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Latent tuberculosis infection screening of adult close contacts: a cost-utility analysis

Nathan Green*[1], Kavina Manalan[2], Manabu Hayama[3,4], Marie O'Donoghue[2], Suranjith Seneviratne[5], Nicholas Drey[6], Onn Min Kon[2,3]

1. **Department of Statistical Science, University College London, UK**
2. **Tuberculosis Service, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK.**
3. **Imperial College London, London, UK**
4. **Medical Science Department, Late Development Oncology TA Division, Research & Development AstraZeneca K.K., Tamachi Station Tower N, 3-1-1, Shibaura, Minato-ku, Tokyo 108-0023, Japan**
5. **Royal Free London NHS Trust, London, UK**
6. **School of Health Sciences, City, University of London, London, UK.**

* corresponding author

Authors' E-mail addresses:

Nathan Green: n.green@ucl.ac.uk

Kavina Manalan: kavina.manalan@nhs.net

Manabu Hayama: manabu.hayama1@astrazeneca.com

Marie O'Donoghue: m.odonoghue@nhs.net

Suranjith Seneviratne: suranjith.seneviratne@nhs.net

Nicholas Drey: n.drey@city.ac.uk

Onn Min Kon: onn.kon@nhs.net

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Take home message

A decision-analytic Markov model was used to compare costs and quality-adjusted life years (QALYs) associated with five screening strategies for close contacts of pulmonary TB cases in London and found IGRA alone strategies were the most cost-effective.

ABSTRACT

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Background: The 2016 National Institute for Health and Care Excellence guidelines recommended the tuberculin skin test (TST), at a 5-mm induration size cut-off, for the diagnosis of latent tuberculosis infection (LTBI) among adult close contacts of active tuberculosis (TB) cases. This study analysed a well characterised cohort of adult close contacts in London and assess the cost-effectiveness of LTBI screening strategies with combinations of TST and interferon-gamma release assays (IGRAs) in a decision-analytic model.

Methods: Close contacts of pulmonary TB cases who were tested with TST and IGRA between January 2008 and December 2010 were retrospectively reviewed. Using a NHS perspective and lifetime horizon, a decision-analytic Markov model was used to compare costs and quality-adjusted life years (QALYs) associated with five screening strategies followed by LTBI treatment: TST alone, IGRA (QuantiFERON-TB Gold In-Tube [QFT] or T-SPOT.TB [T-SPOT]) alone, and TST positive followed by IGRA.

Results: This study included 381 asymptomatic close contacts aged 18 to 65 years (mean 35.2 (SD: 11.3)). 75.3% had received BCG vaccination. Among the five strategies, for a willingness to pay threshold of £25,000 and using incremental net monetary benefit (INMB) with TST as comparator, the IGRA alone strategies were the most cost-effective, marginally QFT over T-SPOT (QFT £214; T-SPOT £199).

Conclusion: Single-step IGRA, particularly QuantiFERON, is preferable for LTBI screening of adult close contacts of pulmonary TB cases.

Key words: TST, IGRA, QFT, T-SPOT, cost-effectiveness, health economic analysis

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INTRODUCTION

Tuberculosis (TB) remains one of the top ten causes of death worldwide. The estimated number of deaths from TB increased between 2019 and 2021, reversing years of decline between 2005 and 2019. [1] England is classified as a low incidence country with a rate of 7.3 per 100,000 [2]. However, there is considerable variation in the TB incidence across England with the main burden concentrated in large urban areas. The TB incidence rate is particularly high in London, and the rate in 2012 was the highest among all high-income European countries [3].

Latent TB infection (LTBI) identification and treatment are imperative to achieve a significant reduction in TB deaths and incidence rates globally. However, there is no gold standard for LTBI diagnosis, and the identification of LTBI can only be indicated by indirect approaches which confirm the immunological sensitization of the individual to TB antigens, such as the tuberculin skin test (TST) and interferon-gamma release assay (IGRA) [4]. Defining a close contact as living in the same household or in frequent contact with a source case, UK National Institute for Health and Care Excellence (NICE) guidelines, updated in 2019, recommend that close contacts of pulmonary TB aged 18 to 65 years should be tested by TST, and that a confirmatory IGRA after positive TST can be considered if further evidence is needed to start LTBI treatment [5]. A positive TST is defined as a 5-mm threshold regardless of BCG vaccination status in the updated guidelines, whereas a 6-mm threshold for non-BCG-vaccinated populations and a 15-mm threshold for BCG-vaccinated populations was previously recommended. These updated guidelines could increase the number of unnecessary TSTs and false-positive cases, particularly in urban areas with high TB incidences as the specificity of TST is low in BCG-vaccinated populations [6].

As healthcare resources are scarce even in high-income countries, the cost-effectiveness of LTBI screening has been reported in many countries. Previous health economic analyses of LTBI screening indicated significant differences in the type of analysis,

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time horizon, outcome measures and modelling methods between the included studies, which resulted in a lack of clarity about the most cost-effective approach for LTBI screening.[7] Though previously assessed in children [8], there is limited evidence about the cost-effectiveness of LTBI screening of adult close contacts in the UK and it is possible that the screening strategies recommended by the national guidelines might not be optimal in the urban areas with a higher TB incidence, such as London [2,3].

Our aim was to determine the most cost-effective strategy for LTBI screening of adult close contacts in a London centre. The objectives were to analyse the characteristics and screening test results of adult close contacts in London following the 2016 NICE guidelines and to assess the cost-effectiveness of LTBI screening strategies with various combinations of TST and IGRAs in a decision-analytic model using a cohort of clinical data.

METHODS

The study was conducted at the TB clinic in St Mary's Hospital, Imperial College Healthcare NHS trust, which is a major acute hospital for Northwest London. Ethical approval was not sought as we utilised fully anonymised data that were collected as part of routine delivery of clinical services.

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Clinical audit data of all close contacts of active TB cases who visited the TB clinic between January 2008 and December 2010 were retrospectively reviewed. In accordance with the 2016 NICE guidelines, asymptomatic close contacts of pulmonary TB cases aged between 18 and 65 years who were offered both TST and IGRA were included in the data review. A TST induration of at least 5-mm was considered a positive result regardless of BCG vaccination status. One of two commercially available IGRAs (QFT or T-SPOT) was performed and results defined as positive, negative or indeterminate depending on the manufacturer's criteria.

A health economic analysis was conducted to compare the cost-effectiveness of LTBI screening strategies with different combinations of TST and IGRAs for adult close contacts of pulmonary TB cases in London from the perspective of the National Health Service (NHS). There was no health economics plan developed before conducting the study. Decision trees and a Markov model were constructed and analysed using Microsoft (MS) Excel and the statistical programming language R [9]. A decision tree is a graphical model that encodes possible patient pathways and outcomes, including costs, health effects, and probabilities. A Markov model simulates the progression of patients through different health states over time, accounting for transitions, costs, and outcomes associated with each state, to evaluate long-term health interventions. By linking the two types of models we can represent the short-term diagnostic pathway and the subsequent lifetime process. Model assumptions of the analysis are presented in Supplementary Material, including the separate decision trees in Figures S1-3. Posterior probability distributions were obtained using the clinical audit data in a Bayesian model using WinBUGS [10] called from R (see Supplementary Material Section 2). By applying Bayes' theorem, the prior knowledge from literature and expert elicitation can be systematically combined with the clinical data to obtain updated estimates. Other model input parameter values used were obtained from literature (see Table 1). The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist [11] is a

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set of guidelines aimed at enhancing the quality of reporting in health economic evaluations. You can find the checklist in the Supplementary Material. All model code and data is publicly available at https://github.com/n8thangreen/LTBIdiagTST.

Five screening strategies were considered based on the combination of TST and IGRAs: “TST alone”, “QFT alone”, “T-SPOT alone”, “TST positive followed by QFT (TST/QFT)”, “TST positive followed by T-SPOT (TST/T-SPOT)”. The TST alone strategy was used as the reference in line with the current UK NICE guidelines [5]. For those who have positive screening results without active TB disease, 3 months of LTBI treatment with daily isoniazid (INH) and rifampicin (RFP) was offered [26]. Decision trees were used to represent the LTBI screening and treatment stage. As there is no gold standard for LTBI diagnosis, the prevalence of LTBI in the model population was estimated based on the clinical data in the TB clinic (Supplementary Material Table S2).

