

Reviewer A

**Comment 1: Overall a good manuscript. In my opinion one point must also be discussed: What is the usual practice in the region under study. Whenever a patient with pleural effusion presents the first thing to do is ultrasound and then if it is simple effusion then a pleural tap is done, in complicated (septated or multiloculated) or organized effusion we prefer going for medical thoracoscopy and in one go it is diagnostic as well as also serves to clear the pleural space. Pleural tissue Xpert MTB ultra and histopathology is sent. Both have a good yield. Also diagnosis other than TB can be excluded. Additionally sometimes evident features are there on pleura like sago like nodules which are also very sensitive for pleural TB so anti-tuberculous treatment can be started straightaway. Can thoracoscopy be more economically favorable?**

Reply 1: The reviewer makes an interesting and excellent point here. We have now discussed this point and amended the discussion section.

The current practice in South Africa is to first perform a pleural tap without ultrasound guidance for subsequent microbiological and immunodiagnostic (ADA) assessment on the collected pleural fluid. However, if no TB diagnosis can be made (and the clinical picture suggests TB) then the patient is usually referred to a secondary or tertiary centre for a closed Abrahams pleural biopsy under ultrasound guidance (biopsies are then sent for Xpert, culture and histopathology). Only if this procedure yields no diagnostic result (and the clinical picture suggests otherwise) then further investigations are performed such as a conventional bronchoscopy, endobronchial ultrasound-guided (EBUS) bronchoscopy, CT-guided FNA biopsy or a video-assisted thoracoscopic biopsy. It should also be noted that, unlike some TB endemic settings, thoracoscopy is not widely available in Africa due to the lack of technical expertise, high costs, a shortage of thoracic surgeons and logistical requirements (bronchoscopies and CT FNA are much more accessible). In fact, given these considerations, even a ‘blind’ pleural biopsy is often unavailable or inaccessible in the majority of cases. In part, this is due to the very high burden of pleural TB cases (almost 50,000 newly diagnosed cases per annum).

Furthermore, clinical procedures such as US guided-pleural biopsies and thorascopies are inpatient procedures requiring expertise and significant resources compared to the usual TB diagnosis infrastructure. This means these procedures will be much more expensive compared to rapid diagnostic tests such as Xpert, ADA, etc., and will likely delay the diagnosis (at which point empiric treatment will be initiated anyway), and will thus unlikely be cost-effective, at least in a South African setting.

Having said this, the main goal of the manuscript was to assess the cost effectiveness of first-line diagnostic tests for a rapid pleural TB diagnosis. We are not assessing the clinical procedures for sample collection but rather the performance of diagnostic assays that utilize the clinical samples. A more appropriate analysis would be to compare the diagnostic yield of pleural tap, thoracoscopy, bronchoscopy, CT guided FNA, etc using Xpert, ADA or another diagnostic assay. Although this is outside the scope of the study, this will be an interesting analysis but will require clinical data from appropriate TB cases, which is currently not available.

Nonetheless, we have addressed this concern in the limitations section of the discussion, and inserted the following text:

Page 11, line 316-322:

“We did, not in our analysis, consider medical procedures such as thoracoscopy (which is more widely used in some settings). However, while such operative procedures can have a high diagnostic yield and may also aid in improving treatment outcomes (Vorster et al), its implementation as a frontline diagnostic tool for pleural TB in many endemic settings is limited by a lack relevant of expertise, high costs and limited resources (particularly in Africa). Future setting-specific cost effectiveness analyses should also include medical procedures such as thoracoscopy and their impact on diagnosis and management.”

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**Comment 2: Secondly there are many patients who present with advanced pleural effusions complicated with septations and loculations, slough which does not simply go away with TB treatment, they need to be cleared by thoracoscopy better in the early phases of presentation. Is there any data from the region that how prevalent is this presentation? If more patients need some intervention in addition to ATT then thoracoscopy maybe more cost effective serving both purposes: early diagnosis and clearing of pleural space.**

Reply 2: Published data on the prevalence of such advanced cases is limited in South Africa. However, based on our clinical experience, ~15% of pleural TB cases have residual effusions of varying size. Some, are persistent for months and even a few years. However, we have found that patients generally do well and as long as there are thriving clinically the effusions slowly resorb. Clinically symptomatic cases (with ongoing chronic symptoms) is usually associated with empyema (TB or bacterial) or undiagnosed drug resistant TB.

