Author's response to reviews

Title: Childhood TB epidemiology and treatment outcomes in Thailand: a TB Active Surveillance Network, 2004 to 2006

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Author's response to reviews: see over
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Dear Biomed Central Editors,

Thank you for the reviewing our manuscript (“Childhood TB epidemiology and treatment outcomes in Thailand – TB Active Surveillance Network, 2004–2006”) and providing us an opportunity to revise. Below you will find a point-by-point response to the comments from the reviewers. Where indicated, we have revised the manuscript. The major revisions include that we have re-analyzed and updated the treatment outcome data, as suggested by reviewer #1, and we have excluded patients with a final diagnosis other than TB from the denominators.

Sincerely,

Rangsima Lolekha, MD
Reviewer #1: Dick Menzies
Reviewer’s report:
The authors have undertaken a description of 289 children with active tuberculosis. This represents two percent of the total number of active cases reported in their jurisdiction. They have described clinical characteristics including HIV testing results and treatment outcomes and perform some analysis to look at factors associated with death and default.

Major comments

1. There is no single clear or coherent message. What are the authors trying to convey? Is this paper about HIV testing? Or the impact of HIV in pediatric TB? or is it about treatment outcomes?
Response to reviewer: This paper reports childhood TB epidemiology and treatment outcomes in Thailand as written in the title of this paper. In the final paragraph of background section, we describe the main objective of this paper: “We analyzed data from a multi-province demonstration project to understand characteristics, treatment outcomes, and risk factors for death and default in childhood TB cases.”

WHO has recently called for more studies about the epidemiology of childhood TB in high-burden TB countries, because the literature remains scant, dominated primarily by studies from industrialized countries and South Africa. This paper is the only population-based study about childhood TB epidemiology and treatment outcomes in Asia, a region which contributes to 60% of the global burden of TB but, effectively, to 0% of the pediatric TB literature. As reviewer #4 noted, this paper “contributes to the neglected field of pediatric TB and to the surprisingly poorly documented area of treatment outcomes in HIV-positive TB patients.”

2. Numbers often do not add up, for example Table 1 listed 289 patients but tables 2 and 3 there are only 228 patients.
Response to reviewer: The difference in numbers was due to how outcomes were classified and how patients were deemed eligible for different analyses. We have updated our database and, per the reviewers’ comments, re-analyzed data for patients who were classified as “on treatment” and “missing.” Among 289 patients, 10 patients with an outcome of “changed diagnosis” have now been excluded from the initial analysis. Please see updated data in the Results section and in Tables 1-5. In the updated data, there are 279 patients and numbers are reported consistently.

3. Program results are quite poor, only 57% of children with active TB were cured or completed treatment. This is far from WHO benchmarks.
Response to reviewer: In the updated analysis, 72% of children with active TB were cured or completed treatment. The purpose of this manuscript was not to describe a successful model of TB treatment; rather it was to document the current epidemiology and treatment outcomes of patients in a high-burden TB country. The fact that treatment outcomes do not achieve WHO benchmarks is an important
finding that has never been documented before. Except for reports from specialty referral centers, there are few reports of TB treatment outcomes across populations (e.g., multiple provinces). We simply do not know how many countries have achieved WHO benchmarks for pediatric TB treatment; that is one of the reasons to publish studies such as ours.

4. A few were given another diagnosis; ideally these should have been excluded from the initial analysis, certainly from the cohort treatment result analysis. **Response to reviewer:** We have now excluded 10 patients with “change diagnosis” outcome from the initial analysis and paper.

5. Fourteen percent are still on treatment - really I would suggest that the authors wait until all members of a given cohort complete treatment so they can analyze treatment outcomes completely. **Response to reviewer:** We have updated data as mentioned in #2.

6. Patients who are transferred out without known outcomes should be considered as default particularly in the analysis of factors associated with default. In other studies it has been shown that most patients who "transfer out" actually are lost to follow up and never complete treatment. **Response to reviewer:** In Thailand, we cannot conclude that patients who “transfer out” have “defaulted.” We have found that most patients in this group were transferred to tertiary care hospitals or to hospitals closer to their residence according to their public health insurance. Unfortunately, we do not have outcomes for this group, but it would be incorrect to classify them all as “defaulted.”