After the LTBI screening and treatment stage, a Markov model was used to simulate the whole cohort to death. Six exhaustive and mutually exclusive Markov states were defined (see Figure 1): 1) Active TB, 2) LTBI with complete treatment, 3) LTBI with incomplete treatment, 4) LTBI without treatment, 5) No LTBI and 6) Death. The cycle of the Markov model was 1 year. Cycles continue until time of death to capture all QALYs and costs. Lifetimes were constrained to no more than 100 years old. We assumed that there would be no drug-resistant TB case in the model population and all of the individuals with active TB would complete the standard regimen of the intensive phase with INH, RFP, pyrazinamide (PZA) and ethambutol (EB) for two months followed by the continuation phase with INH and RFP for four months. Transition probabilities in the decision trees and Markov model were calculated using relevant literature and the clinical data.

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Figure 1.

In the model, only direct costs incurred by the NHS were included. [5,12,19,21,22,27] All costs were uplifted to 2024 pound sterling using current annual Consumer Prices Index [28]. Age-specific utilities of normal health states were obtained from the literature [23]. The utility losses by the treatments of LTBI, hepatitis and active TB were fixed during the time horizon and obtained from the literature. [8,24] Future costs and quality-adjusted life years (QALYs) were discounted at 3.5% per year as per NICE recommendations (NICE CHTE Methods review discounting). A baseline willingness-to-pay (WTP) threshold of £25,000 per QALY was used[29]. Net monetary benefit (NMB) were compared to determine the most cost-effective strategy. Probabilistic sensitivity analysis (PSA) used posterior draws from the Bayesian model. One-way deterministic sensitivity analysis (DSA) evaluated the impacts of the input parameters on the NMBs varying each parameter within the ranges as shown in Table 1. Results are shown in tornado plots where each bar represents the impact of a single input parameter on the INMB. Parameters are ordered from largest to smallest impact. This thus highlights which parameters have the most significant impact on the INMB and making it easier to understand model uncertainty [30].

RESULTS

Clinical data review

Overall, 381 asymptomatic close contacts of pulmonary TB cases were analysed. The mean age (± standard deviation) was 35.2 (± 11.3) years, and 200 participants (52.5%) were male. Among all participants, 179 (47.0%) were categorised as White ethnic, 132 (34.6%) UK born, and 287 (75.3%) were BCG-vaccinated (see Table 2). Of the 381 participants who were offered both TST and IGRA, 374 (98.2%) accepted TSTs and 366 (97.9%) attended the TST reading. Further, 378 out of 381 participants (99.2%) accepted

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the IGRAs. Among 204 participants with positive TST results, 203 (99.5%) accepted the IGRAs. Among the 203 participants, 78 (38.4%) had positive IGRA results. Among 162 participants with negative TST results, 161 (99.4%) accepted the IGRAs. Among the 161 participants, 9 (5.6%) had positive IGRA results. The full set of test results are presented in Figure 2.

Figure 2.

Health economic analysis

The model population's age at the start of the simulation was set to 35 years old, based on the clinical cohort's average age. The estimated prevalence of LTBI was 23% in the base-case analysis (Supplementary Material Figure S7). All other transition probabilities in the decision trees and Markov model are presented in Supplementary Material Table S1. Table 3 shows total costs, total QALYs and NMBs in the model cohort of 1,000 close contacts in the base-case analysis. The QFT alone strategy was the least costly with £277.05 per person, whereas the TST alone strategy was the most costly with £451.52. The TST followed by IGRA strategies were the least effective with the lowest QALYS but in fact the QALYs between study were very similar. Among the five strategies, the two IGRA alone strategies were the most cost-effective with the highest NMB of £213.9 and £198.64 for QFT and T-SPOT, respectively and at the cost-effectiveness threshold of £25,000 per QALY in the base-case analysis. Figure 3 shows the corresponding cost-effectiveness plane, which shows the difference in costs and QALYs against the TST alone baseline scenario.

The deterministic sensitivity analysis results are presented in tornado plots in the Supplementary Material Figures S5 and S6. They showed that reactivation probability, test

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costs and test performance are factors affecting cost-effectiveness but no input parameter was sensitive to the superiority of the IGRA alone strategies.

Figure 3.

DISCUSSION

In the main analysis, we estimated the total costs and QALYs of five strategies, with different combinations of TST and IGRAs, in the lifetime periods of close contacts aged 35 years old at the time of entering the model. Our results suggest that T-SPOT or QFT alone was the best strategy for LTBI screening of adult close contacts in terms of the cost-effectiveness, although the 2016 NICE guidelines recommend TST-based strategies [5].

Two-stage testing may be justified to avoid unnecessary LTBI treatment particularly for individuals with risk of complications due to the treatment. It has been reported that the risk of progression to active TB was significantly higher in individuals with positive IGRA results than in those with positive TST results. [31] This could justify the confirmatory IGRA after positive TST. A cost-utility analysis of LTBI screening in the U.S., in which only individuals with positive TST results were included, reported that confirmatory QFT was cost-effective. [32] In Germany, it was shown that TST positive at a 5-mm threshold followed by QFT was the most cost-effective, in close contacts aged 20 [33]. However, the estimated prevalence of LTBI in this study was 11%, which was significantly lower than our study estimate. In the UK and within a similar population, Pooran *et al*. reported that TST positive followed by IGRA strategy was more cost-effective for LTBI screening of close contacts than both TST alone and IGRA alone strategies. However, the outcome measure was the number of active TB cases prevented rather than QALY and the time horizon was only two years [19].

Reasons for our results are that the TST alone pathway demonstrates relatively poor

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performance, yielding a high number of false positives and incurring additional costs due to the requirement of two clinical visits[5]. Given the relatively low prevalence, even in London where this study is based[3], overdiagnosis emerges as a significant concern, particularly in light of the comparatively low rates of progression to active TB[17].

Even though healthcare systems are different by countries, many other studies in high-income countries reported the superiority of single-step IGRA strategies. Over a 20 year time horizon, T-SPOT alone was the most cost-effective strategy for 20 year- and 40 year-old close contacts in Switzerland [34]. In Japan, Kowada *et al*. concluded that QFT was the most-cost-effective strategy in a model cohort with the age of 20 years over a lifetime horizon (26). In Canada, QFT was an optimal strategy for close contacts aged 35 [35].

In the clinical data review, two main findings were made. Firstly, the demographic patterns were highly heterogeneous in the cohort of adult close contacts in London. Almost half of the participants were categorised in the non-White ethnic groups, and only one third had been born in the UK. Considering high TB incidence rates in the non-UK born populations and the non-White ethnic groups, the demographic results of the present study could suggest that there are more LTBI cases among adult close contacts in London than the rest of England [2].

Secondly, the majority of the participants were BCG-vaccinated despite of the high proportion of the non-UK born participants, and only 38.4% of the participants with positive TST results had positive IGRA results. International studies have demonstrated a discordance between TST and IGRA results in BCG-vaccinated populations. A study in Saudi Arabia using a cohort with a high BCG vaccination rate indicated that among the participants who had positive TST results, at a 10-mm threshold, 54.8% had negative QFT results [36]. The 2016 NICE guidelines recommend that TST should be performed for LTBI screening of adult close contacts, and that individuals with the induration size of 5-mm or larger are considered positive regardless of BCG vaccination status [5]. The high level of

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discordance between the TST and IGRA results in our cohort, as well as the high BCG coverage, suggests that TST alone based strategies may not be appropriate for LTBI screening of adult close contacts in London.

Our analysis was limited by the retrospective nature and the assumption of HIV negativity and fully drug sensitive TB. The clinical data review was a retrospective analysis at a single institution; therefore, the selection of those who were offered the screening tests might have been biased [37]. In the health-economic analysis, we did not consider HIV infected individuals in the model cohort because the HIV status was not available in the clinical data review and a low and reducing background rate was assumed[38]. Also, we did not consider drug-resistant TB cases in the present study because the number and proportion of multidrug-resistant TB (MDR-TB) cases have been decreasing and the transmission of MDR-TB in the UK is still rare. [2,39] We have had to make several assumptions and considered several model inputs that had been estimated in different populations and countries. However, the sensitivity analysis showed the robustness of the superiority of the IGRA alone strategy among adult close contacts in London.

