although the TB registry was separate from the death registration system in Shanghai, the death reports of these two systems are conducted by same local institutes, except that the TB registry doesn’t record the actual cause of non-TB deaths. We could not exclude the possibility of misclassification of TB deaths or non-TB deaths, but this misclassification should be minimized by the death registration system. We thank the reviewer’s comment to clarify our death data, and we added additional information describing the limitations of the death certificates in the Discussion Section. In the univariate and multivariate analysis, we identified the factors associated with all deaths (TB death + non-TB deaths).

(b) I am not clear what the exact follow up was. Does this mean that all patients were followed during TB treatment and then for one year after TB treatment? The results section makes it sound as if all patients were followed up for one year after they initiated treatment rather than “one year after treatment”. Is it standard practice for the Chinese national TB program to follow TB patients for 6 months (6 months of treatment + 6 months after treatment = 12 months treatment) after treatment? If so, the nature and duration of follow-up after TB treatment should be described, since this is not normally done in other high-burden TB countries.

Response: We apologize for the confusion about the patient follow-up in the first version of the manuscript. To clarify, all TB patients in Shanghai are followed up after they initiate treatment and until they stop treatment for whatever reason. The duration of follow-up depends on the treatment regimen. For example, new patients infected with drug susceptible *M. tuberculosis* receive 6 months of a standardized treatment regimen and are followed-up for just the 6 months that they are on treatment. However, MDR TB patients receive
long-term treatment and are followed for a longer period during that treatment. In this study follow-up was continued for those who were treated for more than 1 year, but the data was censored at one year. TB patients who required a treatment regimen of more than 12 months were excluded from the analysis. We did not perform any follow-up of the patients once they stopped their treatment. We modified information in the Methods Section to clarify this point.

7. What is “serious H. pylori infection”? Are the authors referring to peptic ulcer disease and characterizing “severe” as upper gastrointestinal bleeding? I am not aware that there is a standardized, clinically relevant definition of “severe” H. pylori infection — the severity of infection is measured by the clinical presentation (symptoms, hemorrhage, gastric cancer, etc) and H. pylori is a causative agent in some, but not all, ulcers.

Response: Yes, we defined serious H. pylori infection as measured by clinical presentation, such as upper gastrointestinal bleeding. Since the definition is not standardized and is confusing, we deleted mention of H. pylori infection in the manuscript. We thank the reviewer for the suggestion.

8. The statistical methods are appropriate if follow-up was identical for all patients, e.g., using the WHO definition of death during treatment as a TB death and follow-up extends only as long as treatment does. If follow-up occurred after TB treatment and/or the duration of TB treatment varied, then a proportional hazards analysis should be done.

Response: Follow-up was identical for all patients. We used the WHO definition of death during treatment as a TB death, and follow-up extended only as long as treatment does. We also performed Cox regression modeling to consider the variable duration of treatment for each TB patient. Similar risk factors were identified in the Cox regression models and logistic regression models, with the exception of the variable for comorbidity. However, the model didn’t satisfy assumption of proportionality very well, and the goodness of fit of the model was not good. We chose to not show the Cox regression model results in the manuscript. The results of Cox regression is below.

Table. Results of Cox regression models of the characteristics of pulmonary TB patients
9. How were missing values handled? Was data highly complete (>90%) for most variables? (Data on MDR is presented later so it’s clear later on that a complete case analysis was done to handle missing MDR data).

**Response:** In this study, the proportion of missing data is very low for variables other than MDR TB. The observations with missing data (6.6%, 526/7999) were excluded in our multivariate analysis.

10. What methods are used for culture? How many sputum specimens are routinely tested?

**Response:** Lowenstein-Jensen (L-J) solid medium are routinely used for sputum culture in Shanghai. Three pretreatment sputum specimens were routinely collected, among which one is selected for culture.

Results

11. How were patients with treatment failure analyzed? Figure 1 makes it seem as if no patients failed initial TB treatment. This seems impossible given the rate of MDR in the study population. Were failure patients grouped in with the comparison group (those that lived)?

