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Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice

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ABSTRACT

Background: Methods for determining the cost-effectiveness of different treatments are well established, unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers

Objective: We develop and validate a new health economic model by comparing the cost-effectiveness of tuberculin skin test, TST; blood test, IGRA; and TST then IGRA in conditional sequence, in screening health care workers for latent or active TB. We test the impact of key variables to inform health care provision.

Design: We focus on healthy life years gained as the benefit metric, rather than quality adjusted life years (QALYs) given limited data to estimate quality-adjustments of life years with TB and its complementary diseases, such as hepatitis. Healthy life years gained refers to the number of TB or complementary hepatitis cases avoided, and the increase in life expectancy. We incorporate disease and test variables informed by systematic meta-analyses and clinical practice. Health and economic outcomes of each strategy are modelled as a decision tree in Markov chains, representing different health states informed by epidemiology. Cost and effectiveness values are generated as the individual is cycled through 20 years of the model.

Setting: Screening health care workers in secondary and tertiary care.

Results: IGRA is the most effective strategy, with an incremental cost per healthy life year gained of £26,592 to £12,532 at base case and £19,968 to £5,882 for market costs, TST £45, IGRA £90, with IGRA specificities of 97% - 99%.

Conclusions: Incremental costs per healthy life year gained, a conservative estimate of benefit, are comparable to the £20,000 - £30,000 NICE band for IGRA alone, across wide differences in disease and test variables. Health gains justify IGRA costs, even IGRA test costs three times TST costs. This health economic model offers a powerful tool for appraising non-drug interventions in the market and under development. (300 words)

What this paper adds

1. What is already known and why this study is required

- Methods for determining the cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analyses and clinical practice, testing key disease and test variables

2. What this study adds

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- Screening with IGRA appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- These findings are robust for wide differences in disease and test variables, even IGRA test costs three times TST costs suggesting this health economic model is a powerful tool for appraising non-drug interventions

ARTICLE SUMMARY

Article focus

- Methods for determining cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or a TB blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analysis and clinical practice, testing key disease and test variables

Key messages

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- IGRA screening has an incremental cost per healthy life year gained of £19,968 to £5,882 at standard market costs, TST £45, IGRA £90, for IGRA specificities of 97% - 99% respectively

Strengths and limitations of this study

- Screening with IGRA alone appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- Neither TST not IGRA differentiate LTBI from TB, and the specificity of IGRA is inferred from studies in populations at low risk of TB
- These findings are robust for wide differences in disease and test variables, including IGRA test costs three times TST costs, suggesting this health economic model is a powerful tool for appraising non-drug interventions in the market and under development

INTRODUCTION

Economic evaluation is a recognised approach to optimising national health care provision within a limited budget but informed choice requires transparent analysis highlighting key assumptions and critical factors [1]. Methods for determining the cost-effectiveness of different treatments are well established [2], [3], unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers. We develop and validate a new health economic model by focusing on whether a tuberculin skin test, TST, and / or a blood test for tuberculosis, IGRA, is more cost-effective in screening health care workers for latent or active tuberculosis, TB. The screening of health care workers for tuberculosis has economic importance given the impact of disease transmission in each case together with the large number of NHS employees at risk, 1.7 million personnel and 80,000 new employees per annum (National Health Service, 2010). We inform the health economic model by applying insight from epidemiology, meta-analysis, and clinical practice including market costs to compare the cost-effectiveness of new technology supporting or replacing established practice.

Established practice is for trained occupational health staff to administer a TST using cheap readily available reagents injected intradermally at an initial visit. The skin test reaction is measured at a second clinic visit 48 – 72 hours later. The need for two visits is operationally inefficient, and the test itself is limited both by specificity and sensitivity. TST has a low specificity in subjects exposed to BCG vaccination or environmental non-tuberculous mycobacteria (NTM) and moderate sensitivity resulting in false negatives [4], [5]. A new technological approach requires a single clinic visit to draw a blood sample which is transferred to the laboratory for analysis in a TB specific interferon-gamma release assay, IGRA [6]. The approach is operationally efficient and the assay has a high specificity and sensitivity, although simple costs per test are greater than the TST. In principle the advantages of old and new might be combined using TST for all and then applying IGRA blood testing to TST positive cases to exclude false positive TST after previous exposure to

NTM including BCG immunisation. This third approach depends on each test having a similar sensitivity or false negative rate, so the impact of this parameter is subjected to further analysis. Following earlier work, [7] this study has focused on healthy life years gained as the benefit metric, rather than the more common quality adjusted life years. The reason is the lack of robust data to estimate quality-adjustments of life years with TB and its complementary diseases, such as hepatitis. Health life years gained refers to the number of TB or complementary hepatitis cases avoided, and the associated increase in life expectancy.

This study adds to the literature [8], [7], [9], [10] in four key areas by incorporating:

1. Healthy life years to avoid the assumptions inherent in estimating QALYs
2. Key disease variables in a comprehensive model of all relevant health states informed by epidemiology including
   i. The impact of LTBI Tuberculosis treatment side effects [11]
   ii. The higher relapse rate of active TB within three years of treatment [12]
3. Key test variables relevant to clinical practice including
   i. The inability of screening tests to differentiate between active and latent TB [5]
   ii. The sensitivity and specificity of IGRA and TST independently of each other
   iii. Operational inefficiencies of TST prompting repeat testing [13]
4. And we provide a powerful methodology for appraising the cost-effectiveness of non-drug interventions to inform health care policy, including sensitivity analyses of key variables

METHODS

The health and economic outcomes of the three alternatives testing strategies are modelled as a decision tree, representing the health outcomes of each of the strategies as Markov chains over twenty years. The model incorporates economic, medical, epidemiological and operational factors in the analysis. This approach lends itself to the clinical setting where the risks are continuous over time, key events may be repeated, and operational factors may interact with other key variables to influence the base case result.

Data collection

The test, population, and outcome characteristics (**table 1**) include data from the meta-analysis by Pai 2008 [4]. In the absence of a gold standard for latent tuberculosis infection, LTBI, active TB is used as a surrogate to determine assay sensitivity. Specificity for LTBI is derived by testing populations at low risk of TB [4], [14], [15] to determine the rate of false positives. We apply an IGRA specificity of 98% [15] for the base case analysis guided by our clinical and market experience with T-Spot TB, and then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model. The operational characteristics of the three alternative approaches include repeat test rates due to test failure and failure to attend for skin test reading. Direct and indirect costs are shown (**table 2)** drawing on data supplied by NICE [16], the Cambridge TB service, and the NHS National tariff 2010. The impact of regional or national differences in disease variables and costs are examined in sensitivity analyses.

Model construction

We built a decision analysis model, which incorporates the health outcomes as Markov chains over twenty years, to analyze three different diagnostic approaches to LTBI. This model only considers the initial screening for newly hired personnel; the annual testing is beyond the scope of this model. The model is coded and composed using the decision analysis software TreeAge Pro Suite 2009, 2011. The states of the Markov chains represent the health conditions of the individuals; following a LTBI diagnosis test and possible interventions. Each Markov state length is one year. The decision is made at the first node of the decision tree between three diagnosis options: TST, IGRA, and a combined sequential testing strategy. The alternatives are assessed according to their cost and effectiveness values over twenty years; in which the costs are direct and indirect monetary costs and their effectiveness is measured by total number of healthy years. The Markov chain is implemented through 20 years, related cost and effectiveness values due to different health states are recorded as the individual is cycled through the model. All future costs are discounted at 5% per year.

Table 1: Base Case Data for Test, Population and Outcomes Parameters

Parameter	Base-case values	Reference
1. Test characteristics		
Tuberculin skin test (TST)		
Specificity	0.59	[4]
Sensitivity	0.77	[4]
Probability a second TST is placed	0.1737	[13]
Repeat due to operational inefficiency	0.324	Martell 2010
TB specific IFNgamma release assay (IGRA)		
Specificity	0.98	[15]
Sensitivity	0.90	[4]
Probability a second IGRA is required	0.0343	[13]
Repeat due to operational inefficiency	0	Martell 2010
2. Population characteristics		
Age range	20 – 30	
Occupation	Healthcare worker	
BCG vaccination rates	52.8%	[17]
Nationality of majority	English	
Prevalence of LTBI	0.035	[17]
Prevalence of TB	0.0001	[18]
Probability of all causes of death	0.0045	Office for National Statistics 2008
3. Probability of Outcomes		
Efficacy of LTBI treatment	0.65	[19]
Risk of hepatitis caused by treatment	0.0177	[11]
Risk of activation of LTBI	0.01	[5]
Probability of relapse of TB	0.0315	[12]
Probability of death due to TB	0.018	[18]
Probability of death due to hepatitis	0	Assumption

Martell 2010: Martell G, Robinson M-J 2010, Inefficiencies and delays in healthcare worker screening for Mycobacterium tuberculosis – an audit of medical student screening. 3rd HPA Pointers (Prevention of Occupational Infections, Treatment and Exposure Reporting Strategies for Healthcare Workers) Conference, London Dec 2010. Sensitivity analyses test the impact of regional or national differences in disease variables.

Table 2: Costs

Parameter	Base-case values
4. Cost of Interventions	
	NICE [16]
TST	£16
IGRA	£44.78
Chest radiograph (CXR)	£28
	Cambridge TB Service 2010 NHS National Tariff
TB Treatment	£1,637 [16]
Contact tracing	£423
LTBI Treatment	£647
Hepatitis Treatment	£625
5. Healthcare worker costs	**Cambridge TB Service 2010 NHS National Tariff** ***Midpoint band 6 with on costs 2010***
Time for TB treatment	£632
Time for LTBI treatment	£162
Time for Hepatitis treatment	£108
6. Discount rate	0.05

TB treatment costs derived from discussions with NICE 2010 and Cambridge TB service. Total model costs for TB treatment are TB treatment, plus contact tracing x5 contacts per case, plus health care worker time costs; for LTBI, LTBI treatment plus health care worker time costs; for Hepatitis, Hepatitis treatment plus health care worker time costs. Sensitivity analyses examine the impact of four fold variation in costs.

Model construction

This Markov model assumes

i. Each health state is taken as a time periods of one year, can not be left earlier and can only last longer if the return probability is greater than zero.

ii. All patients with positive results for LTBI accept treatment, consistent with conditions of employment in the NHS

iii. Standard Isoniazid and Rifampicin treatment for LTBI lasts three months and all treatments are completed.

iv. Diagnostic tests are repeated once only as required to achieve a result

v. No diagnostic tests are repeated due to operational inefficiencies; this variable is addressed in the sensitivity analysis

vi. The conditional probability of a positive test result in LTBI is the same as for TB

vii. The risk of active TB in cases with false negative results is proportional to the prevalence rates of latent and active TB

viii. The result of the second test is independent of the first in two stage testing

ix. The effects of TB and Hepatitis are the simple sum, rather than synergistic

x. All cases with positive TST or IGRA will have a CXR that identifies all cases of active TB. All positive CXRs are active TB

xi. The relapse rate of TB is higher than the prevalence rate in the general population for the first three years after recovery [12]

xii. The probability of continuing to have TB after standard TB treatment is the probability of relapse

xiii. All TB is diagnosed and treated on time. The effect of late diagnosis of latent or active TB in cases with false negative results is neglected.

xiv. An equal number of males and females make up new NHS healthcare workers

xv. Death of an employee has no monetary cost for NHS.

xvi. Transmission of TB to the community is modeled as a constant monetary cost for contact tracing, including screening the close contacts of the patient, and their treatment in the case of positive Tuberculosis findings.

xvii. All employees are employed for 20 years

The comprehensive decision tree consists of 985 nodes including three similar sub-trees with different probability and cost parameters (**figure 1**). The initial analysis was then subjected to sensitivity analysis applied to key variables including IGRA sensitivity and specificity;

prevalence rates of TB and LTBI, all causes death rates; test repetition rates; market rates for TST and IGRA tests; treatment costs for TB, LTBI, and hepatitis.

RESULTS

Base case analysis indicates the incremental cost of IGRA alone is offset by the increased effectiveness of this approach over the two stage sequential approach of TST followed by IGRA for positive TST results (**table 3a**). IGRA is the most effective strategy with an incremental effectiveness of 0.001 and an incremental cost-effectiveness ratio, ICER, of £19,545 per healthy life year gained. The strategy of TST alone is clearly inferior by all criteria. We therefore focused on further analysis of variables affecting the relative efficacy of TST + IGRA versus IGRA alone.

