Author's response to reviews

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

Authors:

Luciene Cardoso Scherer (luciene.scherer@hotmail.com)
Rosa Dea Sperhacke (deasperhacke@hotmail.com)
Antonio Ruffino-Netto (aruffino@fmrp.usp.br)
Maria Lúcia Rosa Rossetti (rossetti@terra.com.br)
Claudia Vater (mcvater@nesc.ufrj.br)
Paul Klatser (paul.klatser@falw.vu.nl)
Afrânio Lineu Kritski (kritski@gmail.com)

Version: 6 Date: 9 September 2009

Author's response to reviews: see over
Rio de Janeiro, 08 September 2009

Andrea Bucceri PhD
Assistant Editor
BMC-series journals

Tel: +44 (0)20 7631 9921
Facsimile: +44 (0)20 7631 9923
e-mail: editorial@biomedcentral.com
R2

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:** 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 in lines 170-174(new version). 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, from 381 to 404 lines (new version). Information regarding the above items mentioned by reviewer were included, respectively in the lines

Item a – lines 382-385
Item b – lines 386-391
Item c – lines 392-397
Item d – line 398
Item e - line 399
Item f – lines 400-403
Item g – line 404

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 in all manuscript, starting by line 41.

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, in line 208.

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, in lines 221 and 222 (new version).

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 in line 271 (new version).

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

The manuscript has been changed as the reviewer indicates in the first time in line 56 and in all new manuscript version.

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

The manuscript has been changed as the reviewer indicates in new version.

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 in lines 50 to 52 in new version.

ii. Line 75: for ruling out or considering pulmonary tuberculosis

The manuscript has been changed in the background section as the reviewer indicates in line 80 (new version)

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.

It has been changed as the reviewer indicates in all manuscript (including tables), beginning on lines 197.

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, in lines 277 and 278 (new version).
v. Line 284: "evolution" should be "evaluation"

The manuscript has been changed in the discussion section as the reviewer indicates in line 314 (new version).

vi. Line 308: was greater for ZN plus

It has been changed as the reviewer indicates in lines 336 to 338.


The mention to Dowdy reference was deleted in line 357 (new version).

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 \textit{M.tuberculosis} for 100 individuals. Five percent of them will develop TB.
Changes were included in the methods section in lines 213 to 219 and in table 4 as indicated.

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 in order to make clear to readers the figures are associated with different strategies.

   b. Table 2:
      i. Table 2b should be titled Laboratory costs, not Labor costs and the last columns 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.
Income loss of patients was calculated from monthly salary base of Brazil (US$117) and was based on proportional days spent by patients until access to the result of each laboratory procedure. Patient costs were estimated using the average of two visits to the laboratory for the PCR procedure and for AFB smear and culture procedures for outpatients; Travel cost was considered as US$0.8 (one way by bus). Food was considered as US$3.3 per meal. Base salary in Brazil was considered (US$5.83 per day /20 days of the work). For inpatients was considered just income loss

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.

Table 3 was reorganized as indicated: we included the following list: Health Service costs, Laboratory costs, Treatment costs, Diagnostic Service costs per day, Patient cost (ambulatory/outpatients), Patient cost (hospital/inpatients) and corrections in the footnotes.
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.

In Table 4: the Cost per case of TB correctly diagnosed and case of TB falsely diagnosed and treated (true positives and false positives), for the current situation, was 50,460 (Total screening costs/112 (true positives and false positives cases) and 11,555 (Total screening costs/131 (true positives and false positives cases)). In Table 4: the Cost per case of non-TB correctly and incorrectly diagnosed and not treated (true negatives and false negatives), for the current situation, was 34,252 (Total screening costs/165 (true negatives and false negatives cases) and 10,368 (Total screening costs/146 (true negatives and false negatives cases)).

In Table 5: the Cost per case accurately diagnosed and treated, including treatment of falsely diagnosed cases (true positives and false positives), for the current situation, was 55,645 (Total treatment cost plus total screening costs plus Cost per case of TB correctly diagnosed and case of TB falsely diagnosed and treated/111 (case accurately diagnosed) and 15,855 (Total treatment cost plus total screening costs plus Cost per case of TB correctly diagnosed and case of TB falsely diagnosed and treated/109 (case accurately diagnosed).
We assumed that, 10 false negative patients may transmit *M.tuberculosis* to 100 individuals, and active TB is expected to occur in 5% of those infected. In this study, the rate of TB in false negative patients was 13.3% for AFB smear plus Culture strategy and 14.8% for AFB smear plus PCR dot-blot strategy. Assuming the diagnosis of 1,000 TB cases, additional active TB cases is expected to occur with AFB smear plus culture and AFB smear plus PCR dot strategy in 67 and 74, respectively.

In Table 5: Cost per case incorrectly diagnosed and not treated, for the current situation, was 22,107,573 (67* Total screening costs/ 17) (case incorrectly diagnosed and non treated) and 5,895,698 (74* Total screening costs/ 19) (case incorrectly diagnosed and non treated), respectively.
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.

We do agree with the reviewer that the main weakness of the manuscript is the evaluation of in house PCR. We included comments on that matter in Discussion chapter in lines 381 to 404. The issue related to the limitation of in house PCR was described in item b, lines 386-391 as follows: b. In house PCR results used in this study are not necessarily generalizable to other situations, as in house PCR are not standardized and is usually associated with low reproducibility, unless the replicating sites use the exact same in house PCR [5]. We do think the results obtained in this study, highlight the cost-effectiveness of molecular test for TB diagnosis in developing nations, with high TB and HIV prevalence and, it is expected that it will facilitate the acceptance the TB Control Programmes that molecular testing for TB, specially for HIV infected persons or paucibacillary TB suspects may have a great role in the near future. Assuming that the best scenario is to use automated molecular testing but, in developing nations with scarce resources, in house PCR could be useful if we are dealing with a TB laboratory that follows good laboratory practice and is certified by Regulatory Agency.

**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'

Luciene Cardoso Scherer M.D.
Center of Improvement Scientific and Technologic –CDCT
State Foundation by Research in Health –FEPPS/RS
Av Ipiranga 5400, 3° andar
Porto Alegre, Brazil
CEP 90610-000.
phone/fax: (+55) 51 3352 0336
e-mail:luciene.scherer@hotmail.com

Afranio Kritski M.D., PhD.
Tuberculosis Academic Program, Coordinator
IDT-HUCFF Hospital Complex
Internal Medicine Department, Chief
Medical School of Federal University of Rio de Janeiro
Av Brigadeiro Trompowsky s/n - Ilha Fundao - Predio HUCFF 4 andar
Rio de Janeiro, Brazil
CEP 21 941 590/ phone/fax: 55 21 2550 69 03/ email: kritskia@gmail.com