Indeed, it is likely the efficacy of a combination of anti-TB therapy and pleural space drainage will likely improve treatment outcomes (*1*). Having said that, this effect of thoracoscopy on treatment outcomes is somewhat outside the scope of the study. The purpose of the study was to examine the cost effectiveness of tests for diagnosis of pleural TB. Our model was not designed to incorporate effectiveness of treatments (we assume all would undergo the standard 6-month RHZE regimen) so even if thoracoscopy was included, we would not be able to measure its effect on outcomes. More clinical data from a South African setting will be required to determine the cost effectiveness of thoracoscopy, using treatment outcomes as a measure of effectiveness. We have alluded to this in the paragraph above (in the discussion section).

#### **Reviewer B**

**This study analyzed the important role of IRISA-TB in the diagnosis and treatment of TUBERCULOSIS from the perspective of social benefits, and suggested that the inclusion of IRISA-TB in the National TUBERCULOSIS program in South Africa could save high annual health care costs. But there are some problems.**

**Comment 1: It is recommended to use professional statistics software.**

Reply 1: We disagree with the reviewer on this point (in so far as it applies to the analysis conducted here). The basecase and sensitivity analyses in this manuscript were performed using Microsoft Excel and GraphPad Prism Ver 6. While more robust statistical software (STATA, SPSS, or health economics specific software packages such as TreeAge) do provide a broader selection of analyses to be performed, these features are not necessary for this analysis and, in any case, would yield the same result as more generic software such as Excel. Furthermore, several published studies from our group and others, some with the inclusion of more complex modelling, have only used Microsoft Excel and/or Graphpad Prism for analysis of their data (*2-5*)

**Comment 2: How to distinguish SM, MGIT culture, Xpert and ADA, IRISA-TB from multiple or combined use in the same patient?**

Reply 2: Thanks. This is a good point. We chose to examine the cost effectiveness of single test strategies for the various microbiological and immunodiagnostic tests. Indeed, it is common practice in South Africa to concurrently use microbiological i.e. MGIT and/or Xpert, together with immunodiagnostic tests i.e. ADA on pleural fluid (together with any clinical features) to obtain a diagnosis of pleural TB.

However, concurrent testing strategies were not used in this analysis for two reasons (i) there is no available published data on the sensitivity and specificity of a concurrent testing strategy (particularly in the case of Xpert ULTRA, which was only recently replaced the Xpert MTB/RIF assay, and IRISA-TB, which is a brand new assay); (ii) Given the paucibacillary nature of the disease, immunodiagnostic tests are much more sensitive than microbiological tests and thus it is likely that any positive cases detected by Xpert or culture would also be detected by ADA or IRISA-TB. This means that sensitivity of a concurrent test strategy will likely be the same as a single test strategy and thus the cost effectiveness of a dual (Xpert or MGIT + ADA or IRISA) compared to a single test strategy (ADA or IRISA-TB only) will not change. (iii) This combination strategy tends to work only when there is a low cost highly sensitive

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screening test followed by a more expensive but also highly sensitive microbiological test (unfortunately the latter does not exist as Xpert, culture, etc. all have a sensitivity of 30 to 40%.

Nonetheless, we have included this as a limitation in the discussion section:

Page 11, line 309-316:

We only examined the cost effectiveness of single test strategies. There are no published data on the sensitivity and specificity of combined testing strategies, particularly for newer tests such as Xpert ULTRA and IRISA-TB. Furthermore, given the superior sensitivity (and similar specificity) of host biomarker tests (ADA, IRISA-TB) compared to microbiological tests (Xpert ULTRA, MGIT culture), it is highly likely that any cases detected by a combined test strategy would also be detected if using ADA or IRISA-TB alone. Subsequently, combination test strategies are likely to be less cost-effective (due to higher test costs but similar outcomes) than a single test strategy (IRISA or ADA alone).

**Comment 3: The original data in this study are based on existing statistical data rather than actual clinical cases and may not be convincing.**

Reply 3: This is an inherent limitation in modelling the cost effectiveness of new interventions when there is not sufficient ‘real world’ clinical data to input into the model. However, all the estimates are based on clinical studies (with many also including pleural biopsy and thus the level of rigor was high). This is especially true for Xpert ULTRA assay which has only recently replaced the G4 Xpert MTB/RIF assay (and data of its performance on pleural fluid is very limited) and for IRISA TB, which is a new test and thus evaluation studies are limited.

Thus, as performed in several other studies, we used estimates of test performance from existing published clinical evaluation studies to input into our model.