Table 3 Incremental Costs Per Healthy Life Year Gained (ICER) of IGRA or TST

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Effectiveness	ICER
a. Base Case						
IGRA+TST	£77.12	£0.00	19.07609	0.00000	4.04	£0
IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
TST	£387.11	£289.26	19.07000	-0.00715	20.30	-£40,444 *(Dominated)*
b. Market Costs						
IGRA+TST	£130.92	£0.00	19.07609	0.00000	6.86	£0
IGRA	£144.62	£13.70	19.07715	0.00106	7.58	£12,915
TST	£421.15	£276.52	19.07000	-0.00715	22.08	-£38,663 *(Dominated)*

Base case, TST £16, IGRA £45; market costs TST £45, IGRA £90.

Sensitivity analyses of disease and test variables

Sensitivity analysis of the base case model indicates that the ICER for IGRA ranges from £26,592 to £12,532 per healthy life year gained for test specificities of 97% - 99% (**figure 2a-c, suppl. table 1**). Assay sensitivity has a much smaller impact on the ICER (**figure 2d**). The superior cost-effectiveness of IGRA was not threatened by up to ten fold increases in all cause death rates; TB death rates; prevalence of LTBI or TB; relapse rates and hepatitis rates (**figure 2e, suppl. table 2a-f**). Varying the IGRA repeat rate from 1.5% to 15% or TST repeat rate from 2.5% to 25% had little impact on the ICER which increased from £19,346 to £20,744 and £17,991 to £20,591 per healthy life year gained respectively (**suppl. table 2g, h**).

The cost of TST testing by five private medical service providers was a median of £65 per test, range £45 to £75, and £48.50 using itemized costings from Cambridge Occupational Health. Market costs for TST significantly enhance the ICER for IGRA alone across a range of IGRA costs (**figure 2f**, **suppl. table 3a**). In particular, the market standard test costs of £45 per TST and £90 per IGRA generate an ICER of £12,915 per healthy life year gained (**table 3b**). A threshold value of £30,000 per healthy life year gained is still achieved when IGRA test costs are three-times TST test costs.

Examining the impact of assay specificity, this market standard model generates a range of £19,968 to £5,882 per healthy life year gained for an IGRA specificity of 97% - 99%. Sensitivity analysis for TST specificity [4] over a wide range, 0.46 – 0.73, suggests IGRA remains the optimal strategy with costs of £1,455 to £28,455 per healthy life year gained (**suppl. table 3b)**.

The calculation and apportionment of treatment costs is likely to vary between centres, but a four fold variation in treatment costs for LTBI, TB, or hepatitis is also accommodated by the market standard model (**figure 2g**, **suppl. table 4**).

DISCUSSION

The methodology for determining the cost-effectiveness of different treatments is well established [2], [3], [1] in contrast to the analysis of non-drug interventions. Our health economic model suggests a methodology to appraise the host of novel diagnostics [6] and biomarkers generated by clinical science. Healthy life years, despite being a conservative benefit metric, may be particularly useful in evaluating novel screening and monitoring tests by avoiding the assumptions inherent in generating quality adjusted life years [20], [1], [7], [10], [21]. This approach, allied to the use of multiple disease states supported by epidemiological data, is far more powerful than standard comparisons since the IGRA strategy will overcome a two – three fold excess of simple test costs.

We compare the effectiveness of the diagnostic procedures by focusing on healthy life years gained, [1],[7] rather than quality adjusted life years [20], [10], [16]. The reason is there are limited data to base estimates of quality adjusted life years for each of the health states applicable to latent or active TB and its treatment [22].The additional costs of IGRA alone appear justified by the health gains at £19,545 per healthy life year gained, falling to £12,915 per healthy life year when applying market costs where blood tests cost twice as much as skin tests. Our estimates are conservative in that they only take a healthy life year as a benefit (i.e. years without tuberculosis or hepatitis). Since the calculated ratio is at the lower end of the NICE band of £20,000 - £30,000, IGRA is cost-effective, even at the current NICE threshold which may or may not be conservative [2], [3]. There is no validated instrument for determining quality of life with tuberculosis [23], but when such data are available it is likely that we would further improve the cost/benefit ratio.

The health economic model is sensitive to IGRA specificity, which is derived from estimates of false positives in populations at low risk of TB [24 21], [15]. An IGRA specificity of 98% is conservative by current literature [24 21], [15] but higher than analyses potentially confounded by data from studies in populations at intermediate rather than low risk of TB [4], [14], [16]. Our model accommodates substantial enhancement of TST specificity greater than expected in BCG-vaccinated populations, but the outcome may be different in non-BCG vaccinated populations with low NTM infection rates [4]. The study's findings also accommodate wide regional or national differences in disease variables, although health gains are enhanced by a relative increase in the prevalence of LTBI and hampered by doubling costs for the treatment of LTBI.

The one-stop approach of IGRA alone has additional, operational advantages which are likely to enhance the value of this strategy. Testing at a single visit boosts compliance whilst minimising consumption of resources to achieve a test result and the risk of loss to follow up. The health economic model does not include an allowance for health care workers time to attend for testing, but staff costs are greater when two – three visits are required for TST then IGRA. Efficiency is enhanced by combining IGRA with other screening blood tests, although a blood sample is more invasive than TST. Blood testing may offer more flexibility than TST with blood sampling facilities widely available in primary care and hospital settings. In contrast, there is a premium on the skills and training required to accurately place and measure TST which may be limiting during peaks in demand such as in contact tracing. An IGRA strategy transfers costs from the clinic to the laboratory, where cost pressures are intense but responsive to focusing expertise and optimising staffing structures. Critical aspects of blood sampling are defined including the impact of the test population and sampling conditions on the performance characteristics of IGRA [13], [25], [26], [27]. An IGRA strategy also avoids the possibility of TST boosting TST responses after repeat testing [5] or IGRA responses if follow-up testing is delayed [26]. The relative merits of different IGRA tests are controversial [21], [15], [4] but where there is a consensus on the assay characteristics this model should allow further investigation.

Our study suggests health gains justify IGRA costs when screening health care workers for latent or active TB. These findings are robust for wide differences in key disease and test variables including IGRA test costs three times TST costs, whilst maintaining cost-effectiveness at the lower end of the £20,000 - £30,000 NICE band. We suggest this health economic model incorporating healthy life years gained, epidemiology, meta-analyses and clinical practice provides a powerful tool for assessing the potential impact of new technology on established practice.

Figures

Figure 1: The Decision Tree

Health and economic outcomes of TST and / or IGRA modeled as a decision tree in Markov chains representing different health states informed by epidemiology: TB, active tuberculosis; LTBI, LTBI1, latent tuberculosis, with treatment; D, Death; S, S1, healthy, with unnecessary treatment for LTBI ; H, H+TB, H+LTBI, hepatitis, and TB, or LTBI; T1, T2, T1H, T2H, transition states indicating relapse rates within three years of treatment and thereafter, with hepatitis; A – E, node points repeated as Clone A - Clone E. X, Y are probabilities, p, X = pLTBI / (pLTBI + pTB), Y = pTB /(pLTBI + pTB)

Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

a – c IGRA specificity versus **a** overall costs in £ Sterling, **b** cost / effectiveness, **c** ICER, incremental cost per healthy life year gained. **d - f** ICER in the base case model versus **d** IGRA sensitivity, **e** key disease variables increased times ten, prev prevalence, **f** TST and IGRA costs. **g** ICER in the market case model versus four fold variation in treatment costs.

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Competing Interests

NE has no competing interests; SS has no competing interests; GM has no competing interests; RW has no competing interests. AE is the director of the specialist Immunology Laboratory at Papworth Hospital NHS Foundation Trust which provides a supra-regional service for interferon-gamma release assays using the T-Spot TB test (Oxford Immunotech).

Contributor Statement

AE & RW conceived the study. SS and MN developed the economic model with additional clinical data from GM, AE, RW. MN, SS, AE, tested and revised the economic model. All authors contributed to the interpretation of the results and approved the final version.

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

The economic model run on TreeAge Pro is available from the corresponding author.

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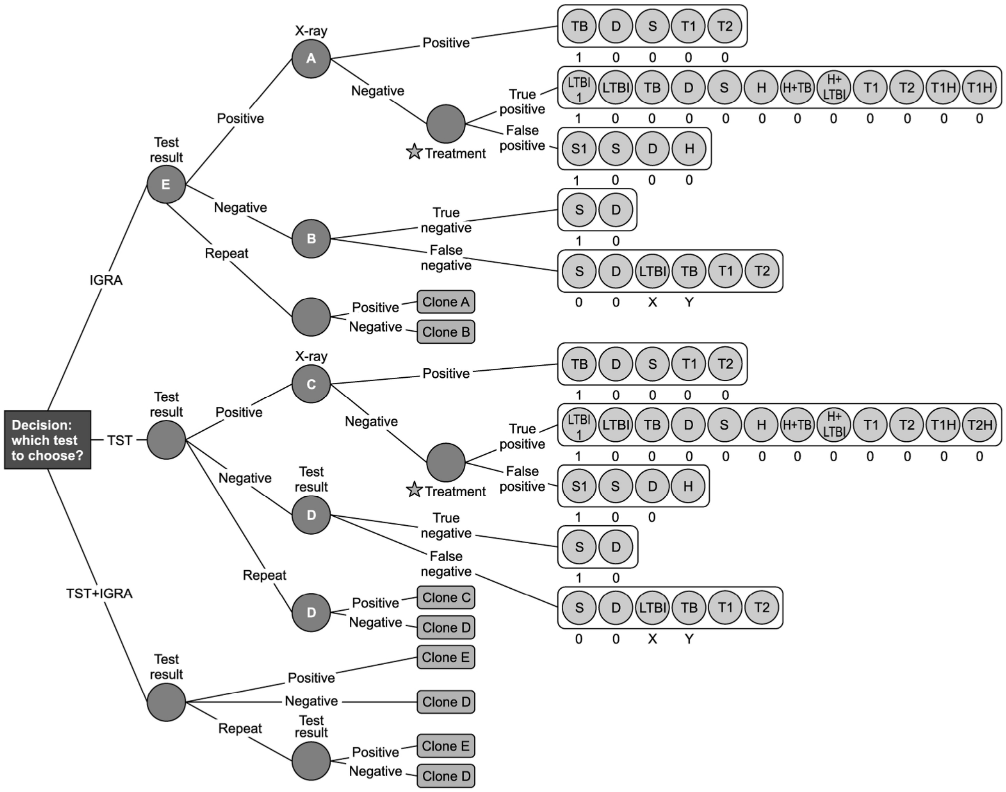

Figure 1: The Decision Tree
Health and economic outcomes of TST and / or IGRA modeled as a decision tree in Markov chains representing different health states informed by epidemiology: TB, active tuberculosis; LTBI, LTBI1, latent tuberculosis, with treatment; D, Death; S, S1, healthy, with unnecessary treatment for LTBI ; H, H+TB, H+LTBI, hepatitis, and TB, or LTBI; T1, T2, T1H, T2H, transition states indicating relapse rates within three years of treatment and thereafter, with hepatitis; A – E, node points repeated as Clone A - Clone E. X, Y are probabilities, p, X = pLTBI / (pLTBI + pTB), Y = pTB /(pLTBI + pTB)

205x161mm (300 x 300 DPI)