**Response:** In our study, we didn’t use the term “treatment failure.” TB patients who were treatment failures, according to the WHO definition, continued receiving therapy but with a retreatment regimen. Patients with a treatment failure were classified as patients who were still on therapy, or, if they died during therapy, they were classified as a TB death. We could not identify treatment failures in our database.

12. Were other patterns of resistance analyzed? For example, INH monoresistance or RIF
monoresistance? Would be worth mentioning that these were analyzed and found not to be risk factors for death?

**Response:** Yes, we analyzed other patterns of resistance besides MDR. None was found to be significantly associated with death.

13. What percentage of patients were HIV-infected? HIV is the most powerful risk factor for death among TB patients. If there is no data about HIV status, this should be stated in the results and the highlighted as an important limitation in the Discussion.

**Response:** In our study, HIV status was not available. However, another ongoing study in Shanghai shows that the prevalence of HIV among TB patients is very low (<0.1%). We assumed HIV was not significantly associated with death among TB patients in Shanghai. We discussed this limitation in the revised manuscript.

14. The authors presented the age cutoff using the median yet present data in Table 1 using categorical age categories. Why not use the categorical age categories for the analysis? These are likely to be epidemiologically more meaningful than simply using the median age of the study population.

**Response:** We used median age as the age cutoff in the univariate and multivariate analysis because there were fewer deaths among the younger groups (aged 11-14, 15-29 and 30-44). If we used same age categories of Table 1 for the multivariate analysis, the statistical power to detect a significant association between age group and death, decreased.

15. Table 3 is unnecessary since only 4 factors are presented and this can easily be summarized in the text.

**Response:** We agree with the reviewer’s comment, and integrated Table 3 into Table 2.

Discussion

16. The authors devote the entire second paragraph of the Discussion to the issue of what proportion of deaths during treatment/follow-up were TB related. This is not appropriate, given that there is no reliable methods or data discussed to let the reader know how
accurately these assessments were made. I would suggest that this section, rather than being a
topic to highlight, should actually be considered a major limitation.

**Response:** According to the WHO definition, any death that occurs during TB treatment is a
considered TB death in the DOTS cohort system. However, deaths that occur during anti-TB
treatment are not always caused by TB. Several previous studies have discussed this
Deaths among TB cases that were due to causes other than TB suggest that TB cases may
require more intensive medical evaluation and care than is usually provided by the traditional
TB control programs. TB control programs should interact with other public health programs,
since such deaths may not be prevented by improvements in the TB services alone. We
recognize that the death certificate data is sometimes unreliable, so we added discussion of
this limitation to the Discussion Section.

17. Other major limitations include the very small number of patient characteristics evaluated
(What about compliance with DOT? What about treatment regimen? What about social or
economic factors? Adverse drug events?) and the lack of data about specific co-morbid
factors, especially HIV infection.

**Response:** We agree that a small number of patient characteristics were analyzed in our study,
and other important characteristics associated with deaths observed in other setting were not
evaluated. As this is a retrospective study, we were not able to collect and analyze other
information on the exact treatment regimen, social or economic factors, and adverse drug
events. We will work to prospectively improve our monitoring system and data collection.

Minor Essential Revisions
[None]

Discretionary Revisions

Discussion

18. I did a quick Medline search to evaluate the authors’ claim to primacy re: first study of
risk factors for death in TB patients. I found at least one other article that looks at factors associated with treatment success, which are, not surprisingly, the inverse of those that are risk factors for death. See: Qing-Song Bao, Yu-Hua Du, Ci-Yong Lu. Treatment outcomes of new pulmonary tuberculosis in Guangzhou, China 1993-2002: a register-based cohort study BMC Public Health, 2007; 7:344. There’s also the well known study from Hong Kong, which admittedly is old and not from mainland China (Allan WG, Snell NJ, Hill LE, Fayers PM, Scadding JG, Fox W. A survey of deaths in Hong Kong attributed to tuberculosis. Tubercle, 1981 Mar;62(1):1-11.)

**Response:** We agree with the reviewer’s comment, and deleted the sentence claiming to be the first study of risk factors for death in TB patients.