Author's response to reviews

Title: Low specificity of HIV-testing on sputum specimens kept at ambient temperatures for 4 to 7 days: a blinded comparison

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Author's response to reviews: see over
Amsterdam, 27 June 2007

Dear dr da Silva

Thank you for the provisional acceptance of our manuscript. We apologize for the delay in responding. We thank the reviewers for their helpful comments. Please find below our point-by-point response.

Note that we changed the manuscript title in order to comply with editorial requirements.

We hope the revisions are reason for final acceptance of our manuscript.

Please let me know if you have any further queries.

On behalf of the authors,
yours sincerely,

Frank GJ Cobelens MD PHD
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Reviewer: Patrick S Sullivan
Major Compulsory Revisions

1. I infer that the EIA-EIA combination was the gold standard in the evaluation, but this is never explicitly stated in the text (appears as a heading in the table). Also, you should address the possibility that the QraQuick device could be more sensitive than your gold standard.
   Both were added to the text. Note that we used the term reference standard instead of gold standard in compliance with the STARD guidelines.

2. The issue of the split specimens is very confusing, especially since you don't explain why the specimens were split until page 15, which is after the split results are presented. The methods should come before the results in any case, but here a much clearer explanation of the reason for the split -- and why it is important to present the results separately -- should be provided.
We had understood (apparently incorrectly) that putting the methods at the end of the manuscript is an editorial requirement. Mentioning methods only at the end is then an inevitable consequence. We now followed the reviewer’s preference.

3. On page 15, need to say which test result was given to the patient -- I assume that it was the EIA result, but should be explicit.
It was, this is now added to the text.

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Minor Essential Revisions
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Page 8 -- you say that 77% specificity is not sufficient for surveillance purposes, but is there an agreed upon standard for specificity for surveillance purposes? If so, what is it?
There is indeed no agreed standard for specificity for surveillance purposes, and WHO, in its guidelines on HIV testing of TB patients, has not set a minimum specificity of the HIV test used. Apart from specificity per se, the expected prevalence of HIV infection in the population under study is also important because it affects the positive predictive value of the test (PPV, or one minus the proportion false-positive). Although there are no agreed standards for this either, some PPVs will be considered acceptable, whereas others will not. We therefore now extended our argument in the discussion section with examples of what the observed specificity would mean in terms of PPV or proportion false-positives.

Page 6, lines 112-114: this sentence ("The proportion ...") is very confusing.
Was revised, see below.

Page 7m line 136: what does it mean that "24 specimens remained unknown"? Does that mean that you do not know what technician tested them?
It was indeed not recorded, now added to text.

Page 6: Last sentence of 1st para, lines 115-116: This sentence seems out of place
We acknowledge this but could not think of any other place to put it. We think it is relevant information because is shows that changes in test performance over time are not due to more tests becoming indeterminate.

Page 21: not clear what the numbers after the clinic names mean
We took them out.

Page 21: The tenths place is not meaningful in a sample of 58. Please present percentages round to the whole number.
Was revised, but in entire table since it would not make sense to this for the right hand column (n=58) only.

Page 21: P values do not need three significant digits. please present 2 SDs or less.
In the field of statistics and epidemiology a 3-digit p-value is customary but we were happy to revise this throughout the manuscript (assuming it is in accordance with editorial policy).
Reviewer: Nelson L Michael

Major Compulsory Revisions

(none)

Minor Essential Revisions

1. Eliminate discussion about the specificity differences between split and unsplit specimens as the differences were not statistically significant. 
We disagree. At least one of the comparisons was significant (day 4: p=0.03), whereas one other was near-significant (day 7: p=0.09). With these small numbers a result that is only just short of significance should, in our view, not be reason to refute the hypothesis that bias occurred (because that is what this is about). We therefore propose to leave this paragraph in.

2. Explain the sentence, “Proportion of sputum samples available for testing on day 7 was lower if the result of testing on day 4 was negative than if it were positive.” I assume that negative day 4 sputum specimens were more likely to be discarded, but this needs to be explained. 
It was due to initial confusion about the study protocol. This was added to the text.