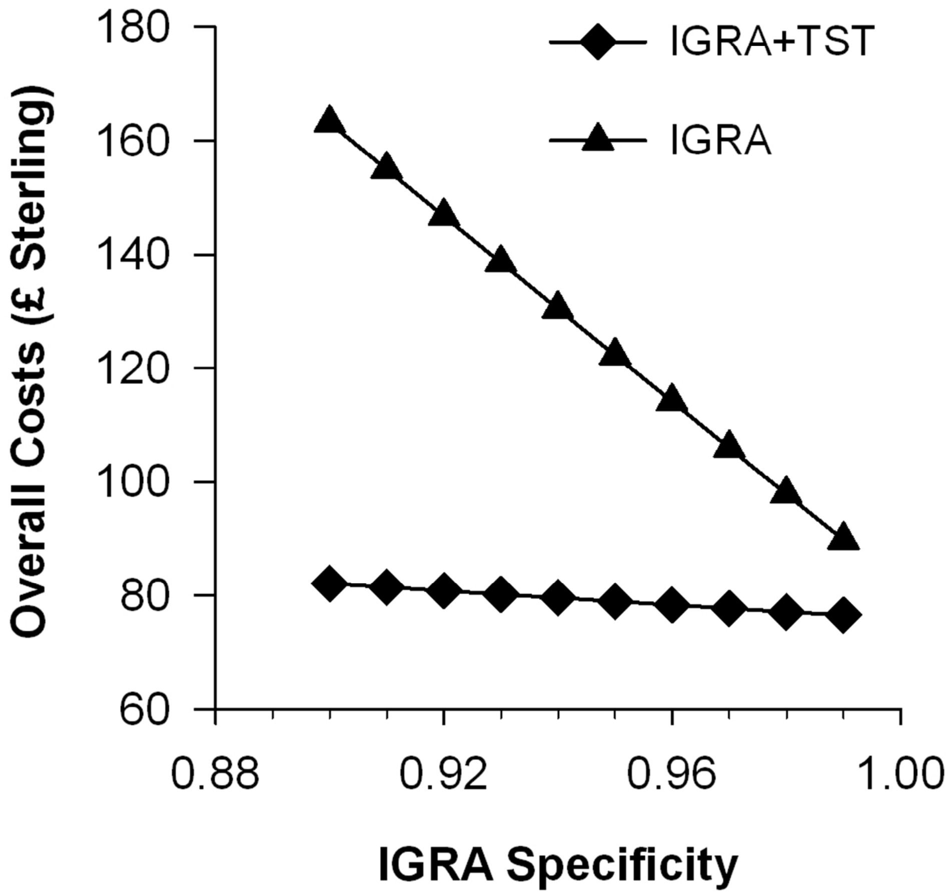

figure 2a
Figure 2: Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

a IGRA specificity versus a overall costs in £ Sterling
88x85mm (300 x 300 DPI)

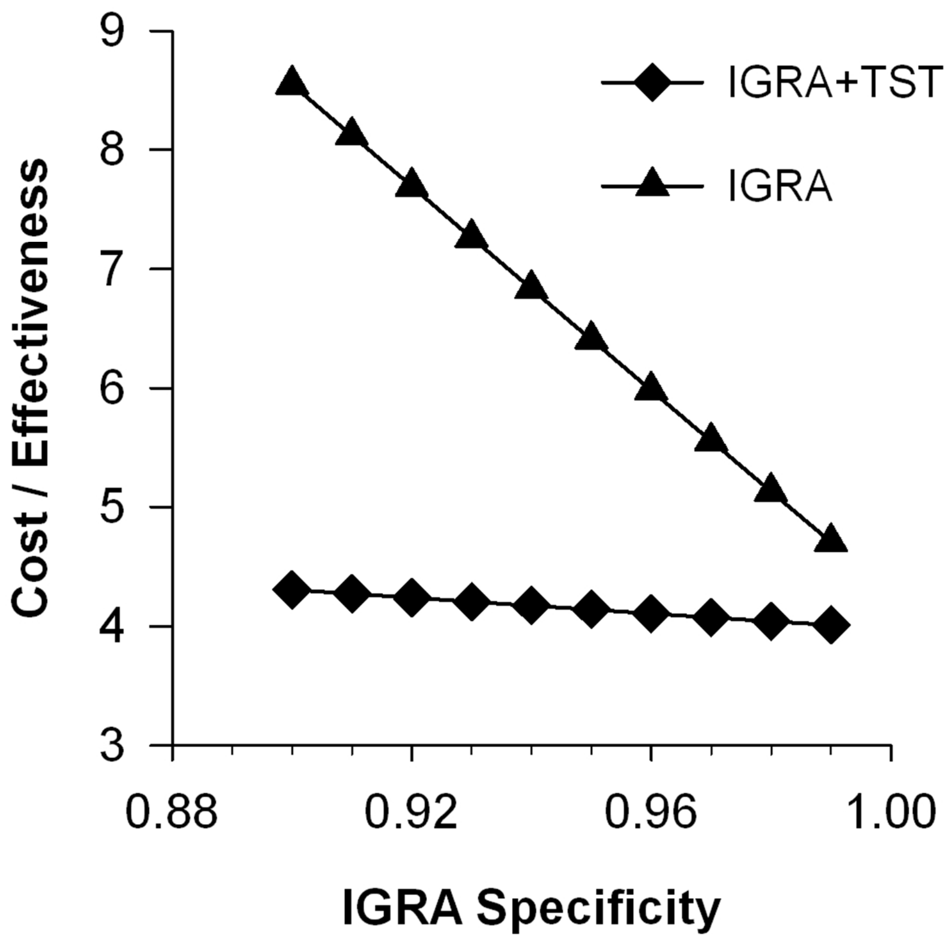

figure 2b
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

IGRA specificity versus cost / effectiveness

88x89mm (300 x 300 DPI)

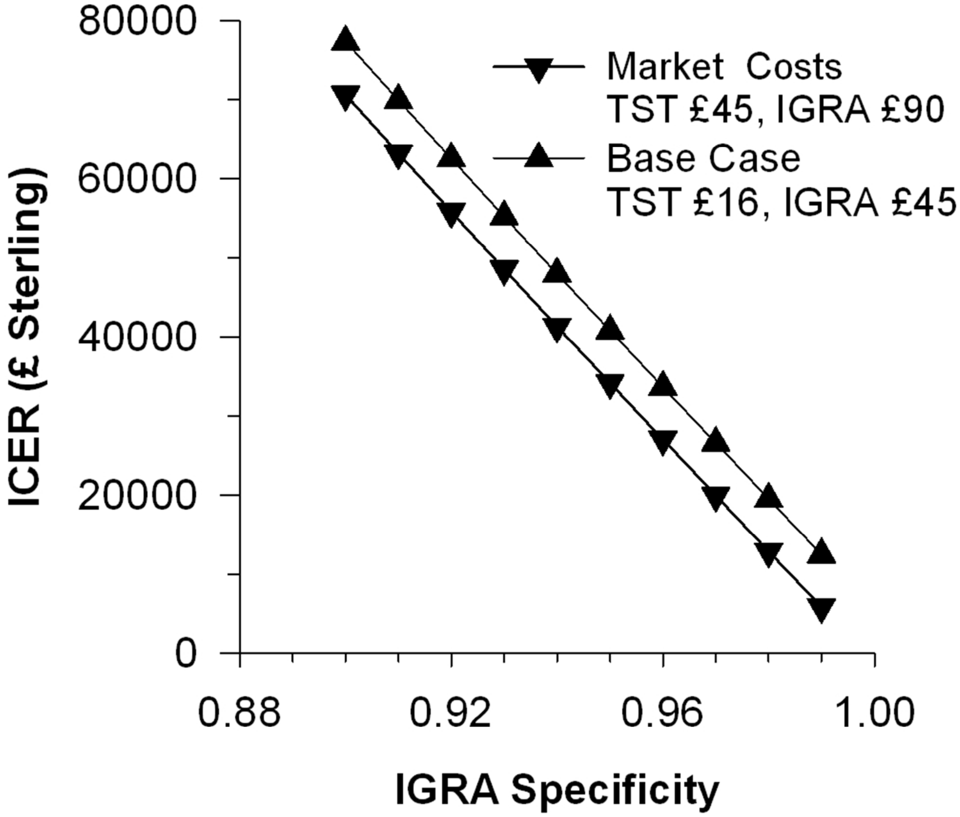

figure 2c
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

IGRA specificity versus ICER, incremental cost per healthy life year gained.

88x77mm (300 x 300 DPI)

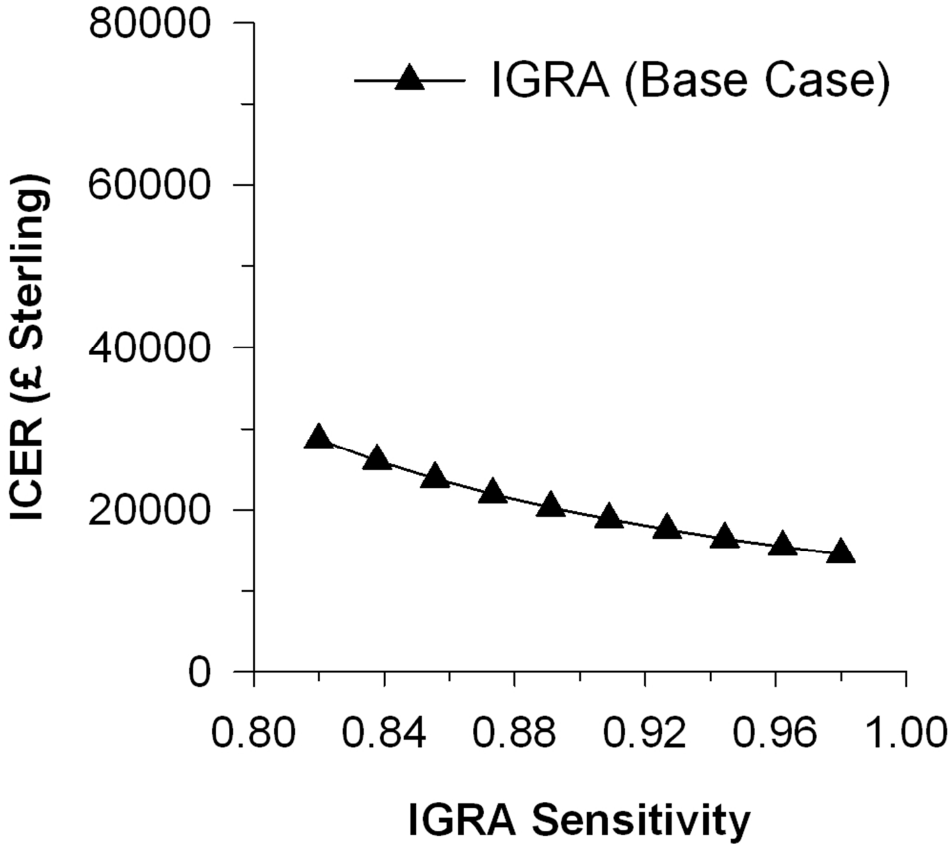

figure 2d
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

IGRA sensitivity vs ICER, incremental cost per healthy life year gained. in the base case model
88x81mm (300 x 300 DPI)

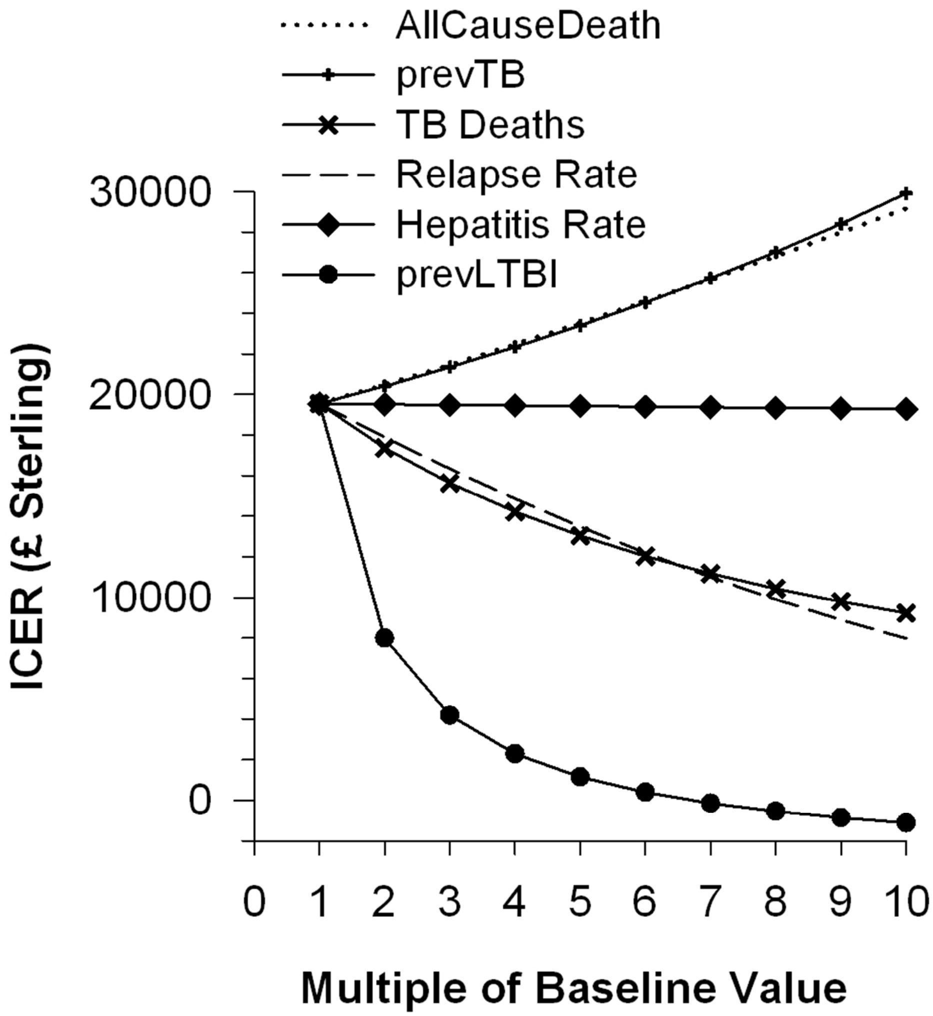

figure 2e
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

ICER, incremental cost per healthy life year gained, in the base case model versus key disease variables increased times ten, prev prevalence
88x94mm (300 x 300 DPI)

