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
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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

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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: 3 Date: 11 May 2009

Reviewer: Suzanne Marks

Reviewer's report:

This version has improved over the previous one, with the authors making many
(but not all) of the suggested changes. I believe another round of edits is needed to make this acceptable for publishing. Here are my comments.

1. the authors should mention that the cohort is the same as from the 2007 BMC publication, which published the median PCR time of 3 days and smear/culture of 30 days.

   We have now used this reference (BMC Public Health. 2007; 7:356) in the methods section. The manuscript has been changed in the methods section as the reviewer indicates. The costs calculations were changed in the results section.

2. the authors need to add a "Limitations" section, which should include mentioning of the following:

   a. Since the respiratory specialists were blinded to culture PCR results and lab technicians blinded to chest radiograph and clinical predictors results, the study is not one of the use of PCR dot-blot in a real world setting, and, as such, the cost-effectiveness is estimated, not measured
   b. In-house PCR results are not necessarily generalizable, unless the replicating site uses the exact same in-house PCR.
   c. The authors should explain the possible impact of including the 23 specimens that were below the PCR detection limit, and why they weren't excluded
   d. Stratification of results by HIV status was not done
   e. Mortality was not measured for either strategy
   f. Isolation use or contact investigation was not included in the analysis
The manuscript has been changed, we included a limitations item in the end of discussion section as the reviewer indicates.

3. Consider making the following language edits:

a. Explain that ZN is acid fast bacillae (AFB) smear, as I believe that is more commonly used

The manuscript has been changed as the reviewer indicates.

b. Use the word "estimated" when explaining what the authors did regarding computing cost-effectiveness

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

c. Delete lines 196-199, replace with "A sensitivity analysis was performed to assess the effect of the various parameters (TB prevalence, sensitivity, specificity, and variable costs) on the conclusions."

The manuscript has been changed in the methods section as the reviewer indicates.
d. Instead of using "current situation" for example on line 243, standard economic language uses "base case" or status quo.

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

e. Replace "non treated" with "not treated"

The manuscript has been changed as the reviewer indicates.

f. Delete the sentence on lines 327-329. you didn’t show this

The manuscript has been changed as the reviewer indicates.

4. Correct the following errors:

i. Abstract results 2nd sentence: The total screening costs were similar for ZN/PCR and ZN/culture. this needs to be changed to say that total screening costs (latest version Table 3) are nearly 8.5 times for ZN/culture vs. those of ZN/PCR

The manuscript has been changed in the abstract section as the reviewer indicates, according to the new figures.

ii. Line 75: for ruling out or considering pulmonary tuberculosis
The manuscript has been changed in the background section as the reviewer indicates.

iii. Line 231 PCR dot-blot $1,577 (not 1,576,60). There are multiple places throughout the document that are using the comma instead of the decimal point.

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

iv. Line 247-248: I believe you are comparing more "rapid" techniques, to standard techniques such as the ZN/culture.

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

v. Line 284: "evolution" should be "evaluation".

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

vi. Line 308: was greater for ZN plus

The manuscript has been changed as the reviewer indicates.

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

viii. Line 189: you are assuming that one FN patient transmits TB to 10 others. While each infectious TB case averages 10 contacts, only about 30-40% become infected with latent TB infection and only 3 to 8 percent of them will develop TB disease. This also needs to be corrected in Table 4.

We assumed that each 10 TB patients not diagnosed, will transmit M.tuberculosis for 100 individuals. Five percent of them will develop TB. Changes were included in the methods section as the reviewer indicates and in table 4.

5. I did not check all the references, but someone needs to look at them again

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

6. I cannot assure that the study conclusions are correct until the tables have been revised:
   a. While Table 1 is fairly comprehensible, the sensitivity and specificity results should be moved for clarity as to which strategy that they are associated with
Modifications were included in table 1 as requested.

b. Table 2:
   i. Table 2b should be titled Laboratory costs, not Labor costs and the last column is showing commas instead of decimal points.

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

ii. Table 2c: I don’t understand why the per patient per day costs differ for each strategy: I get $3.33/day for food under ZN/culture and $5/day under PCR; for income I get $5.83/day under ZN/culture and $8.75/day under PCR

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

c. Table 3 is incomprehensible to me as it is presented. Since many of the changes in the analysis from the previous version to this one are based on this table, it is important that both the authors and reviewers understand what is in them. In one table you have per day costs, another per strategy, and another per patient. Also, I don’t understand why the ZN/culture per day costs changed, since I understand that placing all the culture results into 30 days changed many of the results. I suggest reorganizing it into separate tables that clearly list for each the unit cost, units (e.g., days, patients, etc.), and total costs. The footnotes show commas instead of decimals.

The manuscript has been changed as the reviewer indicates in table 3.
d. Table 5: on the cost per case per TP and FP columns, for the current situation, I could not find the match to 20,587 and 2,665 on Table 4. And, in the FN columns, I could not find the match to 22,933 and 3,363 in Table 4. In the Specificity of PCR row, the current situation should be 85% (not 84%). All the ratio columns are using commas instead of decimal points.

The manuscript has been changed as the reviewer indicates in table 5.
Reviewer's report

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

Version: 4 Date: 4 July 2009

Reviewer: Stephen Weis

Reviewer's report:

It seems that the point of a major compulsory revision of the article was not understood.

I stated "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."

The Perkins article cited in original paper actually makes a statement about in-house PCRs, and I quoted "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. "

This paper has no paragraph on the limitations of the data. It is essential that this paper have in its discussion the limitations of in-house PCR. They are only as good as the in-house they come from. The authors show good results from their in-house PCR however other experienced laboratories have not been able to duplicate that PCR performance. Lack of standardization is part of the problem of in-house PCR. This limitations need to be clearly stated and
discussed in view of inconsistent performance of in house PCR reported by Perkins whom they cite.

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

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

**Quality of written English:** Needs some language corrections before being published

**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'

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