7. The 7% whose treatment outcomes are unknown reflects either a group that has also defaulted or lost to follow up, or poor program organization. I would consider this group to be the same as default or transferred out - I would suggest they analyze them as defaulters. **Response to reviewer:** We have updated our database and reported more complete outcomes.

8. In table 3 only 37% of children with meningitis were cured. Although I anticipated that this would reflect very high mortality, in fact it turns out that 67% defaulted or transferred out. This should be explained. **Response to reviewer:** We have now added the following sentences to the Results section: “Of patients with meningitis, 67% had unknown outcomes (6 defaulted; 7 transferred out). All 13 patients with unknown outcome were from one province that borders Burma and has a large population of migrant Thais and non-Thais; 8 (62%) of these were non-Thai migrants.”

9. Table 4 could be dropped; really the only significant finding is that HIV is associated with mortality. The fact that being cared for at a tertiary care center is associated with mortality is hardly surprising considering it reflects selection of the sickest patients who were referred there.
Response to reviewer: We think this table is useful, because some readers like to see the proportions and odds ratios for all variables analyzed. If the editors would prefer that we delete this table, then we can. For now, we have included it.

10. As noted above, table 5 should be reanalyzed and the default group should include patients whose outcome is unknown and patients who transferred out. This would give larger numbers of the default group providing more statistical power and thus may be helpful.

Response to reviewer: We have re-analyzed as mentioned in #2.
Reviewer 2: Alwyn Mwinga

Reviewer's report:
Minor essential revisions
1. The methods section in the abstract seems to indicate that the researchers actively took part in providing care for the patients, however the text in the actual paper seem to indicate that this was a retrospective review of the data. This needs to be clarified. The lack of some information (of diagnosis etc) are a limitation in the paper and detract from the quality of the paper.

Response to reviewer: This is a prospective study. Data was collected prospectively and then analyzed after the reporting period. The detailed methods of this project are described in reference #14 in the revised manuscript (Varma JK, et al. Bull WHO 2007). In this reference, we describe how we strengthened the public health infrastructure, including access to services, but we were not involved in the clinical care of patients.

2. Table 1 - seems to contain all the information of the cases and is not very clear in the way it is set out. Some discrepancies were noted in the figures. An example of this is the difference between the numbers in the category of TB (3 relapse, 1 failure, 3 treatment after default) compared to the numbers given for previously treated TB (18). For chest radiograph, 194 were put as abnormal but the only abnormality mentioned was presence of a cavity for 17. What were the other abnormalities detected.

Response to reviewer: Previously treated TB can be any of these categories: relapse, failure, treatment after default, transfer in, and other. In our surveillance network database, the only data we collected about abnormal chest x-rays was whether or not the x-ray showed a cavity; we do not know what other abnormalities may have been on x-rays. The reason that we collected data only about the presence or absence of a cavity is: (a) we were conducting surveillance so only collected the minimum number of essential data elements; (b) cavities are known to be a predictor of poor TB treatment outcomes (e.g., U.S. guidelines recommend extending the intensive phase in some patients with cavitary TB).

3. It is a little difficult in the way the table is constructed to link the numbers in the treatment category with the treatment given.

Response to reviewer: We did not stratify the data this way, because the vast majority of patients received the recommended regimen for the type of TB that they had (e.g., category I, category II, etc.)

4. The number indicated for knowing the HIV status prior to the TB visit is different from what is mentioned in the text (71 vs 57).

Response to reviewer: In the revised manuscript, the number indicated for knowing HIV status before TB diagnosis is 68 cases (including both HIV positive and HIV negative). Of 75 total TB patients known to be HIV positive, 55 of these knew their HIV status before TB diagnosis.

Generally the table has too much information and should be revised to include
only the relevant information or broken down into separate tables. Some of the information does not need to be presented in this way.

Response to reviewer: Thank you for your suggestion. However, different reviewers have requested to see more variables in the table. If the editors would prefer that we reduce the size of the table by deleting some variables, then we can do so.

5. Tables 2 and 3 focus on outcomes of treatment by age group/HIV status and anatomic site/microbiologic characteristics. Given that 68% had no microbiological data at the onset of treatment, the value of presenting the data on microbiological classification is questionable.