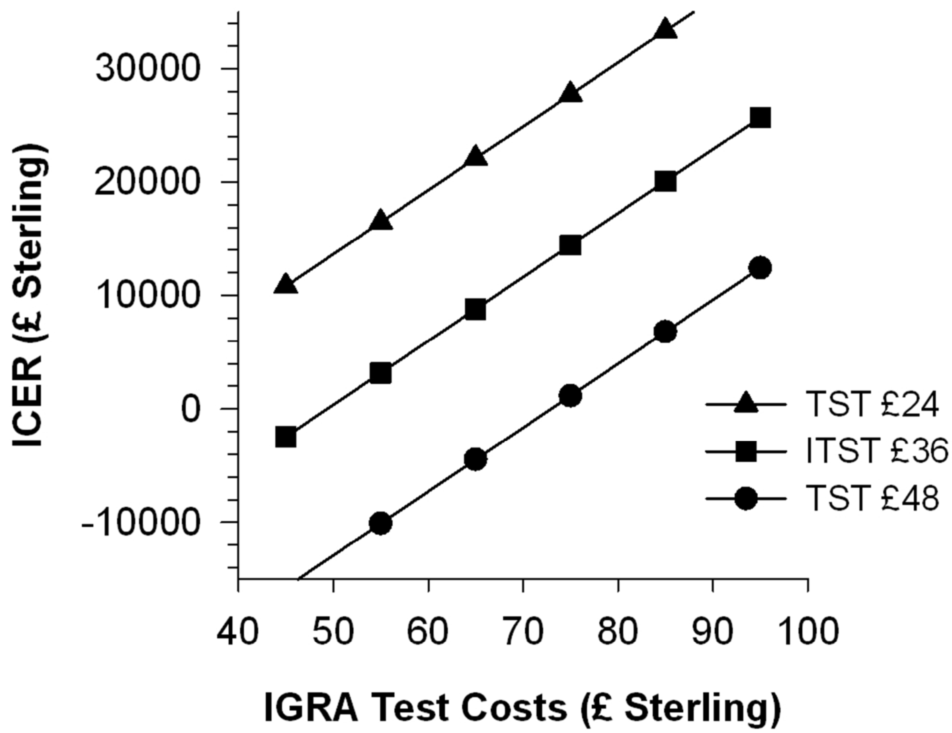

figure 2f
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

ICER, incremental cost per healthy life year gained, in the base case model versus TST and IGRA costs
88x71mm (300 x 300 DPI)

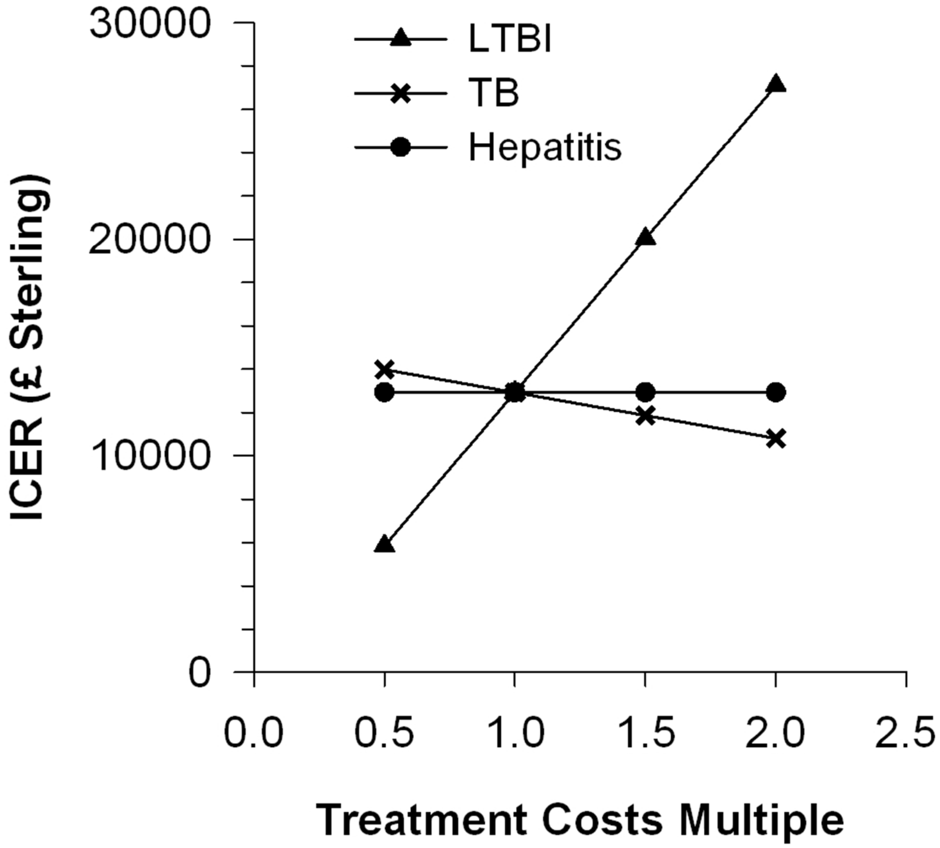

figure 2g
Figure 2:
Impact of Wide Differences in Disease and Test Variables on Cost-Effectiveness

ICER, incremental cost per healthy life year gained, in the market case model versus four fold variation in treatment costs
88x81mm (300 x 300 DPI)

Health Economic Models Inform Screening for Tuberculosis

Suppl.Table 1 Sensitivity Analysis

1a IGRA Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	Incremental Cost-Effectiveness Ratio (ICER) ICER
0.9	IGRA+TST	£82.10	£0.00	19.07479	0	4.30	£0
0.91	IGRA+TST	£81.47	£0.00	19.07495	0	4.27	£0
0.92	IGRA+TST	£80.83	£0.00	19.07511	0	4.24	£0
0.93	IGRA+TST	£80.20	£0.00	19.07528	0	4.20	£0
0.94	IGRA+TST	£79.57	£0.00	19.07544	0	4.17	£0
0.95	IGRA+TST	£78.95	£0.00	19.07561	0	4.14	£0
0.96	IGRA+TST	£78.33	£0.00	19.07577	0	4.11	£0
0.97	IGRA+TST	£77.72	£0.00	19.07593	0	4.07	£0
0.98	IGRA+TST	£77.12	£0.00	19.07609	0	4.04	£0
0.99	IGRA+TST	£76.54	£0.00	19.07625	0	4.01	£0
0.9	IGRA	£163.06	£80.96	19.07583	0.00105	8.55	£77,380
0.91	IGRA	£154.88	£73.41	19.07600	0.00105	8.12	£69,936
0.92	IGRA	£146.71	£65.87	19.07617	0.00105	7.69	£62,562
0.93	IGRA	£138.54	£58.34	19.07633	0.00106	7.26	£55,253
0.94	IGRA	£130.38	£50.80	19.07650	0.00106	6.83	£48,005
0.95	IGRA	£122.22	£43.27	19.07667	0.00106	6.41	£40,816
0.96	IGRA	£114.08	£35.75	19.07683	0.00106	5.98	£33,680
0.97	IGRA	£105.95	£28.24	19.07699	0.00106	5.55	£26,592
0.98	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.99	IGRA	£89.79	£13.25	19.07731	0.00106	4.71	£12,532

1b IGRA Sensitivity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.82	IGRA+TST	£74.96	£0.00	19.07605	0	3.93	£0
0.84	IGRA+TST	£75.44	£0.00	19.07606	0	3.95	£0
0.86	IGRA+TST	£75.92	£0.00	19.07607	0	3.98	£0
0.87	IGRA+TST	£76.40	£0.00	19.07608	0	4.00	£0
0.89	IGRA+TST	£76.88	£0.00	19.07609	0	4.03	£0
0.91	IGRA+TST	£77.36	£0.00	19.07610	0	4.06	£0
0.93	IGRA+TST	£77.84	£0.00	19.07611	0	4.08	£0
0.94	IGRA+TST	£78.32	£0.00	19.07612	0	4.11	£0
0.96	IGRA+TST	£78.80	£0.00	19.07612	0	4.13	£0
0.98	IGRA+TST	£79.28	£0.00	19.07613	0	4.16	£0
0.82	IGRA	£96.44	£21.48	19.07680	0.00075	5.06	£28,691
0.84	IGRA	£96.76	£21.31	19.07688	0.00082	5.07	£26,062
0.86	IGRA	£97.07	£21.15	19.07696	0.00089	5.09	£23,839
0.87	IGRA	£97.38	£20.98	19.07704	0.00096	5.10	£21,937
0.89	IGRA	£97.69	£20.82	19.07711	0.00103	5.12	£20,289
0.91	IGRA	£98.01	£20.65	19.07719	0.00110	5.14	£18,848
0.93	IGRA	£98.32	£20.48	19.07727	0.00117	5.15	£17,578
0.94	IGRA	£98.63	£20.32	19.07735	0.00124	5.17	£16,450
0.96	IGRA	£98.94	£20.15	19.07743	0.00130	5.19	£15,441
0.98	IGRA	£99.26	£19.98	19.07751	0.00137	5.20	£14,533

Health Economic Models Inform Screening for Tuberculosis

Suppl.Table 2

2a

Deaths, All causes	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0045	IGRA+TST	£77.12	0	19.07609	0	4.04	0
0.009	IGRA+TST	£76.77	0	18.20838	0	4.22	0
0.0135	IGRA+TST	£76.44	0	17.38838	0	4.40	0
0.018	IGRA+TST	£76.13	0	16.61329	0	4.58	0
0.0225	IGRA+TST	£75.83	0	15.88045	0	4.77	0
0.027	IGRA+TST	£75.54	0	15.18739	0	4.97	0
0.0315	IGRA+TST	£75.27	0	14.53178	0	5.18	0
0.036	IGRA+TST	£75.01	0	13.91141	0	5.39	0
0.0405	IGRA+TST	£74.76	0	13.32422	0	5.61	0
0.045	IGRA+TST	£74.52	0	12.76828	0	5.84	0
0.0045	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.009	IGRA	£97.59	£20.82	18.2094	0.00102	5.36	£20,489
0.0135	IGRA	£97.34	£20.90	17.38936	9.70E-04	5.60	£21,464
0.018	IGRA	£97.11	£20.98	16.61422	9.30E-04	5.84	£22,470
0.0225	IGRA	£96.88	£21.05	15.88135	9.00E-04	6.10	£23,508
0.027	IGRA	£96.67	£21.13	15.18825	8.60E-04	6.36	£24,577
0.0315	IGRA	£96.46	£21.19	14.5326	8.30E-04	6.64	£25,678
0.036	IGRA	£96.27	£21.26	13.9122	7.90E-04	6.92	£26,810
0.0405	IGRA	£96.08	£21.32	13.32499	7.60E-04	7.21	£27,975
0.045	IGRA	£95.90	£21.38	12.76901	7.30E-04	7.51	£29,171

