Author's response to reviews

Title: Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis

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Author's response to reviews: see over
This is a covering letter with a point-by-point description of the changes made in manuscript

**Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis** MS: 9534281932436370

Manuscript revised with point-by-point description of the changes made.

**Reviewer 1:**

**Reviewer’s report**

**Title:** Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis

**Version:** 2 **Date:** 13 February 2009

**Reviewer:** Suzanne Marks

**Reviewer’s report:**

1. Is the question well defined?
Yes, cost-effectiveness of in-house PCR vs standard smear/culture

2. Are the methods appropriate and well-defined?

Somewhat. There are some issues with language usage, so it is sometimes difficult to understand the current descriptions. However, several items should be better defined.

The definition of several items were better defined in the methods section. The manuscript has been changed as the reviewer indicates.

a. For example, there should be a clear description of the culture method used; I assume this is likely to be MGIT using liquid broth to enable a culture result in 2 days (the same as the period for in-house PCR results). Or, the paper is misleading in suggesting a 2 day result for culture, given that the time period and data appear to be similar to those used in the BMC published paper by the same authors in 2007 (BMC Public Health. 2007; 7:356) in which the median time to MTB culture growth was 30 days and detection by PCR was 3 days. This would dramatically affect the cost calculations, as there would be patient work time lost waiting for culture result and a substantial difference between culture and PCR.

And, both inpatient and outpatient costs would be affected. The current paper under review only finds cost differences for increased PCR lab costs, and not for patient costs and no difference between inpatient and outpatient costs.
We have now used this reference (BMC Public Health. 2007; 7:356) in the methods section. The manuscript has been changed as the reviewer indicates in line 169-172. The cost calculations were changed in the results section.

b. The description of the cost analysis on lines 145-147 is unclear. Was the PCR dot blot not actually used, or why is the word “theoretical” inserted? It seems to me, based on the results section, that 2 strategies were compared: ZN/culture and ZN/PCR dot blot. Since culture is the gold standard, it might have been a better study to compare outcomes and costs of using the ZN alone for decision making compared with ZN/PCR, with sensitivity and specificities taken from each compared to culture or final clinical determination.

The manuscript has been changed in the methods section as the reviewer indicates in line 193-211.

c. The use of the words “at least as cost-effective as ZN plus culture” is not sufficiently descriptive. When comparing 2 strategies, one strategy is either more or less cost-effective than its comparison strategy. If the authors are trying to say that the effectiveness is the same for both methods and that the costs did not differ significantly (and state the statistical method used to determine this), then that should be stated.
The manuscript has been changed as the reviewer indicates in the discussion section.

d. Were results stratified by HIV status? HIV was mentioned several times, but it was unclear what was done in the analysis.

The manuscript has been changed in the results section as the reviewer indicates in line 216-217.

e. You should reword lines 185-186. You are just stating that because culture is the gold standard and the PCR test results in some false positives, that treating those false positives is more expensive than if you had waited for the culture results and not treated them. But, usually, the decision to initiate treatment is based on the smear alone or some other clinical suspicion (as the culture usually takes several weeks to obtain), which also results in false positives that are treated. The real cost-effectiveness question is adding up the costs of treating false positives for each strategy and the costs of missing false negatives and comparing the costs of each strategy.

The manuscript has been changed in the results section as the reviewer indicates in line 240-248 and in table 4.

f. The discussion section mentions that mortality is an outcome that is important, but the current study did not even mention whether it was measured.
With a high HIV prevalence, a missed TB diagnosis could rapidly result in death.

The manuscript has been changed as the reviewer indicates in the discussion section.

g. The discussion section mentions another strategy, ZN/PCR-AG, that was not presented in the methods or results.

The manuscript has been changed as the reviewer indicates in the discussion section.

h. Also in the discussion, a theoretical model for automated PCR is mentioned, but again, not mentioned in the methods or results

The manuscript has been changed as the reviewer indicates in line 302-303, in the discussion section.

i. Treating of returned false-negative patients is mentioned in the discussion, but again, not in the methods or results. Please explain what is a “returned false-negative patient.”
The manuscript has been changed as the reviewer indicates in line 199-206, in the methods section.

j. RX is not defined (chest radiograph?)

The manuscript has been changed as the reviewer indicates.

k. The cost effectiveness of rapid diagnostic methods versus standard smear and culture usually depend on the use and cost of respiratory isolation (rapid methods can quickly rule out infectious TB, usually longer time period to a negative culture result would result in longer treatment, hospitalization, and respiratory isolation), whether or not a contact investigation was initiated (which would not take place for MOTT), and whether a rapid TB diagnosis was not missed (which could result in transmission or death and lifetime productivity losses). However, by blinding the treating physicians to the results of the tests, decisions based on the results of the tests were not measured or modeled. While the current study design allows calculation of the sensitivity and specificity of each test, it does not allow a calculation of the actual costs and benefits of each test in a real world setting in which physicians are not blinded.
The manuscript has been changed as the reviewer indicates in line 127-128 in the methods section.