There are several reasons why this is justified: (i) the estimates we used were obtained from published clinical evaluation studies or clinical trials and thus represents actual clinical data. (ii) We selected published studies which best represents the population under study i.e. the majority of estimates were taken from South African studies or, if no SA data was available, from studies in another TB endemic setting. For example, sensitivity and specificity estimates for IRISA-TB, ADA, Xpert Ultra and smear microscopy were primarily obtained from a clinical evaluation study by Meldau et al JCM 2019 (6), and these were very similar to those from other published studies (see Table 1 in manuscript). (iii) Due to the inherent uncertainty in baseline estimates and to generalize our results to other settings, we also conducted a sensitivity analysis where parameters were changed, one at a time, to determine the effect on overall cost-effectiveness. This was especially the case for pleural TB prevalence and the rate of empirical treatment, which can vary widely in different regions. (iv) There are a number of published economic analysis studies (4, 7) that have used estimates of effectiveness from the literature to calculate cost-effectiveness. (v) Nevertheless, we have already included the use of published estimates in our model as a potential study limitation but we have further expanded on it:

Page 11, line 303-306:

“The pleural TB test performance estimates are based, in some cases, on published studies rather than on empirical clinical or programmatic data. Further cost effectiveness analyses are warranted once more clinical data become available and the impact of these tests on clinical outcomes can be better assessed.

**Comment 4: The sensitivity and specificity of various test methods were derived from literature data, not based on local medical data in South Africa, and their reliability was questionable.**

As stated, the majority of estimates were taken or derived from South African studies and thus offers the best alternative to empirically collected clinical trial data. Furthermore, sensitivity analyses were conducted to measure uncertainty around some of the estimates used. Please also see our response to comment 3 above. The studies were rigorously done and published in very good journals. For example, the key study by Meldau was published in the Journal of Clinical Microbiology (flagship journal of the American Society of Microbiology, with an impact factor

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of > 5). Reviewer C also makes a similar point but nevertheless does see considerable merit in the work (see point 1 below for reviewer C).

## Reviewer C

**Congratulations on your work which gives us practical information about this new commercial test. Below, you will find some comments/suggestions/questions that could improve the research.**

### Major comments:

- 1. The paper brings important information on a new commercial diagnostic test for a TB presentation which is difficult to diagnose. Although the results ratify the cost effectiveness of IRISA-TB, the assay is not recommended yet by WHO. Also, the absence of the real cost of IRISA-TB turns the results a kind of speculative. Nevertheless, it does not take off the merit of the paper.**

The reviewer is quite correct in pointing out the lack of a set commercial cost of the IRISA-TB assay. The test cost of IRISA-TB kit was based on an initial market projection range of costs provided by Antrum Biotech. In order to ensure we were not underestimating the cost of IRISA-TB, we chose to use a higher test cost estimate in our analysis. It is highly likely that the cost of the assay will be lower once it becomes commercially available. Nevertheless, we performed an additional sensitivity analysis to demonstrate the effect of changing the test cost of IRISA-TB on the cost effectiveness of this strategy in relation to other test strategies. This shows that even at a test cost of \$50 (twice that of the basecase estimate), IRISA-TB remains the most cost effective strategy. This has been included in the supplement as Figure S2.

### Minor comments:

- 2. Line 146: Typographical error – “cost=effectiveness”**

This has now been corrected

- 3. Line 301: You should cite the absence of a real commercial cost of IRISA-TB as a limitation.**

Thanks for this useful comment. The following has been added onto the limitations section of the discussion:

Pg 11, line 322-328:

The IRISA-TB assay is not yet commercially available due to COVID-associated manufacturing delays (though it is planned to be available before the end of 2022) and thus the cost of the assay could only be estimated based on a range of values provided by Antrum Biotech, the developers of IRISA-TB. In order not to underestimate the cost of IRISA, we chose to use the higher value of this range as the basecase cost estimate in our analysis. IRISA-TB still remained the most cost effective option, even when the test was further increased to \$50 (Figure S2 in the supplementary appendix).

## References

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  2. J. M. Gauthier *et al.*, Economic evaluation of the specialized donor care facility for thoracic organ donor management. *J Thorac Dis* **12**, 5709-5717 (2020).
  3. A. Pooran *et al.*, Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation. *Lancet Glob Health* **7**, e798-e807 (2019).
  4. A. Pooran *et al.*, Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. *BMC Pulm Med* **10**, 7 (2010).
  5. D. Abushanab, D. Al-Badriyeh, D. Liew, Z. Ademi, First-line Treatment with Empagliflozin and Metformin Combination Versus Standard Care for Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease in Qatar. A Cost-Effectiveness Analysis. *Curr Probl Cardiol* **47**, 100852 (2022).
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6. R. Meldau *et al.*, Same-Day Tools, Including Xpert Ultra and IRISA-TB, for Rapid Diagnosis of Pleural Tuberculosis: a Prospective Observational Study. *J Clin Microbiol* **57**, (2019).
  7. N. A. Menzies, T. Cohen, H. H. Lin, M. Murray, J. A. Salomon, Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med* **9**, e1001347 (2012).
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