2b

TB Deaths	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.018	IGRA+TST	£77.12	0	19.07609	0	4.04	0
0.036	IGRA+TST	£77.11	0	19.07543	0	4.04	0
0.054	IGRA+TST	£77.10	0	19.07476	0	4.04	0
0.072	IGRA+TST	£77.09	0	19.0741	0	4.04	0
0.09	IGRA+TST	£77.08	0	19.07343	0	4.04	0
0.108	IGRA+TST	£77.06	0	19.07277	0	4.04	0
0.126	IGRA+TST	£77.05	0	19.07211	0	4.04	0
0.144	IGRA+TST	£77.04	0	19.07145	0	4.04	0
0.162	IGRA+TST	£77.03	0	19.07079	0	4.04	0
0.18	IGRA+TST	£77.02	0	19.07013	0	4.04	0
0.018	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.036	IGRA	£97.84	£20.74	19.07662	0.00119	5.13	£17,370
0.054	IGRA	£97.83	£20.74	19.07609	0.00133	5.13	£15,633
0.072	IGRA	£97.83	£20.74	19.07555	0.00146	5.13	£14,214
0.09	IGRA	£97.82	£20.74	19.07502	0.00159	5.13	£13,034
0.108	IGRA	£97.81	£20.74	19.07449	0.00172	5.13	£12,037
0.126	IGRA	£97.80	£20.75	19.07396	0.00186	5.13	£11,182
0.144	IGRA	£97.79	£20.75	19.07344	0.00199	5.13	£10,443
0.162	IGRA	£97.78	£20.75	19.07291	0.00212	5.13	£9,796
0.18	IGRA	£97.78	£20.75	19.07238	0.00225	5.13	£9,226

Health Economic Models Inform Screening for Tuberculosis

2c

Prevalence LTBI	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.035	IGRA+TST	£77.12	0	19.07609	0	4.04	0
0.07	IGRA+TST	£114.72	0	19.07118	0	6.02	0
0.105	IGRA+TST	£152.27	0	19.06629	0	7.99	0
0.14	IGRA+TST	£189.78	0	19.0614	0	9.96	0
0.175	IGRA+TST	£227.25	0	19.05653	0	11.92	0
0.21	IGRA+TST	£264.69	0	19.05167	0	13.89	0
0.245	IGRA+TST	£302.09	£1.05	19.04683	-0.0074	15.86	-£142
0.28	IGRA+TST	£339.45	£4.58	19.042	-0.00841	17.83	-£545
0.315	IGRA+TST	£376.77	£8.07	19.03719	-0.0094	19.79	-£859
0.35	IGRA+TST	£414.03	£11.51	19.0324	-0.01037	21.75	-£1,110
0.035	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.07	IGRA	£131.81	£17.09	19.07332	0.00214	6.91	£7,986
0.105	IGRA	£165.69	£13.42	19.0695	0.00321	8.69	£4,176
0.14	IGRA	£199.54	£9.76	19.06568	0.00428	10.47	£2,283
0.175	IGRA	£233.38	£6.13	19.06186	0.00533	12.24	£1,150
0.21	IGRA	£267.21	£2.52	19.05804	0.00637	14.02	£396
0.245	IGRA	£301.04	0	19.05422	0	15.80	£0
0.28	IGRA	£334.87	0	19.05041	0	17.58	£0
0.315	IGRA	£368.70	0	19.04659	0	19.36	£0
0.35	IGRA	£402.52	0	19.04277	0	21.14	£0

2d

Prevalence TB	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
1.00E-04	IGRA+TST	£77.12	0	19.07609	0	4.04	0
2.00E-04	IGRA+TST	£77.54	0	19.07605	0	4.07	0
3.00E-04	IGRA+TST	£77.97	0	19.07602	0	4.09	0
4.00E-04	IGRA+TST	£78.40	0	19.07598	0	4.11	0
5.00E-04	IGRA+TST	£78.82	0	19.07594	0	4.13	0
6.00E-04	IGRA+TST	£79.24	0	19.0759	0	4.15	0
7.00E-04	IGRA+TST	£79.66	0	19.07586	0	4.18	0
8.00E-04	IGRA+TST	£80.09	0	19.07583	0	4.20	0
9.00E-04	IGRA+TST	£80.50	0	19.07579	0	4.22	0
0.001	IGRA+TST	£80.92	0	19.07575	0	4.24	0
1.00E-04	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
2.00E-04	IGRA	£98.56	£21.01	19.07708	0.00103	5.17	£20,422
3.00E-04	IGRA	£99.27	£21.30	19.07701	0.001	5.20	£21,353
4.00E-04	IGRA	£99.97	£21.58	19.07694	9.70E-04	5.24	£22,343
5.00E-04	IGRA	£100.68	£21.86	19.07687	9.30E-04	5.28	£23,398
6.00E-04	IGRA	£101.38	£22.14	19.0768	9.00E-04	5.31	£24,525
7.00E-04	IGRA	£102.08	£22.41	19.07673	8.70E-04	5.35	£25,731
8.00E-04	IGRA	£102.78	£22.69	19.07667	8.40E-04	5.39	£27,024
9.00E-04	IGRA	£103.48	£22.97	19.0766	8.10E-04	5.42	£28,416
0.001	IGRA	£104.17	£23.25	19.07653	7.80E-04	5.46	£29,917

Health Economic Models Inform Screening for Tuberculosis

2e Relapse Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0315	IGRA+TST	£77.12	0	19.07609	0	4.04	0
0.063	IGRA+TST	£78.03	0	19.07569	0	4.09	0
0.0945	IGRA+TST	£79.05	0	19.07524	0	4.14	0
0.126	IGRA+TST	£80.17	0	19.07475	0	4.20	0
0.1575	IGRA+TST	£81.41	0	19.07419	0	4.27	0
0.189	IGRA+TST	£82.77	0	19.07358	0	4.34	0
0.2205	IGRA+TST	£84.28	0	19.07289	0	4.42	0
0.252	IGRA+TST	£85.93	0	19.07213	0	4.51	0
0.2835	IGRA+TST	£87.74	0	19.0713	0	4.60	0
0.315	IGRA+TST	£89.72	0	19.07038	0	4.70	0
0.0315	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.063	IGRA	£98.58	£20.54	19.07684	0.00115	5.17	£17,888
0.0945	IGRA	£99.38	£20.33	19.07649	0.00125	5.21	£16,324
0.126	IGRA	£100.27	£20.10	19.0761	0.00135	5.26	£14,853
0.1575	IGRA	£101.25	£19.85	19.07566	0.00147	5.31	£13,475
0.189	IGRA	£102.34	£19.57	19.07518	0.00161	5.37	£12,191
0.2205	IGRA	£103.54	£19.26	19.07464	0.00175	5.43	£10,999
0.252	IGRA	£104.86	£18.93	19.07405	0.00191	5.50	£9,898
0.2835	IGRA	£106.31	£18.56	19.07339	0.00209	5.57	£8,887
0.315	IGRA	£107.89	£18.17	19.07266	0.00228	5.66	£7,964

2f Hepatitis rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0177	IGRA+TST	£77.12	0	19.07609	0	4.04	0
0.0354	IGRA+TST	£77.73	0	19.07516	0	4.08	0
0.0531	IGRA+TST	£78.35	0	19.07424	0	4.11	0
0.0708	IGRA+TST	£78.96	0	19.07331	0	4.14	0
0.0885	IGRA+TST	£79.58	0	19.07238	0	4.17	0
0.1062	IGRA+TST	£80.19	0	19.07145	0	4.20	0
0.1239	IGRA+TST	£80.81	0	19.07052	0	4.24	0
0.1416	IGRA+TST	£81.42	0	19.0696	0	4.27	0
0.1593	IGRA+TST	£82.04	0	19.06867	0	4.30	0
0.177	IGRA+TST	£82.65	0	19.06774	0	4.33	0
0.0177	IGRA	£97.85	£20.73	19.07715	0.00106	5.13	£19,545
0.0354	IGRA	£98.46	£20.73	19.07623	0.00106	5.16	£19,515
0.0531	IGRA	£99.08	£20.73	19.0753	0.00106	5.19	£19,485
0.0708	IGRA	£99.69	£20.73	19.07437	0.00107	5.23	£19,455
0.0885	IGRA	£100.31	£20.73	19.07345	0.00107	5.26	£19,425
0.1062	IGRA	£100.92	£20.73	19.07252	0.00107	5.29	£19,396
0.1239	IGRA	£101.53	£20.73	19.07159	0.00107	5.32	£19,366
0.1416	IGRA	£102.15	£20.73	19.07067	0.00107	5.36	£19,336
0.1593	IGRA	£102.76	£20.72	19.06974	0.00107	5.39	£19,307
0.177	IGRA	£103.38	£20.72	19.06881	0.00108	5.42	£19,277

Health Economic Models Inform Screening for Tuberculosis

2g

IGRA Repeat Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.015	IGRA+TST	£76.44	0	19.07609	0	4.01	0
0.03	IGRA+TST	£76.97	0	19.07609	0	4.03	0
0.045	IGRA+TST	£77.49	0	19.07609	0	4.06	0
0.06	IGRA+TST	£78.02	0	19.07609	0	4.09	0
0.075	IGRA+TST	£78.54	0	19.07609	0	4.12	0
0.09	IGRA+TST	£79.06	0	19.07609	0	4.14	0
0.105	IGRA+TST	£79.59	0	19.07609	0	4.17	0
0.12	IGRA+TST	£80.11	0	19.07609	0	4.20	0
0.135	IGRA+TST	£80.64	0	19.07609	0	4.23	0
0.15	IGRA+TST	£81.17	0	19.07609	0	4.25	0
0.015	IGRA	£96.98	£20.53	19.07715	0.00106	5.08	£19,346
0.03	IGRA	£97.66	£20.69	19.07715	0.00106	5.12	£19,501
0.045	IGRA	£98.34	£20.85	19.07715	0.00106	5.15	£19,656
0.06	IGRA	£99.02	£21.00	19.07715	0.00106	5.19	£19,811
0.075	IGRA	£99.70	£21.16	19.07715	0.00106	5.23	£19,966
0.09	IGRA	£100.38	£21.32	19.07715	0.00106	5.26	£20,122
0.105	IGRA	£101.06	£21.47	19.07715	0.00106	5.30	£20,277
0.12	IGRA	£101.75	£21.63	19.07715	0.00106	5.33	£20,433
0.135	IGRA	£102.43	£21.79	19.07715	0.00106	5.37	£20,588
0.15	IGRA	£103.11	£21.94	19.07715	0.00106	5.40	£20,744

2h

TST Repeat Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.025	IGRA+TST	£75.22	0	19.0759	0	3.94	0
0.05	IGRA+TST	£75.54	0	19.07593	0	3.96	0
0.075	IGRA+TST	£75.86	0	19.07596	0	3.98	0
0.1	IGRA+TST	£76.18	0	19.07599	0	3.99	0
0.125	IGRA+TST	£76.50	0	19.07603	0	4.01	0
0.15	IGRA+TST	£76.81	0	19.07606	0	4.03	0
0.175	IGRA+TST	£77.13	0	19.07609	0	4.04	0
0.2	IGRA+TST	£77.45	0	19.07613	0	4.06	0
0.225	IGRA+TST	£77.77	0	19.07616	0	4.08	0
0.25	IGRA+TST	£78.09	0	19.07619	0	4.09	0
0.025	IGRA	£97.85	£22.63	19.07715	0.00126	5.13	£17,991
0.05	IGRA	£97.85	£22.31	19.07715	0.00122	5.13	£18,217
0.075	IGRA	£97.85	£21.99	19.07715	0.00119	5.13	£18,456
0.1	IGRA	£97.85	£21.67	19.07715	0.00116	5.13	£18,709
0.125	IGRA	£97.85	£21.36	19.07715	0.00113	5.13	£18,976
0.15	IGRA	£97.85	£21.04	19.07715	0.00109	5.13	£19,260
0.175	IGRA	£97.85	£20.72	19.07715	0.00106	5.13	£19,561
0.2	IGRA	£97.85	£20.40	19.07715	0.00103	5.13	£19,883
0.225	IGRA	£97.85	£20.08	19.07715	9.90E-04	5.13	£20,225
0.25	IGRA	£97.85	£19.76	19.07715	9.60E-04	5.13	£20,591

Suppl. Table 3
TST, IGRA Costs

TST £24			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
45	IGRA+TST	£86.60	0	19.07609	0	4.53989	0
55	IGRA+TST	£90.97	0	19.07609	0	4.76904	0
65	IGRA+TST	£95.35	0	19.07609	0	4.9982	0
75	IGRA+TST	£99.72	0	19.07609	0	5.22735	0
85	IGRA+TST	£104.09	0	19.07609	0	5.4565	0
95	IGRA+TST	£108.46	0	19.07609	0	5.68565	0
45	IGRA	£98.08	£11.47	19.07715	0.00106	5.14114	£10,818
55	IGRA	£108.42	£17.45	19.07715	0.00106	5.68331	£16,447
65	IGRA	£118.76	£23.42	19.07715	0.00106	6.22547	£22,077
75	IGRA	£129.11	£29.39	19.07715	0.00106	6.76764	£27,706
85	IGRA	£139.45	£35.36	19.07715	0.00106	7.30981	£33,336
95	IGRA	£149.79	£41.33	19.07715	0.00106	7.85197	£38,965