3. Are the data sound? I really don’t know

4. Does it adhere to relevant standards of reporting and data deposition? I guess So

5. Is the discussion supported by the data? See 2f-2h above.

The manuscript has been changed as the reviewer indicates.

6. Are limitations of the work clearly stated? I didn’t see a limitations section

7. Do the authors acknowledge any previous or ongoing work? They did not cite the 2007 BMC article that I mentioned in 2a above

The manuscript has been changed as the reviewer indicates.

8. Are the title and abstract accurate? Appears so

9. Is the writing acceptable? There are some problems with language that will need editing. On table 1, specificity of PCR dot blot is 85% not 84%. There are errors on Table 2, using commas instead of decimal points in the last column.

The manuscript has been changed as the reviewer indicates in table 1 and in Table 2.

Major compulsory revisions: please address each item in number 2 above and
cite the previously published work.

The manuscript has been changed as the reviewer indicates.
Reviewer's report

Title: Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis

Version: 2 Date: 3 February 2009

Reviewer: Stephen Weis

Reviewer's report:

Major Compulsory Revisions

The paper estimates the cost effectiveness of using PCR in the diagnosis of tuberculosis. A weakness of this analysis is that using the results of an "in house" PCR make the results less generalizable to other situations. By definition "in house" PCR are not standardized.

1) Line 67-71: It appears that the authors used the wrong references i.e. references used do not support statements authors made? For example Perkins article actually states "a recent performance evaluation of six experienced Latin American laboratories showed poor and inconsistent performance of non-commercial polymerase chain reaction assays, casting further doubt on their appropriateness for disease endemic countries use. " Similarly the Brodie paper cited does not support the statement it is referenced to.

The manuscript has been changed as the reviewer indicates in lines 68-74 and in lines 76-79 in the background section.
2) Line 119: What do the authors mean by "Running costs". Is this the cost more commonly referred to as "variable cost" associated with PCR?

The manuscript has been changed as the reviewer indicates in lines 159-160 in the methods section.

3) Lines 121-123. "In the treatment costs analysis, the cost related to: a) the inadequate use of non anti-TB drugs; and b) the adverse effects of the inadequate use of anti-TB drugs for non-TB subjects were not included." It is not clear to the reviewer what these costs represent? Is this societal cost of death and impairment related to delay of treatment? Please clarify.

The manuscript has been changed as the reviewer indicates in lines 162-167 in the methods section.

4) Lines 150-151. It is stated that an assumption is that a false negative patient transmit TB to 10 persons. The authors do not state how many of these are assumed to develop tuberculosis? This is a critical assumption that needs to be stated.

The manuscript has been changed as the reviewer indicates in lines 199-206 in the methods section.
5) Table 2 C. Estimated costs incurred by patients, including costs for travel, food and income loss.

If I understand the design of the Table 2 there is an error as totals are both 11,667. That is the total for ZN plus PCR dot-blot but not the total of ZN plus culture.

The manuscript has been changed as the reviewer indicates in table 2 C in the results section.

Minor essential revisions

6) Line 50: "blot costs and ZN plus Culture (U$ 123,859 versus U$ 113,506)." I believe the authors S left out after U

The manuscript has been changed as the reviewer indicates in line 52 of abstract.

7) Line 51: "Costs per correctly diagnosed case were U$ 1023 and U$ 1136 for ZN plus culture" I believe the authors S left out after U

The manuscript has been changed as the reviewer indicates in line 53 of abstract.
8) Line 62: "The rapid clinical diagnosis and diagnosis is more challenging" is confusing use of words. Do the authors mean, "The rapid diagnosis is more challenging"?

The manuscript has been changed as the reviewer indicates in line 66 of background.

9) Lines 80-82: "For regions with a high burden of TB and HIV, which urgently needed new strategies for TB control, there are scarce data on cost effectiveness analysis of the PCR technique for TB diagnosis in developing nations."

Do the authors mean "need new strategies"? Please clarify difference between "regions with a high burden of TB and HIV" and "in developing nations" in the same sentence.

The manuscript has been changed as the reviewer indicates in lines 88-90 of background.

10) Line 130: per pill, U$ 131 Should be per pill, US$ 131

The manuscript has been changed as the reviewer indicates.

11) Line 134: RX is not defined in abbreviation list. What does it mean?
The manuscript has been changed as the reviewer indicates.

12) Line 137: RX used again

The manuscript has been changed as the reviewer indicates.

13) Line 234: Culture should not be capitalized

The manuscript has been changed as the reviewer indicates.

14) The references contain many errors a few examples are listed.
Line 362: Methods for quantitative synthesis in medicine. . New York Oxford University this line has an extra period. Another citation error is that it was published by Oxford University Press in New York.

The manuscript has been changed as the reviewer indicates.

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