Decision Tree Model

A simple decision tree model (*Figure S1*) was used to perform a cost-consequence analysis from the South African healthcare provider perspective to evaluate five different single testing strategies for the diagnosis of pleural TB among a hypothetical cohort of 1,000 suspected TB cases presenting at primary care clinics: (I) Smear microscopy (SM); (II) Mycobacterial-Growth-In-tube liquid culture (MGIT); (III) Xpert MTB/RIF ULTRA (Xpert) (IV); Adenosine deaminase (ADA); (V) Interferon-gamma Release Immuno-Suspension Assay or IRISA-TB (IRISA-TB).

Probabilities

Probability estimates were primarily taken from the published literature, specifically using studies performed in similar settings and populations to our model i.e., TB suspects from TB endemic countries. In some instances where no published data was available, base case estimates were informed by advice from clinical experts in the field but ranges were comprehensively explored in sensitivity analyses.

Prevalence of pleural TB

The prevalence of TB was taken from the TB NEAT trial, a multi-centre randomised control trial which assessed the impact of Xpert MTB/RIF on patient outcomes when performed at the point of care in suspected cases attending primary care clinics (17). The prevalence of EPTB was obtained from WHO estimates (1) and that of pleural TB among EPTB cases from two surveillance studies conducted in South Africa (2,3). These estimates were used to calculate the prevalence of pleural TB among all TB suspects. However, given the variation of prevalence in different settings e.g. high HIV burden, pleural TB prevalence was extensively varied in sensitivity analyses.

Diagnostic test sensitivity and specificity

Studies on diagnostic test performance in pleural fluid were primarily obtained from published literature. Estimates on smear microscopy (6,7) and MGIT (7-9) sensitivity and specificity were obtained from studies performed in high TB burden settings such as India, China and South Africa. Only two studies (6,7) were identified where Xpert ULTRA was used for pleural TB diagnosis in a high burden setting, one being in South Africa. There is extensive performance data on the use of ADA for pleural TB diagnosis; estimates used in this model were obtained from a South African study and two recent meta-analyses (6,10,18). Finally, although there are several studies that investigated the performance of unstimulated IFN-γ for pleural TB diagnosis, only two studies evaluated the performance of the IRISA TB format (6,11). Estimates from the more recent publication (6) were chosen because this study evaluated a later version of the assay. In order to assess a reasonable range of test sensitivities and specificities in our model, these parameters were increased or decreased by 20% in the univariate sensitivity analysis.

Treatment initiation and empirical treatment

We assumed all patients with a positive test would be initiated on treatment. We did not account for loss to follow up and other linkage to care components as this would unlikely be influenced by the choice of testing strategy.

There was no available published data on the rate of empirical treatment among suspected EPTB or pleural TB cases. However, given the difficulty in diagnosing pleural TB compared to pulmonary TB using traditional tests, it was assumed that empirical treatment rates would be higher among pleural TB patients. In the TB-NEAT trial, empirical treatment rates among suspected pulmonary TB cases was ~30% (17). In the XTEND trial, which evaluated the impact of Xpert MTB/RIF in a pragmatic setting, empirical treatment rates of 15% among all TB treatment initiations (33). Based on these estimates in pulmonary TB and advice from clinical experts, we chose an empirical treatment rate of 50% in the base case analysis. However, this was extensively varied in the sensitivity analyses.

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Formulas

Bayesian statistics were used to calculate the probability of a positive and negative test result using pleural TB prevalence among suspected TB cases as well as diagnostic test sensitivity and specificity:

Probability of a positive result = (Sensitivity × Prevalence) + [(1 - Specificity) × (1– Prevalence)]

Probability of a negative result = (Specificity × (1– Prevalence)) + [(1– Sensitivity) × Prevalence) × (1– Prevalence)] + [(1– Sensitivity) × Prevalence)]

Furthermore, positive predictive value (true positive) and negative predictive values (true negative) for each test were subsequently calculated:

Positive Predictive Value (PPV) = Sensitivity × Prevalence/Probability of a positive result

Negative Predictive Value (NPV)= Specificity × (1 – Prevalence)/Probability of a negative result

False positive and false negative probabilities were calculated as 1-PPV and 1-NPV, respectively.

References

33. McCarthy K, Fielding K, Churchyard GJ, et al. Empiric tuberculosis treatment in South African primary health care facilities - for whom, where, when and why: Implications for the development of tuberculosis diagnostic tests. PLoS One 2018;13:e0191608.