Response to reviewer: Table 2 does not present microbiologic characteristics. Table 3 presents treatment outcomes for childhood TB cases, categorized by anatomic site and/or microbiologic characteristics. Very few patients with childhood TB have microbiologically-confirmed TB, because of limitations in specimen collection and because TB culture is not routinely available in resource-limited settings. We chose to report the information for those with confirmed TB, to demonstrate that the treatment outcomes for those with confirmed disease were similar to those without confirmed disease. This provides reassurance that the diagnosis of TB in patients without confirmed disease was appropriate.

6. Tables 4 and 5 - it is not clear what is meant by referent and hence it is difficult to comment further on these tables.

Response to reviewer: The term “referent” is used, because statistical analysis requires that one level of the variable serve as the comparison group. For a calculation of odds ratio, the referent group has an odds ratio equal to 1.

7. As the paper mentions that physicians used their discretion to do CD4, provide treatment for OI or prescribe ART and given the high death rate in HIV infected individuals, perhaps the authors should consider a recommendation to standardize the approach to treatment for HIV infected TB patients.

Response to reviewer: Thailand has national standardized guidelines for the treatment of HIV-associated TB, but a non-surprising finding is that patients in the real world do not always received treatment according to guidelines. We have added one sentence in the discussion page 18: “Our data shows that despite national TB and HIV treatment guidelines, coverage of some key aspects of TB and HIV care was low.”

8. It is not clear why the gastric lavage specimens were classified as sputum given the different sensitivities of direct smear examination sputum and gastric lavage.

Response to reviewer: In this surveillance database, there is no separate gastric lavage variable. However, some providers sent gastric lavage specimens for AFB stain. The gastric lavage specimens with positive AFB stains were classified as sputum-smear positive, but, if negative, they were not reported. There are no clear guidelines for how to characterize gastric lavage specimens in WHO guidelines and in Thailand. Routine program practice in Thailand and in many countries is to
classify patients with AFB-positive gastric lavage specimens as sputum smear-positive, because it is assumed that the gastric contents are derived from the sputum. Hence, for the purposes of our surveillance system, we used this coding system. We have added one sentence to the Methods to explain this: “Gastric aspirate specimens were classified as sputum specimens, in accordance with the routine TB program practice of classifying patients with abnormal chest radiographs and AFB-positive gastric aspirates as having smear-positive, pulmonary TB.”
Reviewer 3: Wendy Wobeser

Reviewer's report:
Discretionary revisions

Additional comments from the authors regarding the potential impact of BCG on low rates of meningitis would strengthen the paper. There is no specific mention of meningitis, however, given the very low mortality and extrapulmonary cases among those less than 4 years of age, it would appear that the rate is unexpectedly low.

Response to reviewer: We have added the following sentences to the discussion on page 17: “We found a low rate of extra-pulmonary TB compared to other reports. It is possible that high coverage of BCG vaccination can prevent invasive TB disease. We did not collect data on history of BCG vaccination or BCG scar; however, national coverage of BCG vaccine in 2006 was more than 99%.”

Also, it would be worth discussing the contributors to having children with undiagnosed HIV infection. Again, these appear to be among older children and may be a result of birth at a time of poor coverage of prenatal screening for HIV. Clarification of this would be of assistance.

Response to reviewer: We have added a sentence to explain this in the discussion pages 17-18: “The HIV prevalence was higher in older children than in younger children, likely because of the effectiveness of Thailand’s highly effective mother-to-child HIV transmission that began in 2000.”

In abstract the rate of MDR that is reported should reflect the proportion which are submitted for DST.

Response to reviewer: For the abstract, we only chose to report the absolute number. In the Results, we reported the rate of MDR among all pulmonary cases and among those that had DST performed.
Reviewer 4: Catherine Watt

Reviewer's report:
This is a nicely written analysis contributing to the neglected field of paediatric TB, and to the surprisingly poorly documented area of treatment outcomes in HIV-positive TB patients. The authors clearly acknowledge the main weaknesses of the study: its small size, and the difficulty of diagnosis of TB in children.

