Reviewer’s report

Title: Meta-analysis to compare the accuracy of a molecular test with rapid culture and the WHO 2007 algorithm for diagnosis of smear-negative pulmonary tuberculosis

Version: 1 Date: 16 April 2013

Reviewer: Colleen Hanrahan

Reviewer’s report:

Discretionary Revisions
For the most part the article is clearly written, but would benefit from a grammar review—some parts read awkwardly and could be worded or punctuated more naturally.

Minor Essential Revisions:
Overall:
- Periods missing at ends of several sentences throughout manuscript.

Background:
- Do not hyphenate “smear-microscopy”. (Background, paragraph 1).
- M. tuberculosis should be unabbreviated at the first mention (Background paragraph 1), and the abbreviation should be consistent throughout the manuscript (elsewhere, Background paragraph 3 it is again unabbreviated and un-italicized, and then later abbreviated as “M.tb”).

Figure 4:
- Legend should explain all abbreviations—SROC, AUC, SE. Legend could also assist in interpretation of uncommon statistical measures such as Q*.

Table 1:
- Legend should explain all abbreviations – TP, FP, FN, TN.

Discussion:
Paragraph 3: do not hyphenate “in-experienced”.

Major Compulsory Revisions
Title:
Title should be specific as to what tests are being compared—Xpert and MODS. “Rapid culture” is often thought to be MGIT. Title is awkwardly and confusingly worded, I would prefer: “Meta-analysis to compare the accuracy of x,y and z for diagnosis of…. “.

Abstract:
Background should give a 1 sentence detail of what the WHO 2007 algorithm is comprised of. Methods should detail eligibility criteria in brief.
Background:

Sentence 3 referring to sensitivity of smear microscopy should have a reference.

In general, the background does not support the rationale behind the inclusion of MODS in the study. The first sentence of paragraph 3 is misleading: The WHO recommendation is for the use of MODS for MDR-TB, rather than as a first-line test to detect TB, or as a follow-up to smear. It is worth comparing the characteristics of MODS and Xpert—the two tests are so different. MODS is non-commercial and requires substantial infrastructure— the ability to do culture, biosafety, etc—it is unsuited to point-of-care or clinic placement. Xpert is commercial, can be done by a non-skilled technician, does require some infrastructure and still may be priced outside of the reach of many countries for full scale implementation. Still, the two tests are being implemented at radically different paces- Xpert is being implemented in many countries, and MODS is in use in only a few. I’m not saying that it is inappropriate to include MODS in this analysis, just that the case is not really made by the background presented by the authors.

Methods:

Inclusion criteria, sentence two is misleading. The authors write “The publications must have used the GeneXpert, MODS and WHO 2007 algorithm” when they must mean “OR” rather than “AND”.

The authors point out that the WHO 2007 algorithm is difficult to follow in many settings- it would be helpful if, for the studies included for WHO 2007, to note in some way how well the algorithm was adhered to, if that is possible. Is the sens/spec of this algorithm representative of a sort of “best case scenario” by studies that were able to fully adhere to the algorithm, or is it simply a reflection of how the algorithm is operationalized in a real world scenario? Discussion around this point would be helpful.

The authors include a measure of country HIV prevalence for each study. While this is interesting, what matters more is the prevalence of HIV in the study itself. To me, this is a glaring omission that must be corrected. For example, some publications might be done in a country with low HIV prevalence, but the study itself might be done among all HIV positive individuals, therefore the HIV prevalence in the study is 100%. This information would be useful to include in Table 1.

Figure 1:

Should focus on the follow-up of smear negative patients only, the algorithm for smear positive patients can be excluded.

Figure 2:

In the legend the authors note that “there was one publication with two results for rural and urban sites”. It’s not clear what this means at all and how the reader should consider this note along with the results. Did the authors combine results for these sites? Did they report them separately, should we know specifically which study this was? This note needs more explanation, and if needed, to be addressed in body of the paper (methods and/or results).
Table 1:
Presentation of absolute numbers of true positive, false positive etc doesn’t really help the reader evaluate anything about this study, and seem best left off this table. STUDY HIV prevalence would be a helpful addition to this table. Specimen type is interesting but is not mentioned anywhere else- if it is not discussed, it should be excluded.

Discussion:
Would be helpful to discuss how well 2007 WHO algorithm was followed in the 4 studies included- the authors mention that is burdensome to follow the algorithm but could provide some direct evidence as to this from the included studies, if possible.

Paragraph 2, the authors note their sensitivity is lower than that found by another publication and hypothesize that it could be because of different methodology. This leads to a natural question, did the authors choose a more appropriate methodology, can they defend their use of this in a brief sentence here?

In general all discussion of HIV prevalence should be restricted to study prevalence rather than country prevalence, which may be meaningless.

The exclusion of 2 large landmark studies on Xpert is very unfortunate and lowers the impact of this study. However, the exclusion is hidden in the legend Figure 2, but certainly deserves mention as a limitation to the study within the discussion.

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests