Reviewer’s report

Title: Diagnostic Accuracy of the Xpert MTB/Rif Ultra for tuberculosis adenitis

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Reviewer: David Boulware

Reviewer's report:

This is a prospective cohort study investigating the diagnostic accuracy of Xpert MTB/RIF Ultra for diagnosis of TB in patients with lymphadenitis. The authors report according to the STARD criteria. This is a very nice study that could really perform clinical practice. There are some very minor limitations in that not everyone had every diagnostic test, but that is reality. Overall, this manuscript has very exciting data, and the this reviewer has a few suggestions to improve the presentation of the exciting data -- which seems buried.

Major:

1. Authors should list in the abstract the sensitivity of AFB microscopy or histopathology as a "rapid" diagnostic tests of comparison. This comparison might be a more important to present than the 95%CI. Yes, the 95%CI is important to present as per the STARD criteria, but it is not of utmost importance to report in the abstract. Similarly, the detailed description of probable TB is unnecessary for the abstract (if readers want to know -- they should read the manuscript!) For optimal use of a limited word count, the authors might consider listing the sensitivity of AFB microscopy on FNA (26%), on lymph node core biopsy (33%), and granulomas on histopathology (83%). Or list the sensitivity of various methods for definite/probable TB (this probably would be best). In other words, give more actual results in the abstract! that will entice readers to read the whole manuscript. Sell the sizzle.

-- The authors conclusion (in the discussion) is that "Our findings support the use of Ultra on FNA as an initial test when tuberculosis adenitis is suspected." -- however this is not at all obvious in the abstract or first 3/4 of the manuscript. This reviewer assumed through the first 10 pages of the manuscript that Ultra was a suboptimal test with only ~70% sensitivity, which is "reasonable" but not optimal. Only 10 pages into the manuscript is this reviewer surprised to learn that the Ultra diagnostic performance is pretty good -- better than AFB microscopy and better than culture. Yet this is not obvious (nor actually stated anywhere in any result). This is an important result!
2. Consider listing in the results the diagnostic performance in comparison to definite/probable TB for Xpert Ultra, AFB microscopy on FNA, AFB on lymph node core biopsy, granulomas on histopathology, and culture. Overall, providing information which informs clinical practice would be ideal. AFB on FNA had 26% (7/27) sensitivity for definite/probable TB. Culture from FNA had 36% (13/36) sensitivity for definite/probable TB. Histopathology for granulomas had 83% (20/24) sensitivity for definite/probable TB. Ultra had sensitivities of: 70% (21/30) on FNA and 67% (16/24) on lymph node core biopsy. From the data provided, it appears that Xpert Ultra by FNA followed by core biopsy with histopathology would be a preferred diagnostic algorithm in a middle income setting (where there is a pathologist).

3. Among persons with both testing modalities (FNA and core biopsy), was there discordence? Was there anything gained by repeat testing? A Venn Diagram might be nice. Alternatively, one could state of those initially negative by Ultra on FNA, XYZ% (X/Y) were positive by Ultra on the lymph node core biopsy. Also, one could report this for repeated AFB microscopy. The authors recommend repeat testing in the discussion (Page 13, line 12), but presenting actual data to support this statement would be good. It might be more cost efficient to send for histopathology instead of repeat Ultra testing, if the diagnostic yield was low. (But what was the yield?)

-- An alternative way to present this would to be the present 1-2 sentences on the incremental diagnostic yield. If Xpert was the first test, how many would be picked up? (69% ish), then if histopath was the second test, how many would be picked up? (or what if repeat Xpert Ultra was done, then histopath)? If these two tests are done, are there any additional cases detected by AFB or by culture, which were Xpert Ultra and histopath negative?

2. Page 3, Line 53-55 -- consider adding a reference citation here regarding CSF diagnostic performance. What study is being referenced is unclear. This reviewer is unaware of the lower "specificity" of Xpert Ultra in CSF. Others have suggested this is enhanced sensitivity. Do the authors believe that Xpert Ultra gives false positives in CSF among HIV-infected persons with lymphocytic meningitis and negative other testing?

3. Minor - use of non-standard abbreviations (CRS, LN) make this more challenging to read. If the authors choose to abbreviate, this reviewer would recommend to avoid these abbreviations in Table and Figure Titles.
4. Tables 3 consider also listing the combined data for each of the 3 categories. As the results are similar on FNA vs. lymph node biopsy, the larger denominator may give a better estimation and would also narrow the 95%CI. Saying a test has a 90% CI width of 50% meets the STARD criteria but isn't very useful. Similarly reporting 69% (37/54) sensitivity and 98% (98/100) specificity on FNA or tissue is slightly better than saying the sensitivity was 67-70% and specificity 96-100% on FNA or tissue. Just

5. Table 4 has a confusing title. One is displaying the semi-quantitative Xpert Ultra distribution and the false positive distribution. Overall, this isn't very interesting. Listing the diagnostic performance of all the diagnostic modalities against probable/definite TB would be a better use of a table.

6. Figure 2 - % listed for granulomas 2% (5/8) -- is incorrect. Is it 63%? or is the numerator/denominator incorrect?

7. Sensitivity of AFB on FNA and tissue (26%) - page12, line 35. Is this "and" or "or"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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