TST £36			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
45	IGRA+TST	£100.69	£2.61	19.07609	-0.00106	5.27822	-£2,460
55	IGRA+TST	£105.06	0	19.07609	0	5.50737	0
65	IGRA+TST	£109.43	0	19.07609	0	5.73652	0
75	IGRA+TST	£113.80	0	19.07609	0	5.96567	0
85	IGRA+TST	£118.17	0	19.07609	0	6.19483	0
95	IGRA+TST	£122.54	0	19.07609	0	6.42398	0
45	IGRA	£98.08	0	19.07715	0	5.14114	0
55	IGRA	£108.42	£3.36	19.07715	0.00106	5.68331	£3,170
65	IGRA	£118.76	£9.33	19.07715	0.00106	6.22547	£8,799
75	IGRA	£129.11	£15.31	19.07715	0.00106	6.76764	£14,429
85	IGRA	£139.45	£21.28	19.07715	0.00106	7.30981	£20,058
95	IGRA	£149.79	£27.25	19.07715	0.00106	7.85197	£25,688

TST £48			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
45	IGRA+TST	£114.77	£16.69	19.07609	-0.00106	6.01655	-£15,738
55	IGRA+TST	£119.14	£10.72	19.07609	-0.00106	6.2457	-£10,108
65	IGRA+TST	£123.51	£4.75	19.07609	-0.00106	6.47485	-£4,478
75	IGRA+TST	£127.89	0	19.07609	0	6.704	0
85	IGRA+TST	£132.26	0	19.07609	0	6.93315	0
95	IGRA+TST	£136.63	0	19.07609	0	7.1623	0
45	IGRA	£98.08	0	19.07715	0	5.14114	0
55	IGRA	£108.42	0	19.07715	0	5.68331	0
65	IGRA	£118.76	0	19.07715	0	6.22547	0
75	IGRA	£129.11	£1.22	19.07715	0.00106	6.76764	£1,151
85	IGRA	£139.45	£7.19	19.07715	0.00106	7.30981	£6,781
95	IGRA	£149.79	£13.16	19.07715	0.00106	7.85197	£12,410

Health Economic Models Inform Screening for Tuberculosis

Suppl. Table 4
Market Costs Model
Sensitivity Analysis

IGRA Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.9	IGRA+TST	£135.91	0	19.07479	0	7.12	0
0.91	IGRA+TST	£135.27	0	19.07495	0	7.09	0
0.92	IGRA+TST	£134.64	0	19.07511	0	7.06	0
0.93	IGRA+TST	£134.01	0	19.07528	0	7.03	0
0.94	IGRA+TST	£133.38	0	19.07544	0	6.99	0
0.95	IGRA+TST	£132.75	0	19.07561	0	6.96	0
0.96	IGRA+TST	£132.13	0	19.07577	0	6.93	0
0.97	IGRA+TST	£131.52	0	19.07593	0	6.89	0
0.98	IGRA+TST	£130.92	0	19.07609	0	6.86	0
0.99	IGRA+TST	£130.34	0	19.07625	0	6.83	0
0.9	IGRA	£209.83	£73.92	19.07583	0.00105	11.00	£70,657
0.91	IGRA	£201.65	£66.38	19.07600	0.00105	10.57	£63,236
0.92	IGRA	£193.48	£58.84	19.07617	0.00105	10.14	£55,882
0.93	IGRA	£185.31	£51.30	19.07633	0.00106	9.71	£48,591
0.94	IGRA	£177.15	£43.77	19.07650	0.00106	9.29	£41,360
0.95	IGRA	£169.00	£36.24	19.07667	0.00106	8.86	£34,182
0.96	IGRA	£160.85	£28.72	19.07683	0.00106	8.43	£27,054
0.97	IGRA	£152.72	£21.20	19.07699	0.00106	8.01	£19,968
0.98	IGRA	£144.62	£13.70	19.07715	0.00106	7.58	£12,915
0.99	IGRA	£136.56	£6.22	19.07731	0.00106	7.16	£5,882

TST Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.46	IGRA+TST	£142.80	0	19.07601	0	7.49	0
0.49	IGRA+TST	£140.06	0	19.07603	0	7.34	0
0.52	IGRA+TST	£137.32	0	19.07605	0	7.20	0
0.55	IGRA+TST	£134.58	0	19.07607	0	7.05	0
0.58	IGRA+TST	£131.84	0	19.07609	0	6.91	0
0.61	IGRA+TST	£129.09	0	19.07611	0	6.77	0
0.64	IGRA+TST	£126.35	0	19.07613	0	6.62	0
0.67	IGRA+TST	£123.61	0	19.07614	0	6.48	0
0.7	IGRA+TST	£120.87	0	19.07616	0	6.34	0
0.73	IGRA+TST	£118.13	0	19.07618	0	6.19	0
0.46	IGRA	£144.49	£1.69	19.07717	0.00116	7.57	£1,455
0.49	IGRA	£144.51	£4.45	19.07717	0.00114	7.58	£3,915
0.52	IGRA	£144.54	£7.22	19.07716	0.00112	7.58	£6,478
0.55	IGRA	£144.57	£10.00	19.07716	0.00109	7.58	£9,153
0.58	IGRA	£144.61	£12.77	19.07715	0.00107	7.58	£11,952
0.61	IGRA	£144.65	£15.55	19.07715	0.00104	7.58	£14,889
0.64	IGRA	£144.70	£18.34	19.07715	0.00102	7.58	£17,981
0.67	IGRA	£144.75	£21.14	19.07714	0.00099	7.59	£21,250
0.7	IGRA	£144.82	£23.94	19.07713	0.00097	7.59	£24,728
0.73	IGRA	£144.90	£26.76	19.07712	0.00094	7.60	£28,455

Health Economic Models Inform Screening for Tuberculosis

Treatment LTBI	Costs Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£405	IGRA+TST	£117.92	0	19.07609	0	6.18	0
£810	IGRA+TST	£130.95	0	19.07609	0	6.86	0
£1,215	IGRA+TST	£143.99	0	19.07609	0	7.55	0
£1,620	IGRA+TST	£157.02	0	19.07609	0	8.23	0
£405	IGRA	£124.12	£6.20	19.07715	0.00106	6.51	£5,846
£810	IGRA	£144.67	£13.72	19.07715	0.00106	7.58	£12,932
£1,215	IGRA	£165.22	£21.24	19.07715	0.00106	8.66	£20,018
£1,620	IGRA	£185.77	£28.75	19.07715	0.00106	9.74	£27,105

TB	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£2,192	IGRA+TST	£125.58	0	19.07609	0	6.58	0
£4,384	IGRA+TST	£130.92	0	19.07609	0	6.86	0
£6,576	IGRA+TST	£136.26	0	19.07609	0	7.14	0
£8,768	IGRA+TST	£141.61	0	19.07609	0	7.42	0
£2,192	IGRA	£140.40	£14.82	19.07715	0.00106	7.36	£13,972
£4,384	IGRA	£144.62	£13.70	19.07715	0.00106	7.58	£12,915
£6,576	IGRA	£148.84	£12.58	19.07715	0.00106	7.80	£11,858
£8,768	IGRA	£153.06	£11.46	19.07715	0.00106	8.02	£10,801

Hepatitis	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£367	IGRA+TST	£130.61	0	19.07609	0	6.85	0
£734	IGRA+TST	£130.92	0	19.07609	0	6.86	0
£1,101	IGRA+TST	£131.24	0	19.07609	0	6.88	0
£1,468	IGRA+TST	£131.55	0	19.07609	0	6.90	0
£367	IGRA	£144.31	£13.70	19.07715	0.00106	7.56	£12,915
£734	IGRA	£144.62	£13.70	19.07715	0.00106	7.58	£12,915
£1,101	IGRA	£144.93	£13.70	19.07715	0.00106	7.60	£12,914
£1,468	IGRA	£145.25	£13.70	19.07715	0.00106	7.61	£12,914

Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice

Merve Nazli Eralp[1], Stefan Scholtes[1] , Geraldine Martell[2] , Robert Winter[3] , Andrew Robert Exley[4]

Reporting Checklist after Drummond and Jefferson, BMJ Economic Evaluation Working Party, BMJ 1996; 313 : 275 :

STUDY DESIGN

(1) Research question	*Yes*
(2) Economic importance of the research question	*Yes*
(3) Viewpoint of the analysis	*Yes*
(4) Rationale for choosing the alternatives	*Yes*
(5) The alternatives being compared	*Yes*
(6) The form of economic evaluation	*Yes*
(7) Justification of economic evaluation used	*Yes*

Data Collection

(8) The sources of effectiveness estimates used	*Yes*
(9) Details of the design and results of effectiveness study	*Yes*
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	*Yes referenced*
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	*Yes*
(12) Methods to value health states and other benefits are stated	*Yes*
(13) Details of the subjects from whom valuations were obtained are given	*referenced*
(14) Productivity changes (if included) are reported separately	*not applicable*
(15) The relevance of productivity changes to the study question is discussed	*see discussion*
(16) Quantities of resources are reported separately from their unit costs	*Yes*
(17) Methods for the estimation of quantities and unit costs are described	*Yes*
(18) Currency and price data are recorded	*Yes*
(19) Details of currency of price adjustments for inflation or currency conversion are given	*No*
(20) Details of any model used are given	*Yes*
(21) The choice of model used and the key parameters on which it is based are justified	*Yes*
(21) The choice of model used and the key parameters on which it is based are justified	
(22) Time horizon of costs and benefits is stated	*Yes*
(23) The discount rate(s) is stated	*Yes*
(24) The choice of rate(s) is justified	*standard rate*
(25) An explanation is given if costs or benefits are not discounted	*not applicable*
(26) Details of statistical tests and confidence intervals are given for stochastic data	*ranges cited*
(27) The approach to sensitivity analysis is given	*Yes*
(28) The choice of variables for sensitivity analysis is justified	*Yes*
(29) The ranges over which the variables are varied are stated	*Yes*
(30) Relevant alternatives are compared	*Yes*
(31) Incremental analysis is reported	*Yes*
(32) Major outcomes are presented in a dissaggregated as well as aggregated form	*Yes*
(33) The answer to the study question is given	*Yes*
(34) Conclusions follow from the data reported	*Yes*
(35) Conclusions are accompanied by the appropriate caveats	*Yes*

Andrew Exley, on behalf of the authors

Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice

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ABSTRACT

Background: Methods for determining cost-effectiveness of different treatments are well established, unlike appraisal of non-drug interventions, including novel diagnostics and biomarkers

Objective: We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST; blood test, IGRA; and TST followed by IGRA in conditional sequence, in screening health care workers for latent or active TB.

Design: We focus on healthy life years gained as the benefit metric, rather than quality adjusted life years (QALYs) given limited data to estimate quality-adjustments of life years with TB and complications of treatment, like hepatitis. Healthy life years gained refers to the number of TB or hepatitis cases avoided, and the increase in life expectancy. We incorporate disease and test parameters informed by systematic meta-analyses and clinical practice. Health and economic outcomes of each strategy are modelled as a decision tree in Markov chains, representing different health states informed by epidemiology. Cost and effectiveness values are generated as the individual is cycled through 20 years of the model. Key parameters undergo one-way and Monte Carlo probabilistic sensitivity analyses.

Setting: Screening health care workers in secondary and tertiary care.

Results: IGRA is the most effective strategy, with incremental costs per healthy life year gained of £10,614 - £20,929, base case, £8,021 - £18,348, market costs TST £45, IGRA £90, IGRA specificities of 99% - 97%; mean (5%, 95%), £12,060 (£4,137 - £38,418) by Monte Carlo analysis.