Future work should aim to confirm our findings and obtain sufficient data to enable subgroup analyses among patients who are not BCG vaccinated and with TST cut off of 10 or 15-mm.

LTBI screening of adult close contacts is essential for TB control in London, which has the highest incidence in England. Considering the high BCG coverage and the high level of discordance between TST and IGRA results in our cohort, TST at a 5-mm threshold might not be appropriate for adult contact screening in London, contrary to the latest recommendation by NICE. Single-step IGRA is preferred with respect to cost-effectiveness according to the results of the present study. Further economic studies in other areas and populations in England are needed to evaluate whether this approach is also applicable to other regions and to allow usage of resources of the NHS most effectively.

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Authors' contributions are as follows. Study design and set up by NG, MH and MO'D with input by OMK, SS and ND. MO'D collected and analysed the clinical data in St Mary's Hospital. NG and MH analysed the data and designed the economic model with input from KM and OMK. NG, KM, MH drafted the manuscript with input from all other authors. All authors approved the final version.

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***Table 1. Model parameter values* for the decision trees and Markov model. † inflated to 2024 value.**

Name	Label	Base-case value	Range	Reference
Probability				
Probability of accepting LTBI treatment	$pAccept_chemo$	0.95	0.5 - 1.0	[8,12]
Probability of developing hepatitis due to LTBI treatment	$pHep$	0.002	0.001 - 0.003	[12]
Probability of completing LTBI treatment	$pComp_chemo$	0.8	0.5 - 0.9	[13]
Efficacy of complete LTBI treatment	Eff_comp	0.65	0.5 - 0.8	[12]
Efficacy of incomplete LTBI treatment	Eff_incomp	0.21	0.1 - 0.3	[12]
Sensitivity of TST	TST_sens	0.79	0.69 - 0.89	[14]
Specificity of TST	TST_spec	0.59	0.46 - 0.73	[14]
Sensitivity of QFT	QFT_sens	0.886	0.812 - 0.944	[15]
Specificity of QFT	QFT_spec	0.995	0.959 - 1	[15]
Sensitivity of T-SPOT	$TSPOT_sens$	0.872	0.643 - 0.991	[15]
Specificity of T-SPOT	$TSPOT_spec$	0.998	0.996 - 1	[15]
Lifetime risk of TB reactivation (for individual aged 35 years) Annual probability of TB reactivation without treatment partial treatment completed treatment	pTB $pReact$ $pReact_incomp$ $pReact_compl$	0.12 0.0072 0.0059 0.0026	0.08 - 0.19	[16] [17] [12] [12]
Age-specific annual probability of death for TB active patients 15 – 44 45 – 64 > 64	$pDeath_tb$	 0.02 0.087 0.31		[18]
Cost (£)				
TST†	c_TST	25.02	12.51 – 50.05	[19]
QFT (including phlebotomy)†	c_QFT	29.11	15.16 – 55.67	Imperial College NHS Trust, [20]
T-SPOT (including phlebotomy)†	c_TSPOT	43.17	22.21 – 83.87	Imperial College NHS Trust, [20]
TB nurse appointment (Band 6)	c_Ns	53	43 - 63	[21]
Outpatient consultation (first visit; WF02B)	c_out	224		[22]
Outpatient consultation (follow-up visit; WF02A)	c_fuout	166		[22]
Chest X-ray (service code 812)	c_CXR	46	40 - 52	[20]
Liver function tests†	c_LFT	3.95	2.63 – 5.27	[20]
TB treatment†	c_TB	6055	3028 - 12110	[5]
Hepatitis treatment†	c_Hep	984	492 - 1968	[19]
Utility				
Age-specific utilities for normal health (years)				

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< 25 25 - 34 35 - 44 45 - 54 55 - 64 65 - 74 >74		0.94 0.93 0.91 0.85 0.8 0.78 0.73		[23]
Utility loss				
LTBI treatment (complete) Hepatitis B (per year) Active TB		0.001 0.14 0.15		[8,24] [25] [8,24]

Abbreviations; LTBI, latent tuberculosis infection; TST, tuberculin skin test; QFT, QuantiFERON-TB Gold In-Tube; T-SPOT, T-SPOT.TB assay; TB, tuberculosis.

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Table 2. Baseline characteristics of the sample of adult close contacts of pulmonary TB cases.

Description	Value
Sample size, n	381
Age, mean (±SD) (years)	35.2 (±11.3)
Gender, n (%)	
Male	200 (52.5)
Female	181 (47.5)
Ethnicity, n (%)	
White	179 (47.0)
Black	108 (28.3)
South Asian	35 (9.2)
Other ethnic groups or unknown	59 (15.5)
Country of birth, n (%)	
UK	132 (34.6)
Other	249 (65.4)
BCG, n (%)	
Vaccinated	287 (75.3)
Unvaccinated	94 (24.7)

Abbreviations; TB, tuberculosis; SD, standard deviation; BCG, Bacillus Calmette-Guérin.

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Table 3. Cost-effectiveness results of LTBI screening strategies per adult close contacts in London.

Strategy	QALY (95% CI)	Cost (£) (95% CI)	ΔQALY	ΔCost (£)	ICER (£/QALY)	INMB (£)
TST alone (reference)	18.726 (18.722, 18.728)	451.52 (425.37, 486.1)	-	-	-	-
QFT alone	18.727 (18.724, 18.73)	277.05 (251.82, 307.74)	0.001577	-174.473	-110641	213.9
T-SPOT alone	18.727 (18.724, 18.73)	289.93 (263.55, 317.49)	0.001482	-161.595	-109053	198.64
TST/QFT	18.725 (18.722, 18.727)	332.55 (299.87, 361.56)	-0.00094	-118.971	126611.2	95.48
TST/T-SPOT	18.724 (18.722, 18.727)	342.71 (312.04, 367.23)	-0.00118	-108.81	92421.06	79.38

NMBs were calculated at the cost-effectiveness threshold of £25,000 per QALY.

Abbreviations; LTBI, latent tuberculosis infection; QALY, quality-adjusted life year; NMB, net monetary benefit; TST, tuberculin skin test; QFT, QuantiFERON-TB Gold In-Tube, T-SPOT, T-SPOT.TB assay; TST/QFT, TST positive followed by QFT; TST/T-SPOT, TST positive followed by T-SPOT.

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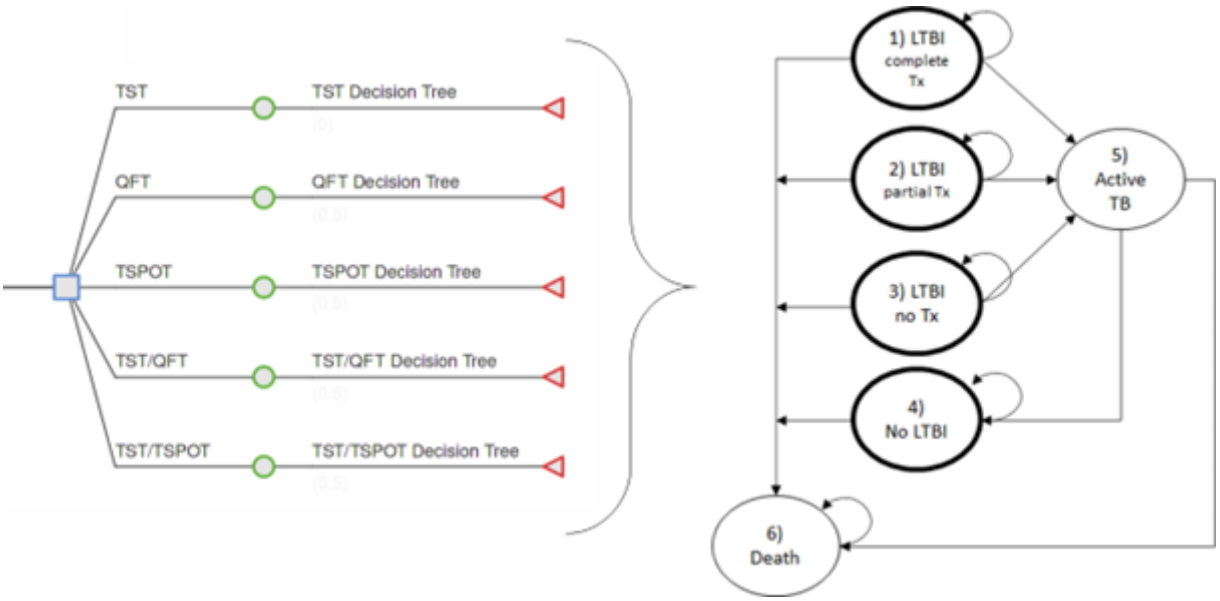