I recommend making the following minor essential revisions:
1. Abstract, first sentence. On what basis "at least"? And what is source of 10%?
Response to reviewer: We changed "at least" to "about" 10% in background. Source of 10% are from reference #2, 3, and 4.
In reference #3: reported 9%
In reference #4: reported 6-20%

2. The first number mentioned under "Background" should, in fact, be 9 million. The authors might like to add the word "estimated" to the sentence.
Response to reviewer: This is correct. We updated the reference#1 to WHO report 2008 and changed background data from 8 million to 9.2 million.

3. The cited paper doesn't give estimates by age. Unpublished estimates can be obtained from WHO/TME (contact me on wattc@who.int).
Response to reviewer: In the background, we only discuss TB in children, but do not describe the breakdown by age.

4. WHO recommendations about recording age have changed. Please check http://www.who.int/tb/dots/r_and_r_forms/en/index.html
Response to reviewer: This is correct, but had not occurred at the time we drafted this paper. We have revised the sentence about WHO recommendations for recording age to: “Historically, TB surveillance systems in high-burden countries only recorded age categories for smear-positive cases; as a result, few NTPs have been able to report reliably the total number of childhood TB cases diagnosed and treated annually.”

5. Page 13, second paragraph. 50% of pulmonary cases had culture. On what basis were these cases chosen, if any?
Response to reviewer: Please see details in Methods section. In our surveillance network, we built capacity to perform TB culture and encouraged its use, but clinicians could choose whether or not to access this service. Clinicians used their own judgment so we do not know why 50% had culture performed.

6. Page 17, second paragraph. Prevalence of HIV of 27% assumes all un-tested children were HIV-negative. What grounds for doing this. If only tested children are included, get prevalence of 43%.
Response to reviewer: This is correct. The true HIV prevalence in this paper should be between 27-43%. We have chosen to report the minimum estimate (27%). We have revised the discussion in page 17 to specify “The minimum prevalence of HIV
infection in children (27%) was similar to that in adults (31%) recorded in our surveillance system.”

7. Treatment outcomes. These should be presented excluding the 7 with final diagnosis other than TB from denominator.

Response to reviewer: This is correct. We updated the database and excluded all patients with an outcome of “changed diagnosis” from the initial analysis as mentioned above in response to reviewer#1, item#2.

Also the following discretionary revisions:
8. Second sentence of paper - it is not only high-burden countries which focus on smear-positive cases. Most countries do.

Response to reviewer: We changed “high-burden” countries to “most” countries in Background section. “In most countries, national TB programs (NTPs) focus case finding and treatment on pulmonary, acid-fast bacilli (AFB) smear-positive cases, which can be rapidly and reliably diagnosed and contribute greatest to community TB transmission.”

9. Last paragraph of Background: the rank changes from year to year, as some countries’ estimated incidences increase and others decrease. Suggest wording "Thailand is among the 22…." or similar

Response to reviewer: We changed wording to “Thailand is among the 22 high-burden TB countries on WHO’s list and has a generalized HIV epidemic.”

10. Page 13, bottom of page. Suggest dividing 78 HIV+ve by (78+105) cases with known status to give prevalence among those tested of 43%.

Response to reviewer: Please see response to reviewer#4, item#6.

11. Suggest presenting cross-tabulation of HIV status vs. type and anatomical site.

Response to reviewer: We didn’t report the cross-tabulation of HIV status vs. type and anatomical site, because, in our data, anatomical site was not statistically different between HIV + and HIV-.

12. Suggest comparing outcomes with adults (in discussion - could use either adults in this study, or national statistics)

Response to reviewer: We chose not to do this, because we have found (in other analyses) that the factors associated with adult TB treatment outcomes are likely quite different than in children, including a higher migration rate, injection drug use, and diabetes.

13. Table 1 - suggest combining information presented under “type and anatomical site” with "Microbiological characteristics"

Response to reviewer: We did not combine these, because we wanted readers to be able to review the disaggregated data. From pre-submission discussions, we know
that some readers would prefer to see these presented separately, as they are currently.

14. Table 3 - a little unusual to present bacteriologically negative cases first (last 3 rows - suggest reversing order). Also, suggest presenting pulmonary then extrapulmonary.

Response to reviewer: We revised as suggested. Please see in table 3.