https://dx.doi.org/10.21037/jtd-22-106

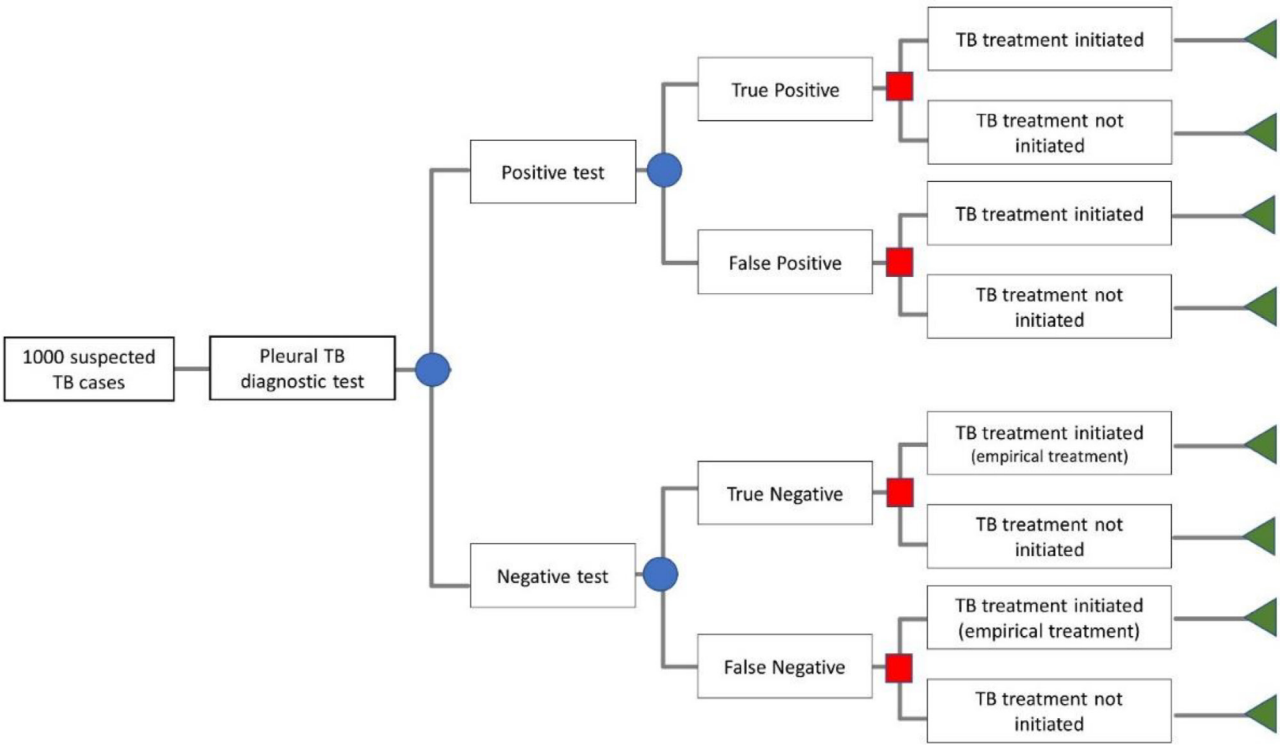

Figure S1 Decision tree of each pleural TB diagnostic strategy. Decision tree used to calculate cost and effectiveness of 5 different strategies for the diagnosis of pleural TB. TB, tuberculosis.

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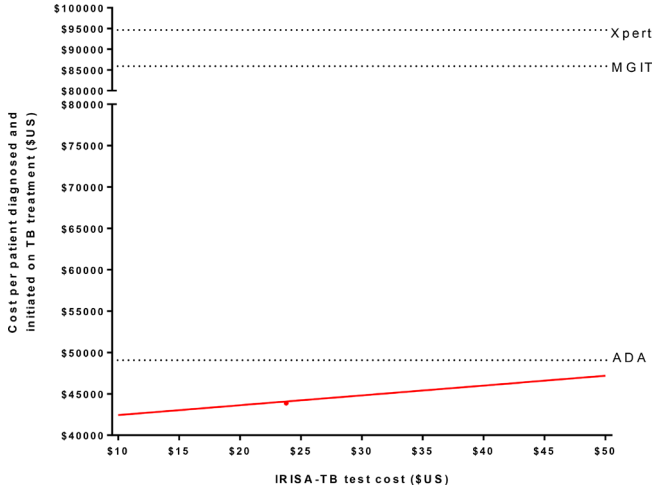

Figure S2 The effect of Interferon-gamma Release Immuno-Suspension Assay (IRISA-TB) test cost on cost-effectiveness of the IRISA-TB diagnostic strategy. The effect of varying IRISA-TB test cost on the cost per pleural TB patient diagnosed and initiated on TB treatment. The red dot represents the base case cost-effectiveness of IRISA-TB ($44,084) at a test cost of $23.82. Each dotted line represents the cost-effectiveness (y-axis) of each of the other diagnostic strategies: Mycobacterial-Growth-In-tube liquid culture (MGIT); Xpert MTB/RIF ULTRA (Xpert); Adenosine deaminase (ADA).

Table S1 Component costs used to calculate the unit cost of the IRISA-TB assay

Component	Cost ($US)
Consumables	$20.55*
Staff time	$0.57
Equipment	$0.53
Overheads	$2.17
Total	$23.82

*, note that the IRISA-TB assay is expected to cost ~$12 once it becomes commercially available.

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