Figure 1

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Figure 2

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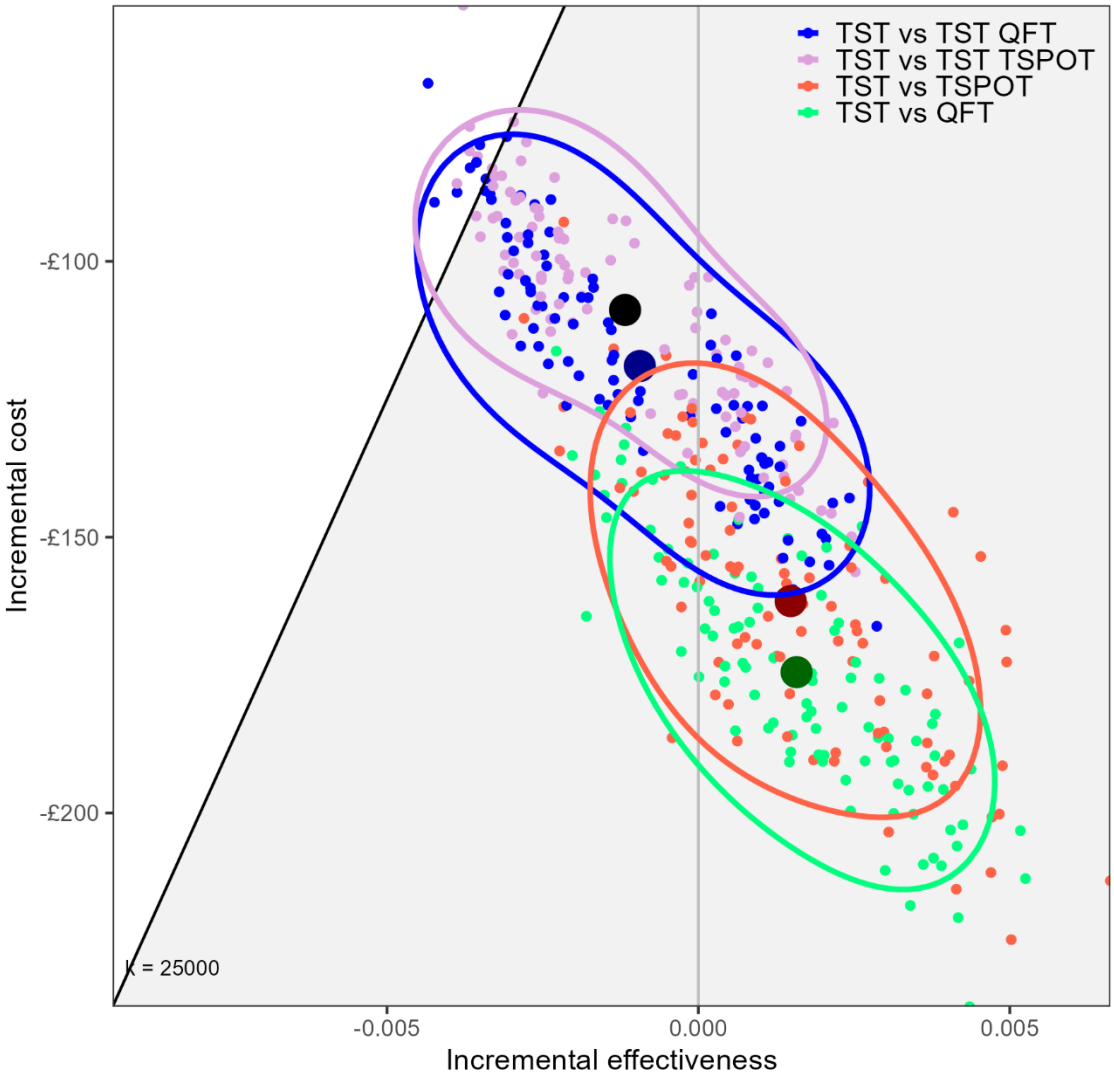


Figure 3

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Supplementary Material

We present here more detailed modelling, results and analysis to complement the main paper. All figure and table numbers are preceded by S to indicate that they are from the Supplementary Material.

1. FIGURES

Figures S1, S2, S3 show the full decision trees used for each diagnostic pathway. The first branch is always the decision of which tests to perform and follows the test decision branch in the decision tree in Figure 1 in the main manuscript. The trees are structured in terms of test results and positive or negative predicted value. An alternative structure would be to represent the LTBI prevalence and then test sensitivity and specificity. The subpopulations at terminal nodes are appropriately aggregated to feed into the subsequent Markov model starting states.

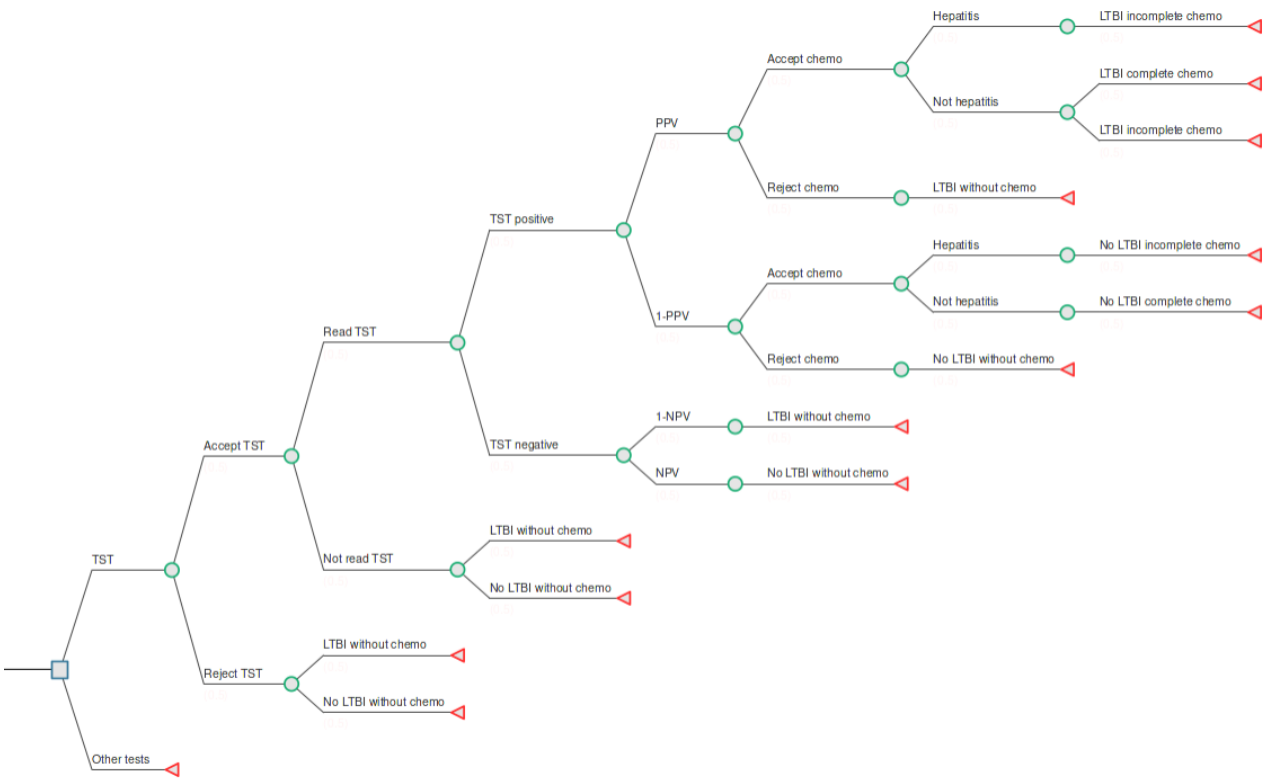


Figure S1. Decision tree for TST alone strategy.

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Abbreviations; TST, tuberculin skin test; LTBI, latent tuberculosis infection; PPV, positive predictive value of TST; NPV, negative predictive value of TST.