Conclusions: Incremental costs per healthy life year gained, a conservative estimate of benefit, are comparable to the £20,000 - £30,000 NICE band for IGRA alone, across wide differences in disease and test parameters. Health gains justify IGRA costs, even if IGRA tests cost three times TST. This health economic model offers a powerful tool for appraising non-drug interventions in the market and under development. (300 words)

What this paper adds

1. What is already known and why this study is required

- Methods for determining the cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analyses and clinical practice, testing key disease and test parameters by one-way and Monte Carlo probabilistic sensitivity analyses

2. What this study adds

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- Screening with IGRA appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- These findings are robust for wide differences in disease and test parameters, even if IGRA test costs are three times TST costs suggesting this health economic model is a powerful tool for appraising non-drug interventions

ARTICLE SUMMARY

Article focus

- Methods for determining cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or a TB blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analysis and clinical practice, testing disease and test parameters by one-way and Monte Carlo probabilistic sensitivity analyses

Key messages

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- IGRA screening has an incremental cost per healthy life year gained of £10,614 - £20,929, base case, £8,021 - £18,348, market costs, TST £45, IGRA £90, IGRA specificities 99% -97%; mean (5%, 95%), £12,060 (£4,137 - £38,418) by Monte Carlo analysis

Strengths and limitations of this study

- Screening with IGRA alone appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- Neither TST not IGRA differentiate latent from active TB, and the specificity of IGRA is inferred from studies in populations at low risk of TB
- These findings are robust for wide differences in disease and test parameters, including IGRA test costs three times TST costs, suggesting this health economic model is a powerful tool for appraising non-drug interventions in the market and under development

INTRODUCTION

Economic evaluation is a recognised approach to optimising national health care provision within a limited budget but informed choice requires transparent analysis highlighting key assumptions and critical factors [1]. Methods for determining the cost-effectiveness of different treatments are well established [2], [3], unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers. We develop and validate a new health economic model by focusing on whether a tuberculin skin test, TST, and / or a blood test for tuberculosis, IGRA, is more cost-effective in screening health care workers for latent or active tuberculosis, TB. The screening of health care workers for tuberculosis has economic importance given the impact of disease transmission in each case together with the large number of NHS employees at risk, 1.7 million personnel and 80,000 new employees per annum (National Health Service, 2010). We inform the health economic model by applying insight from epidemiology, meta-analysis, and clinical practice including knowledge of market costs to compare the cost-effectiveness of new technology supporting or replacing established practice. The analysis is from the NHS and societal perspective.

Established practice is for trained occupational health staff to administer a TST using cheap readily available reagents injected intradermally at an initial visit. The skin test reaction is measured at a second clinic visit 48 – 72 hours later [4]. The need for two visits is operationally inefficient, and the test itself is limited both by specificity and sensitivity. TST has a low specificity in subjects exposed to BCG vaccination or environmental non-tuberculous mycobacteria (NTM) and moderate sensitivity resulting in false negatives [5], [6]. A new technological approach requires a single clinic visit to draw a blood sample which is transferred to the laboratory for analysis in a TB specific interferon-gamma release assay, IGRA [7]. The approach is operationally efficient and the assay has a high specificity and sensitivity, although simple costs per test are greater than the TST. In principle the advantages of old and new might be combined using TST for all and then applying IGRA blood testing to TST positive cases to exclude false positive TST after previous exposure to

NTM including BCG immunisation. Following earlier work, [8] this study has focused on healthy life years gained as the benefit metric, rather than quality adjusted life years. The reason is the lack of robust data to estimate quality-adjustments of life years with TB and complications of treatment such as hepatitis. Health life years gained refers to the number of TB or hepatitis cases avoided, and the associated increase in life expectancy.

This study adds to the literature [9], [8], [10], [11] in four key areas by incorporating:

1. Healthy life years to avoid the assumptions inherent in estimating QALYs

2. Key disease parameters in a comprehensive model of all relevant health states informed by epidemiology including

i. The impact of LTBI Tuberculosis treatment side effects [12]

ii. The higher relapse rate of active TB within the first three years of treatment in comparison to the years thereafter [13]

3. Key test parameters relevant to clinical practice including

i. The inability of screening tests to differentiate between active and latent TB [6]

ii. The sensitivity and specificity of IGRA and TST independently of each other

iii. Operational inefficiencies of TST prompting repeat testing [14]

4. And we provide a powerful methodology for appraising the cost-effectiveness of non-drug interventions to inform health care policy, including sensitivity analyses of key parameters

METHODS

The health and economic outcomes of the three alternatives testing strategies are modelled as a decision tree, representing the health outcomes of each of the strategies as Markov chains over twenty years. The model incorporates economic, medical, epidemiological and operational factors in the analysis. This approach lends itself to the clinical setting where the risks are continuous over time, key events may be repeated, and operational factors may interact with other key parameters to influence the base case result.

Data collection

The test, population, and outcome characteristics (**table 1**) include data from the meta-analyses by Menzies 2007 [15] and Pai 2008 [5]. In the absence of a gold standard for latent tuberculosis infection, LTBI, active TB is used as a surrogate to determine assay sensitivity [15]. Specificity for LTBI is derived by testing populations at low risk of TB [5], [16], [17] to determine the rate of false positives. The analysis is guided by our clinical and market experience with the T-Spot TB test, applying an an IGRA specificity of 98% [17] for the base case. We then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model. The operational characteristics of the three alternative approaches include repeat test rates due to test failure and failure to attend for skin test reading. Direct and indirect costs are shown (**table 2)** drawing on data supplied by NICE (*see appendix 6)* [18], the Cambridge TB service, and the NHS National tariff 2010 [19] with costs adjusted to the 2010-2011 financial year (**suppl. table 1**). The impact of regional or national differences in disease parameters and costs are examined in one-way sensitivity analyses. The impact of uncertainty within multiple parameters is then examined using Monte Carlo probabilistic sensitivity analysis.

Model construction

We built a decision analysis model, which incorporates the health outcomes as Markov chains over twenty years, to analyze three different diagnostic approaches to LTBI. This model only considers the initial screening for newly hired personnel; the annual testing is beyond the scope of this model. The model is coded and composed using the decision analysis software TreeAge Pro Suite 2009, 2011. The states of the Markov chains represent the health conditions of the individuals; following a LTBI diagnosis test and possible interventions. Each Markov state length is one year. The decision is made at the first node of the decision tree between three diagnosis options: TST, IGRA, and a combined sequential testing strategy. The alternatives are assessed according to their cost and effectiveness values over twenty years; in which the costs are direct and indirect monetary costs and their effectiveness is measured by total number of healthy years. The Markov chain is implemented through 20 years, related cost and effectiveness values due to different health states are recorded as the individual is cycled through the model. All future costs are discounted at 5% per year.

Table 1: Base Case Data for Test, Population and Outcomes Parameters

Parameter	Base-case values	Range Tested	Reference
1. Test characteristics			
Tuberculin skin test (TST)			
Specificity	0.66	0.46 – 0.86	[15]
Sensitivity	0.70	0.65 – 0.74	[15]
Probability a second TST is placed	0.1737	0.025 – 0.25 *	[14]
TB specific IFNgamma release assay (IGRA)			
Specificity	0.98	0.90 – 0.99	[17]
Sensitivity	0.90	0.82 – 0.98	[5]
Probability a second IGRA is required	0.0343	0.015 – 0.15 *	[14]
2. Population characteristics			
Age range	20 – 30		
Occupation	Healthcare worker		
BCG vaccination rates	52.8%		[20]
Nationality of majority	English		
Prevalence of LTBI	0.035	0.035 – 0.35 *	[20]
Prevalence of TB	0.0001	0.0001 – 0.001 *	[21]
Probability of all causes of death	0.0045	0.0045 – 0.045 *	Office for National Statistics 2008
3. Probability of Outcomes			
Efficacy of LTBI treatment	0.65		[22]
Risk of hepatitis caused by treatment	0.0177	0.0177 – 0.177 *	[12]
Risk of activation of LTBI	0.01		[6]
Probability of relapse of TB	0.0315	0.0315 – 0.315 *	[13]
Probability of death due to TB	0.018	0.018 – 0.18 *	[21]
Probability of death due to hepatitis	0		Assumption

Key

* Ten-fold range tested in sensitivity analyses to highlight potential impact on incremental cost per healthy life year gained

Table 2: Costs

Parameter	Base-case values	Range tested
4. Cost of Interventions		
	NICE [18]	
TST	£16	£16 - £64
IGRA	£44.78	£30 - £120
Chest radiograph (CXR)	£28	
	Cambridge TB Service 2010 NHS National Tariff [19]	
TB Treatment	£1,637	0.5 – 2 times
Contact tracing	£426	0.5 – 2 times
LTBI Treatment	£647	0.5 – 2 times
Hepatitis Treatment	£640	0.5 – 2 times
5. Healthcare worker costs	**Cambridge TB Service 2010** NHS Pay 2/2010 [23]	
Time to attend for TB treatment	£662	0.5 – 2 times
Time to attend for Contact tracing	£95	0.5 – 2 times
Time to attend for LTBI treatment	£172	0.5 – 2 times
Time for Hepatitis treatment	£114	0.5 – 2 times
6. Discount rate	0.05	

Key

TB treatment costs are derived from the NHS National Tariff 2010-11 [19] applied to the Cambridge TB service. Healthcare worker costs are derived from the NHS Pay Circular (AforC) 2/2010 [23], point 26 £30,460, plus 22% overheads £37,161 per annum, applied to the Cambridge TB service. Total model costs for TB treatment are TB treatment, plus contact tracing x5 contacts per case [22], plus health care worker time costs, £4908; for LTBI, LTBI treatment plus health care worker time costs, £819; for Hepatitis, Hepatitis treatment plus health care worker time costs, £755, (**suppl. table 1**).

Model construction

This Markov model assumes

i. Each health state is taken as a time periods of one year, can not be left earlier and can only last longer if the return probability is greater than zero.

ii. All patients with positive results for LTBI accept treatment, consistent with conditions of employment in the NHS. The impact of limited compliance is allowed for within the efficacy of LTBI treatment [22].

iii. Standard Isoniazid and Rifampicin treatment for LTBI lasts three months and all treatments are completed.

iv. Diagnostic tests are repeated once only as required to achieve a result

v. The repeat rate for diagnostic tests is further addressed in the sensitivity analyses

vi. The probability that LTBI generates a positive result is assumed to be the same as the probability that active TB generates a positive result, as there is no gold standard for LTBI

vii. The risk of active TB in cases with false negative results is proportional to the prevalence rates of latent and active TB

viii. The result of the second test is independent of the first in two stage testing

ix. The effects of TB and Hepatitis are the simple sum, rather than synergistic

x. All cases with positive TST or IGRA will have a CXR that identifies all cases of active TB. All positive CXRs are active TB

xi. The relapse rate of TB is higher than the prevalence rate in the general population for the first three years after recovery [13]

xii. The probability of continuing to have TB after standard TB treatment is the probability of relapse

xiii. All TB is diagnosed and treated on time. The effect of late diagnosis of latent or active TB in cases with false negative results is neglected.

xiv. An equal number of males and females make up new NHS healthcare workers

xv. Death of an employee has no monetary cost for NHS.

xvi. Transmission of TB to the community is modeled as a constant monetary cost for contact tracing, including screening the close contacts of the patient, and their treatment in the case of positive Tuberculosis findings.

xvii. All employees are employed for 20 years

The comprehensive decision tree consists of 985 nodes including three similar sub-trees with different probability and cost parameters (**figure 1**). The initial analysis was then subjected to one-way sensitivity analyses applied to key parameters including IGRA sensitivity and specificity; prevalence rates of TB and LTBI, all causes death rates; test repetition rates; market rates for TST and IGRA tests; and treatment costs for TB, LTBI, and hepatitis. We tested the impact of variation in multiple parameters by first generating triangular distributions using minimum, mode or peak, and maximum values for key parameters [24]. Probabilistic sensitivity analysis was then carried out by Monte Carlo simulation using 100, 000 iterations to estimate the total impact of uncertainty on the model, TreeAge Pro 2011.

RESULTS

Base case analysis indicates the incremental cost of IGRA alone is offset by the increased effectiveness of this approach over the two stage sequential approach of TST followed by IGRA for positive TST results (**table 3a**). IGRA is the most effective strategy with an incremental effectiveness of 0.0015 and an incremental cost-effectiveness ratio, ICER, of £15,757 per healthy life year gained. The strategy of TST alone is clearly inferior by all criteria. We therefore focused on further analysis of parameters affecting the relative efficacy of TST + IGRA versus IGRA alone.