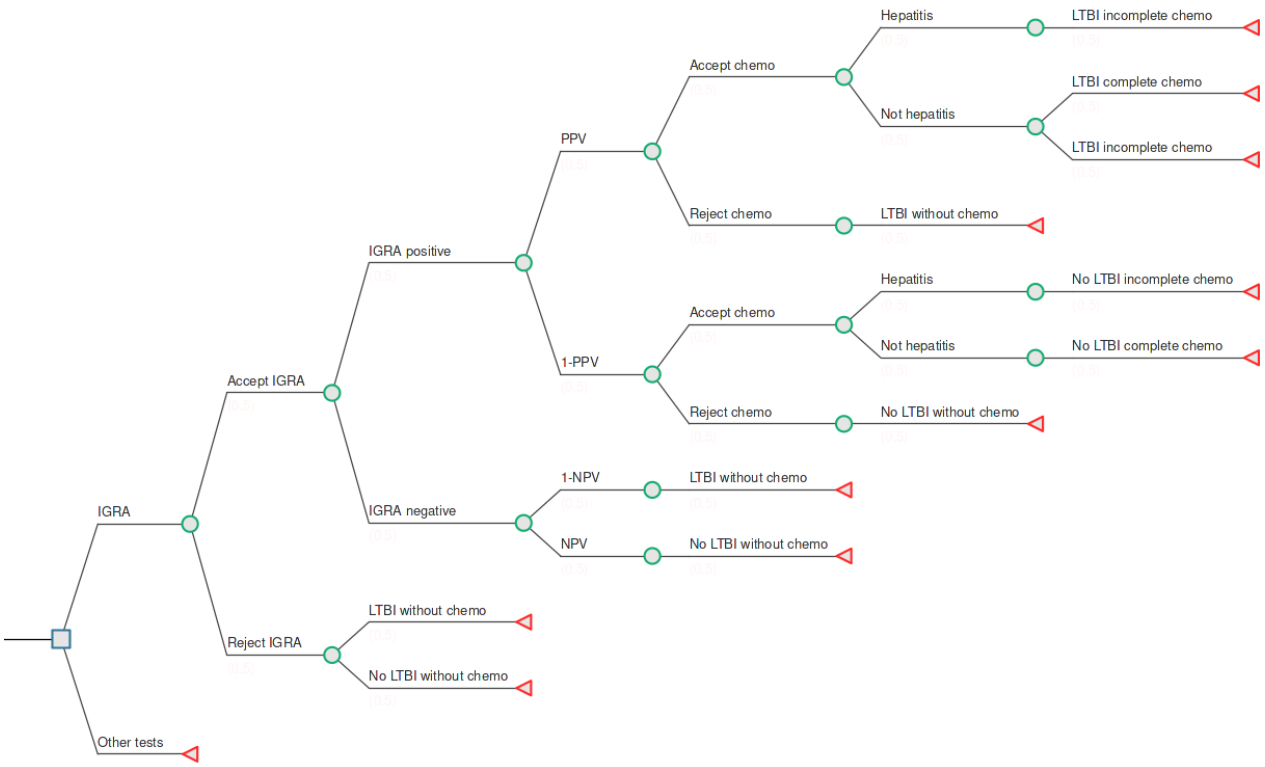


Figure S2. Decision tree for IGRA alone strategy.

Abbreviations; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; PPV, positive predictive value of QFT-GIT (T-SPOT); NPV, negative predictive value of QFT (T-SPOT); .

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Figure S3. Decision tree for TST positive followed by IGRA strategy.

Abbreviations; TST, tuberculin skin test; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; NPV, negative predictive; PPV, Positive predictive value.

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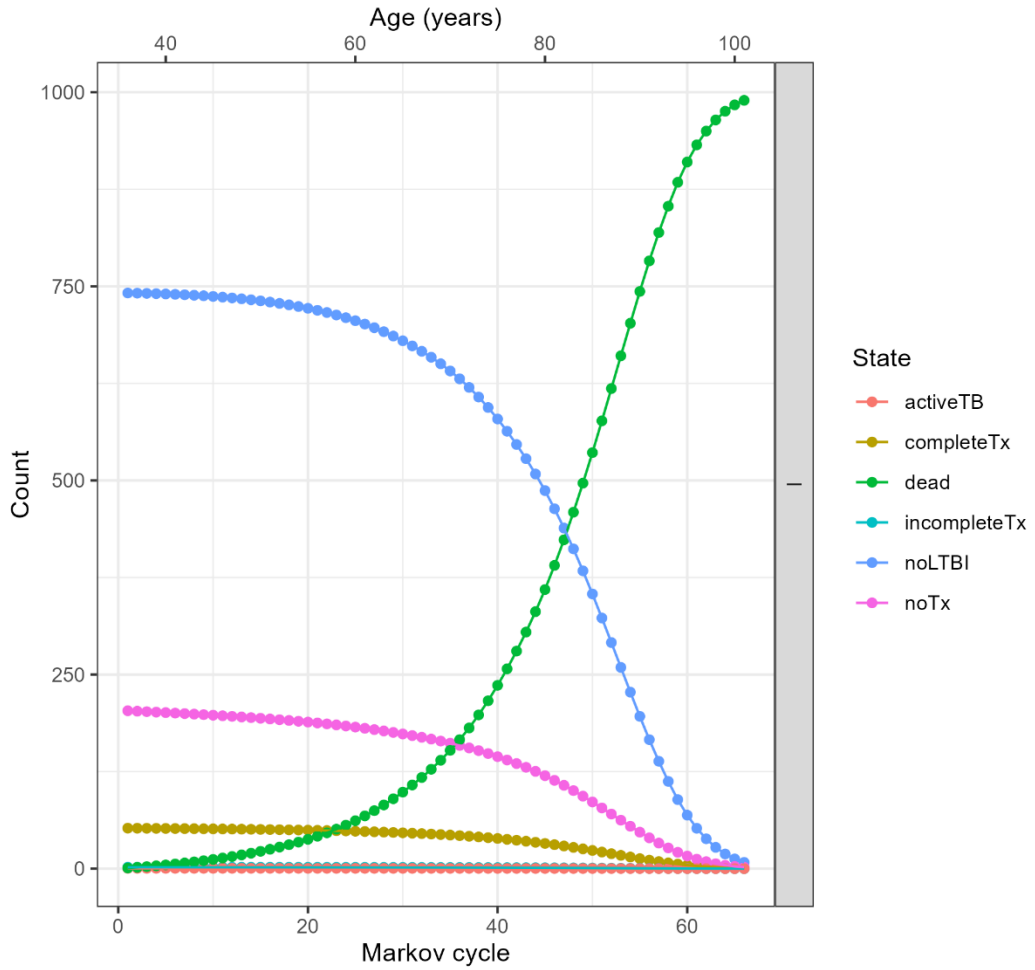


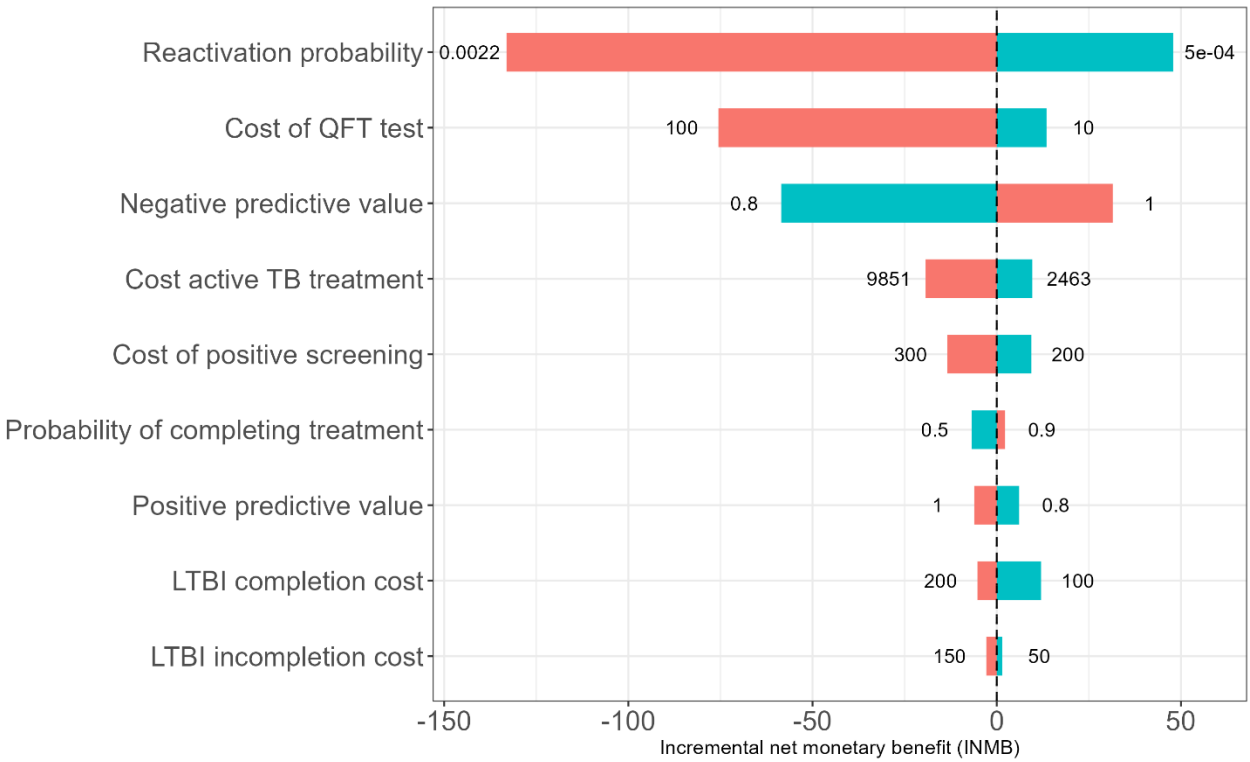
Figure S4. State counts over time for the population-level Markov model. Example simulation.

Abbreviations; TST, tuberculin skin test; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; NPV, negative predictive; PPV, Positive predictive value.

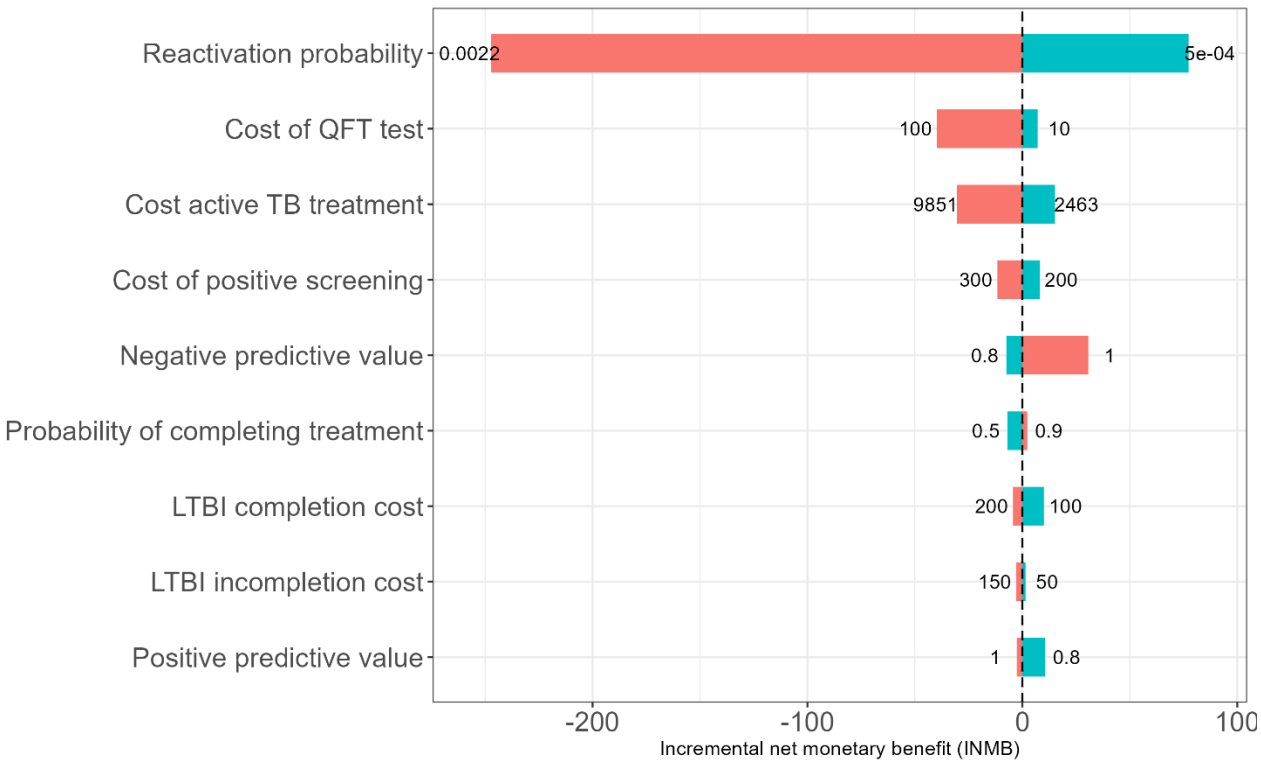
Figure S4 shows and example of the change in state occupancy over time during a typical Markov model simulation for a synthetic cohort of 1000 patients. Both age and Markov cycle time axes are shown. The distribution amongst the states determined by the decision tree is show by the starting proportions at cycle 0. As time progresses the counts in completeTx, incompleteTx, noLTBI and NoTx states decrease as patients enter the absorbing death state. The active TB state (red line) is the only other state which has a positive entry probability but the scale on the plot doesn't show the relatively small sizes.

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a)



b)



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Figure S5. Tornado plots of deterministic sensitivity analyses for incremental net monetary benefit comparing within diagnostic pathway. Willingness-to-pay of £25,000. Scenarios are relative to primary analysis with baseline values.

a) One-step QFT diagnostic pathway scenario; b) two-step TST followed by QFT scenario.

Abbreviations; LTBI, latent tuberculosis infection; TB, tuberculosis; IGRA, interferon-gamma release assay.

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Figure S6. Tornado plots of deterministic sensitivity analyses for incremental net monetary benefit comparing between diagnostic pathway. Willingness-to-pay of £25,000. Scenarios are relative to equivalent TST diagnostic pathway.

a) One-step QFT diagnostic pathway scenario; b) two-step TST followed by QFT scenario.

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Abbreviations; LTBI, latent tuberculosis infection; TB, tuberculosis; IGRA, interferon-gamma release assay.

Figure S5 and S6 show tornado plots for the deterministic sensitivity analysis (DSA). S5 gives the incremental net monetary benefit comparing within diagnostic pathway, meaning that the change in INMB due to a change in a parameter value is relative to the same pathway with the value unchanged. Alternatively, S5 compared between the TST alone diagnostic pathway.

Figure S7 shows density plots of the posterior distributions obtained from the Bayesian model. The code used for this is given in Section 4.

Figure S8 shows the starting state distributions for each of the diagnostic decision tree strategies. The bar plot omits the non-LTBI patients since this is much larger and would dominate the scale. We see that the IGRA alone strategies have the most patients treated. The proportion of patients for whom the treatment was completed and effective are accounted for by adjusting the transition probability from LTBI complete treatment.

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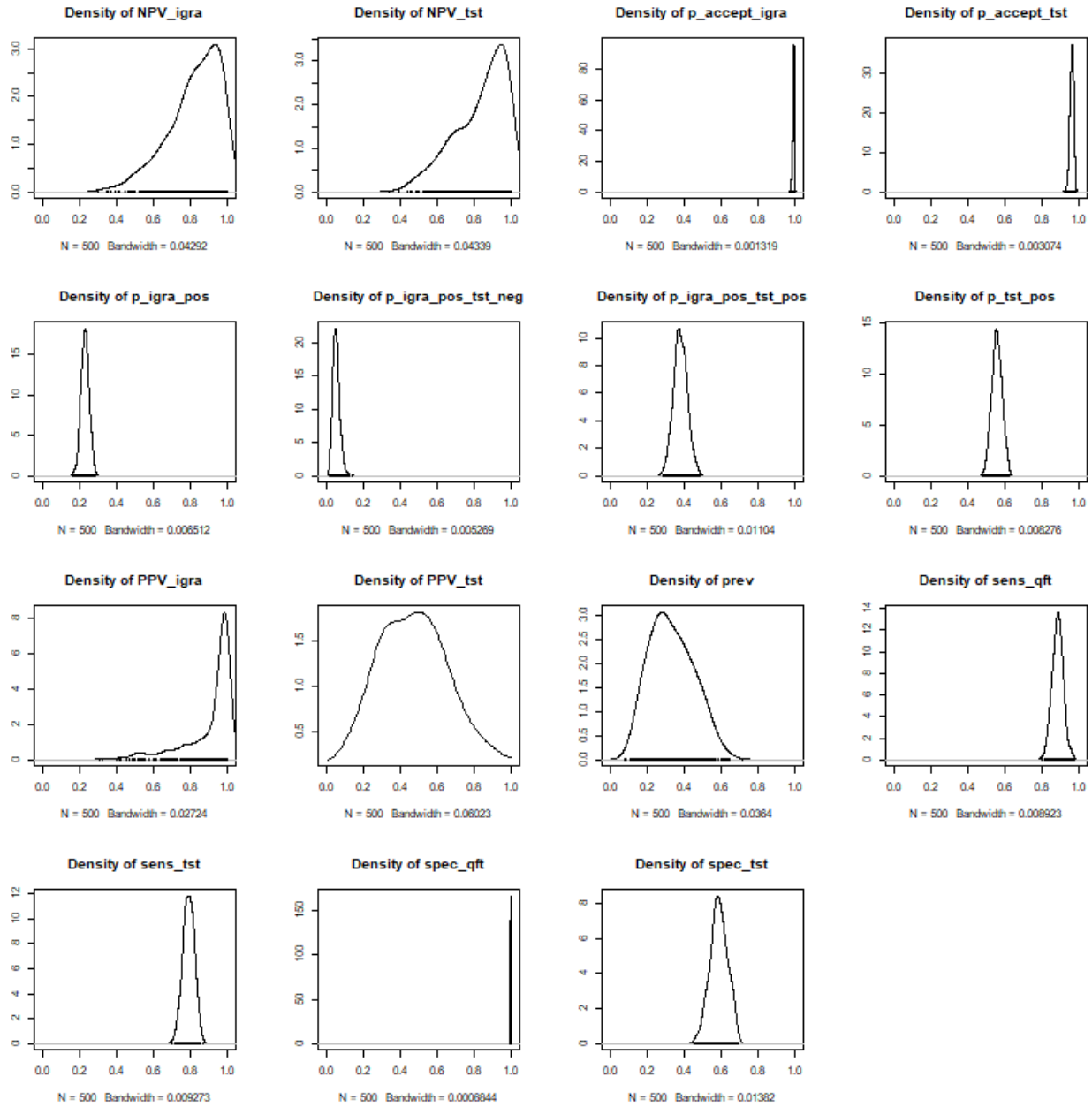


Figure S7. Model parameter posterior distributions.

Abbreviations; TST, tuberculin skin test; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; NPV, negative predictive; PPV, Positive predictive value.

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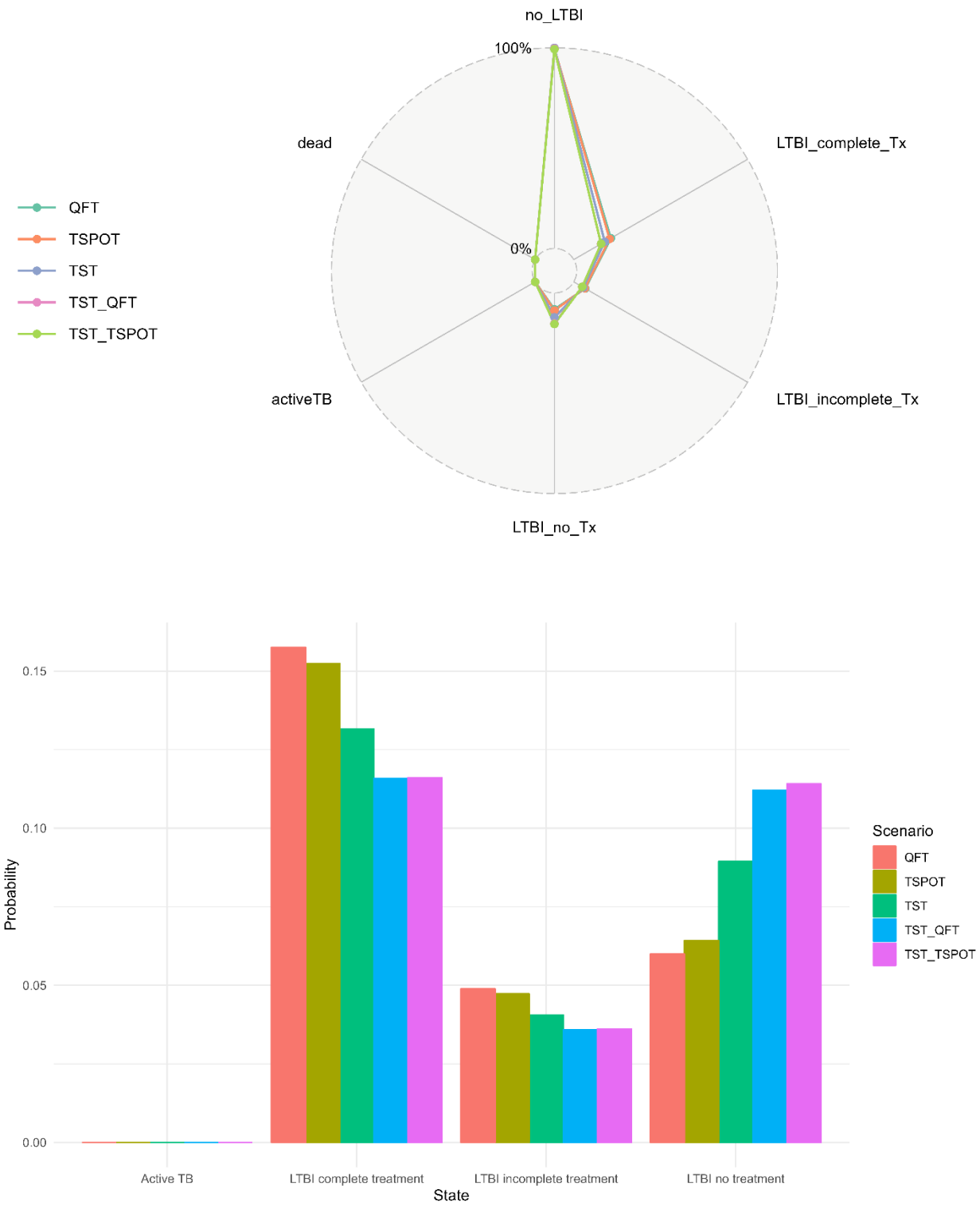


Figure S8. Radar plot and bar plot of Markov model starting state proportions by strategy.

Abbreviations; TST, tuberculin skin test; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; NPV, negative predictive; PPV, Positive predictive value.

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2. EQUATIONS

This section presents the main equations used in the model. The likelihoods in the Bayesian inference were Binary distributions using the observed event and sample size cohort data. Additional constraints were imposed and generated values are given in the BUGS code in Section 4.

2.1 Bayesian model equations

$$n_{accept\ TST} \sim \mathrm{Bin}\left(p_{accept_{TST}}, N\right)$$

$$n_{accept\ IGRA} \sim \mathrm{Bin}\left(p_{accept_{IGRA}}, N\right)$$

$$n_{IGRA\ pos} \sim \mathrm{Bin}\left(p_{IGRA_{pos}}, n_{accept_{IGRA}}\right)$$

$$n_{TST\ pos} \sim \mathrm{Bin}\left(p_{TST_{pos}}, n_{accept_{TST}}\right)$$

$$n_{IGRA\ pos\ TST\ neg} \sim \mathrm{Bin}\left(p_{IGRA_pos_TST_neg}, n_{TST\ neg}\right)$$

$$n_{IGRA\ pos\ TST\ pos} \sim \mathrm{Bin}\left(p_{IGRA\ pos\ TST\ pos}, n_{TST\ pos}\right)$$

Since the clinical data in Table S2 only identify test results as from an IGRA, rather than specific T.SPOT or QFT, then the same data were used to estimate T.SPOT and QFT posteriors using different prior distributions corresponding to the different tests.

2.2 Cost-effectiveness equations

The total cost and QALYs were derived from simple functions of the unit values.

Costs:

Complete treatment

$$c_{drugs} \times t_{drugs} + c_{Ns} \times n_{appts}$$

Incomplete treatment

$$c_{drugs} \times t_{drugs}/2 + c_{Ns} \times \lfloor n_{appts}/2 \rfloor$$

Positive screening

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$$c_{out} + c_{CXR} + c_{LFT}$$

2.3 Model checking

The TST only and the T-SPOT only diagnostic pathways are special cases of the TST/T-SPOT pathways. Therefore, we can define specific parameter values for the TST/T-SPOT decision tree which will transform it to an equivalent TST only or T-SPOT only decision tree. By doing this, we can check that the different model implementations were consistent and correct.

The parameter values to change in the TST/T-SPOT decision tree model are as follows.

For the T-SPOT only pathway:

pAccept_TST = 1

pTSTread = 1

p_TST_pos = 1

PPV_TST = pLTBI

TSPOT_pos_TST_pos = p_TSPOT_pos

pAccept_IGRA_TST_pos = pAccept_IGRA

PPV_TSPOT_TST_pos = PPV_TSPOT

NPV_TSPOT_TST_pos = NPV_TSPOT

c_TST = 0

Ns_cost = 0

For the TST only pathway:

pAccept_IGRA_TST_pos = 1

TSPOT_pos_TST_pos = 1

PPV_TSPOT_TST_pos = PPV_TST

NPV_TSPOT_TST_pos = 0

c_TSPOT = 0

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3. TABLES

Tabel S1 shows summary statistics of the posterior distribution obtained from the Bayesian inference. These are then used in base case analysis with the cost-effectiveness model. Estimating all of the parameters jointly in the Bayesian model ensure consistency across the values.

Table S1. ***Estimated model parameter posterior distribution values for a cohort of adult close contacts in London using Bayesian inference.***

Name	Label	Base-case value	Range
Negative Predictive Value QFT	NPV_QFT	0.96	0.94 - 0.98
Negative Predictive Value QFT TST	NPV_QFT_TST_pos	0.93	0.89 - 0.96
Negative Predictive Value T-SPOT	NPV_TSPOT	0.95	0.93 - 0.98
Negative Predictive Value QFT	NPV_TSPOT_TST_pos	0.92	0.89 - 0.96
Negative Predictive Value TST	NPV_TST	0.88	0.84 - 0.92
Probability accept IGRA	p_accept_IGRA	0.99	0.98 - 1
Probability accept TST	p_accept_TST	0.96	0.94 - 0.98
QFT positivity	p_QFT_pos	0.24	0.2 - 0.27
QFT positivity after TST positive	p_QFT_pos_TST_pos	0.34	0.29 - 0.41
T-SPOT positivity	p_TSPOT_pos	0.23	0.2 - 0.26
T-SPOT positivity after TST positive	p_TSPOT_pos_TST_pos	0.34	0.29 - 0.4
TST positivity	p_TST_pos	0.54	0.5 - 0.58
Positive Predictive Value QFT	PPV_QFT	0.99	0.97 - 1
Positive Predictive Value QFT after TST positive	PPV_QFT_TST_pos	0.99	0.98 - 1
Positive Predictive Value T-SPOT	PPV_TSPOT	0.99	0.97 - 1
Positive Predictive Value T-SPOT after TST positive	PPV_TSPOT_TST_pos	0.99	0.99 - 1
Positive Predictive Value TST	PPV_TST	0.39	0.33 - 0.45

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Table S2. Screening test results of sample of adult close contacts.

		IGRA result			
		Positive	Negative or indeterminate	Not accepted	**Total**
TST result	Positive	78	125	1	204
	Negative	9	152	1	162
	Not read	0	7	1	8
	Not accepted	0	7	0	7
	Total	87	291	3	381

Abbreviations; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

4. BUGS code

Below we give the BUGS code, implemented in jags and called from R, which infers the posterior distributions of probabilities for the decision trees. These use prior distributions obtained from relevant literature and the cohort data described in Table S2.

```
model {
  # ltbi decision tree values
  # N: total suspected cases
  # likelihood
  n_accept_tst ~ dbin(p_accept_tst, N)

  n_accept_igra ~ dbin(p_accept_igra, N)

  n_qft_pos ~ dbin(p_qft_pos, n_accept_igra)
  n_tspot_pos ~ dbin(p_tspot_pos, n_accept_igra)

  n_tst_pos ~ dbin(p_tst_pos, n_accept_tst)

  # priors

  p_accept_igra ~ dbeta(0.5, 0.5)
  p_accept_tst ~ dbeta(0.5, 0.5)

  prev ~ dbeta(5, 10)

  sens_tst ~ dnorm(mu_sens_tst, pow(sd_sens_tst, -2))T(0,1)
  spec_tst ~ dnorm(mu_spec_tst, pow(sd_spec_tst, -2))T(0,1)

  sens_qft ~ dnorm(mu_sens_qft, pow(sd_sens_qft, -2))T(0,1)
  spec_qft ~ dnorm(mu_spec_qft, pow(sd_spec_qft, -2))T(0,1)

  sens_tspot ~ dnorm(mu_sens_tspot, pow(sd_sens_tspot, -2))T(0,1)
  spec_tspot ~ dnorm(mu_spec_tspot, pow(sd_spec_tspot, -2))T(0,1)

  # generated values

  p_tst_pos = sens_tst*prev + (1 - spec_tst)*(1 - prev)
  p_qft_pos = sens_qft*prev + (1 - spec_qft)*(1 - prev)
  p_tspot_pos = sens_tspot*prev + (1 - spec_tspot)*(1 - prev)

  p_qft_pos_tst_pos = sens_qft*PPV_tst + (1 - spec_qft)*(1 - PPV_tst)
  p_tspot_pos_tst_pos = sens_tspot*PPV_tst + (1 - spec_tspot)*(1 - PPV_tst)

  PPV_tst ~ dnorm((sens_tst*prev)/p_tst_pos, pow(0.001, -2))T(0,1)
  PPV_qft ~ dnorm((sens_qft*prev)/p_qft_pos, pow(0.001, -2))T(0,1)
  PPV_tspot ~ dnorm((sens_tspot*prev)/p_tspot_pos, pow(0.001, -2))T(0,1)

  NPV_tst ~ dnorm((spec_tst*(1 - prev))/(1 - p_tst_pos), pow(0.001, -2))T(0,1)
  NPV_qft ~ dnorm((spec_qft*(1 - prev))/(1 - p_qft_pos), pow(0.001, -2))T(0,1)
```

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```
54.   NPV_tspot ~ dnorm((spec_tspot*(1 - prev))/(1 - p_tspot_pos), pow(0.001, -2))T(0,1)
55.
56.   spec_qft_tst = 1 - (1 - spec_qft) * (1 - spec_tst)
57.   sens_qft_tst = 1 - (1 - sens_qft) * (1 - sens_tst)
58.
59.   spec_tspot_tst = 1 - (1 - spec_qft) * (1 - spec_tst)
60.   sens_tspot_tst = 1 - (1 - sens_tspot) * (1 - sens_tst)
61.
62.   PPV_qft_TST_pos = (sens_qft*PPV_tst)/p_qft_pos_tst_pos
63.   NPV_qft_TST_pos = (spec_qft*(1 - PPV_tst))/(spec_qft*(1-PPV_tst) + (1 - sens_qft)*PPV_tst)
64.
65.   PPV_tspot_TST_pos = (sens_tspot*PPV_tst)/p_tspot_pos_tst_pos
66.   NPV_tspot_TST_pos = (spec_tspot*(1 - PPV_tst))/(spec_tspot*(1-PPV_tst) + (1 -
sens_tspot)*PPV_tst)
67.
68.   # constraints
69.
70.   # no LTBI ie 1 - prev
71.   # in TST decision tree
72.   no_ltbi_tst = (1 - p_accept_tst) * (1 - prev) +
73.                 p_accept_tst * (1 - p_tst_pos) * NPV_tst +
74.                 p_accept_tst * p_tst_pos * (1 - PPV_tst)
75.
76.   # in QFT decision tree
77.   no_ltbi_qft = (1 - p_accept_igra) * (1 - prev) +
78.                 p_accept_igra * (1 - p_qft_pos) * NPV_qft +
79.                 p_accept_igra * p_qft_pos * (1 - PPV_qft)
84. }
```

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