Table 3 Incremental Costs Per Healthy Life Year Gained (ICER) of IGRA or TST

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Effectiveness	ICER
a. Base Case						
IGRA+TST	£76.60	£0.00	19.07569	0	4.02	£0
IGRA	£99.52	£22.92	19.07714	0.001455	5.22	£15,757
TST	£333.42	£233.90	19.07088	-0.00626	17.48	-£37,358 *(Dominated)*
b. Market Costs						
IGRA+TST	£127.13	£0.00	19.0757	0	6.66	£0
IGRA	£146.29	£19.16	19.0771	0.00145	7.67	£13,173
TST	£367.45	£221.16	19.0709	-0.0063	19.27	-£35,324 *(Dominated)*

Base case, TST £16, IGRA £45; market costs TST £45, IGRA £90.

Sensitivity analyses of disease and test parameters

Sensitivity analysis of the base case model indicates that the ICER for IGRA ranges from £20,929 to £10,614 per healthy life year gained for test specificities of 97% - 99% (**figure 2a-c, suppl. table 2**). Assay sensitivity has a much smaller impact on the ICER (**figure 2d**). The superior cost-effectiveness of IGRA was not threatened when base case values were inflated ten fold for all cause death rates; TB death rates; prevalence of LTBI or TB; relapse rates and hepatitis rates (**figure 2e, suppl. table 3a-f**).

TST repeat rates were estimated using the 17.4% rate of failure to achieve a TST result in a UK study of routine practice [14]. This compares with 53%, 35/66, of medical students who failed to attend their first Mantoux appointment [25] and a 12% failure rate to read the 1st TST [11]. Varying the IGRA repeat rate from 1.5% to 15% or TST repeat rate from 2.5% to 25% had little impact on the ICER which increased from £15,573 to £16,860 and £14,242 to £16,776 per healthy life year gained respectively (**suppl. table 3g, h**).

The cost of TST testing was investigated by eliciting costs from five private medical service providers, median £65 per test, range £45 to £75, and by using estimated itemized costs from Cambridge Occupational Health (**suppl, table 1.V**), total cost £48.53. We used £45 as a market cost for TST and tested the impact of test costs on ICER. Market costs for TST significantly enhance the ICER for IGRA alone across a range of IGRA costs (**figure 2f**, **suppl. table 4**). In particular, the market standard test costs of £45 per TST and £90 per IGRA generate an ICER of £13,173 per healthy life year gained (**table 3b**). A threshold value of £30,000 per healthy life year gained is still achieved when IGRA test costs are three-times TST test costs.

Examining the impact of assay specificity and sensitivity, this market standard model generates a range of £18,348 to £8,021 per healthy life year gained for an IGRA specificity of 97% - 99%. Sensitivity analysis for TST test characteristics over a range of 0.46 – 0.86 for specificity, and 0.65 – 0.74 for sensitivity [15], suggests IGRA remains the optimal strategy with costs of £354 to £31,069, and £10, 385 - £16, 484 per healthy life year gained respectively. (**suppl. table 5)**.

The calculation and apportionment of treatment costs is likely to vary between centres, but a four fold variation, 0.5 times – 2 times baseline, in treatment costs for LTBI, TB, or hepatitis is also accommodated by the market standard model (**figure 2g**, **suppl. table 6**).

Probabilistic sensitivity analysis by Monte Carlo simulation was carried out with uncertainty in each of 12 key parameters defined as triangular distributions (**suppl. table 7**). Mean incremental cost per healthy life year gained was £12,060, with 5% and 95% values of £4,137 and £38, 418 respectively.

DISCUSSION

The methodology for determining the cost-effectiveness of different treatments is well established [2], [3], [1] in contrast to the analysis of non-drug interventions. Our health economic model suggests a methodology to appraise the host of novel diagnostics [7] and biomarkers generated by clinical science. Healthy life years, despite being a conservative benefit metric, may be particularly useful in evaluating novel screening and monitoring tests by avoiding the assumptions inherent in generating quality adjusted life years [26], [1], [8], [11], [27]. This approach, allied to the use of multiple disease states supported by epidemiological data, is far more powerful than standard comparisons since the IGRA strategy will overcome a two – three fold excess of simple test costs.

In our study we compare the effectiveness of the diagnostic procedures by focusing on healthy life years gained, [1,8] rather than quality adjusted life years [26], [11], [18]. The reason is there are limited data to base estimates of quality adjusted life years for each of the health states applicable to latent or active TB and its treatment [28].The additional costs of IGRA alone appear justified by the health gains at £15,757 per healthy life year gained, falling to £13,173 per healthy life year when applying market costs where blood tests cost twice as much as skin tests. Our estimates are conservative in that they only take a healthy life year as a benefit (i.e. years without tuberculosis or hepatitis). Since the calculated ratio is at the lower end of the NICE band of £20,000 - £30,000, IGRA is cost-effective, even at the current NICE threshold which may or may not be conservative [2], [3]. These findings are supported by the probabilistic sensitivity analysis of multiple disease and test parameters. There is no validated instrument for determining quality of life with tuberculosis [29], but when such data are available it is likely that additional health gains would be identified, further improving the cost/benefit ratio.

The health economic model is sensitive to IGRA specificity, which is derived from estimates of false positives in populations at low risk of TB [30 27], [17]. An IGRA specificity of 98% is conservative by current literature [30 27], [17] but higher than analyses potentially confounded by data from studies in populations at intermediate rather than low risk of TB [5], [16], [18]. Our model accommodates substantial enhancement of TST specificity greater than expected in BCG-vaccinated populations or mixed populations including non-BCG vaccinated health care workers [15]. The outcome may be different in non-BCG vaccinated populations with low NTM infection rates [5] but NTM infection is an increasing problem in adults [31]. Studies testing children prior to BCG immunisation have revealed false positive TST rates of 14% in SE England [32] and 79% in Norway [33]. It seems likely therefore that previous infection with NTM has a significant role in reducing the specific of TST. The study's findings accommodate wide regional or national differences in disease parameters, although health gains are enhanced by a relative increase in the prevalence of LTBI and hampered by doubling costs for the treatment of LTBI.

Studies including the relative risk of progression to active TB suggest additional limits to TST specificity, reviewed recently [34]. IGRA positive cases with LTBI are more likely to progress to active TB than TST positive cases. In particular, IGRA positive cases showed a 19% greater chance of progression to active TB than expected solely from the increased specificity of IGRA over TST [10]. This advantage would lead to further domination of TST only approaches, by sequential TST then IGRA and IGRA alone strategies.

The one-stop approach of IGRA alone has additional, operational advantages which are likely to enhance the value of this strategy. Testing at a single visit boosts compliance whilst minimising consumption of resources to achieve a test result and the risk of loss to follow up. The health economic model does not include an allowance for health care workers time to attend for testing, but these staff costs would be greater when two – three visits are required for TST then IGRA further limiting cost-effectiveness of strategies incorporating TST. Efficiency is enhanced by combining IGRA with other screening blood tests, although a blood sample is more invasive than TST. Blood testing may offer more flexibility than TST with blood sampling facilities widely available in primary care and hospital settings. In contrast, carrying out a TST requires registered nurses with proven competence and recent training or administration of TSTs [4], which is more expensive than phlebotomy and may be limiting during peaks in demand such as in contact tracing. An IGRA strategy transfers costs from the clinic to the laboratory, where cost pressures are intense but responsive to focusing expertise and optimising staffing structures. Critical aspects of blood sampling are defined including the impact of the test population and sampling conditions on the performance characteristics of IGRA [14], [35], [36], [37]. An IGRA strategy also avoids the possibility of TST boosting TST responses after repeat testing [6] or IGRA responses if follow-up testing is delayed [36]. The relative merits of different IGRA tests are controversial [27], [17], [5] but where there is a consensus on the assay characteristics this model should allow further investigation.

Our study suggests health gains justify IGRA costs when screening health care workers for latent or active TB. These findings are robust for wide differences in key disease and test parameters including IGRA test costs three times TST costs, whilst maintaining cost-effectiveness at the lower end of the £20,000 - £30,000 NICE band. We suggest this health economic model incorporating healthy life years gained, epidemiology, meta-analyses and clinical practice provides a powerful tool for assessing the potential impact of new technology on established practice.

Figures

Figure 1: The Decision Tree

Health and economic outcomes of TST and / or IGRA modeled as a decision tree in Markov chains representing different health states informed by epidemiology: TB, active tuberculosis; LTBI, LTBI1, latent tuberculosis, with treatment; D, Death; S, S1, healthy, with unnecessary treatment for LTBI ; H, H+TB, H+LTBI, hepatitis, and TB, or LTBI; T1, T2, T1H, T2H, transition states indicating relapse rates within three years of treatment and thereafter, with hepatitis; A – E, node points repeated as Clone A - Clone E. X, Y are probabilities, p, X = pLTBI / (pLTBI + pTB), Y = pTB /(pLTBI + pTB)

Figure 2:
Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness

a – c IGRA specificity versus **a** overall costs in £ Sterling, **b** cost / effectiveness, **c** ICER, incremental cost per healthy life year gained. **d - f** ICER in the base case model versus **d** IGRA sensitivity, **e** key disease parameters increased times ten, prev prevalence, **f** TST and IGRA costs. **g** ICER in the market case model versus four fold variation in treatment costs.

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Competing Interests

MNE has no competing interests; SS has no competing interests; GM has no competing interests; RW has no competing interests. ARE is the director of the specialist Immunology Laboratory at Papworth Hospital NHS Foundation Trust which provides a supra-regional service for interferon-gamma release assays using the T-Spot TB test (Oxford Immunotech).

Contributor Statement

ARE & RW conceived the study. SS and MNE developed the economic model with additional clinical data from GM, ARE, RW. MNE, SS, ARE, tested and revised the economic model. All authors contributed to the interpretation of the results and approved the final version of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

The economic model run on TreeAge Pro is available from the corresponding author.

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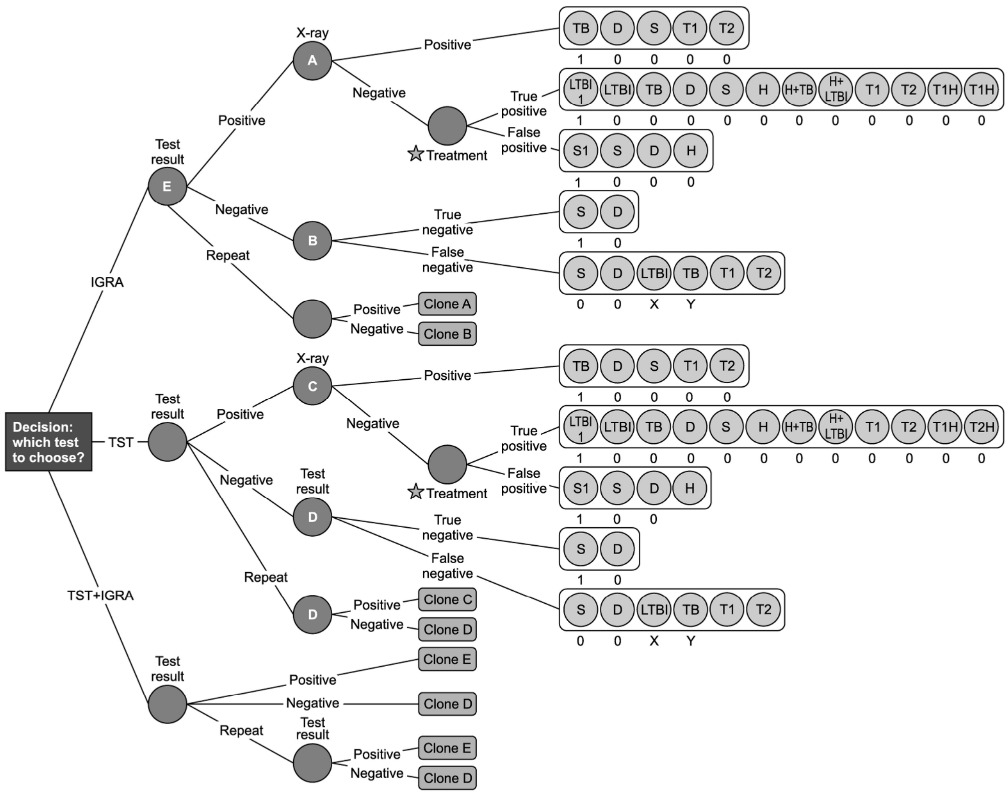

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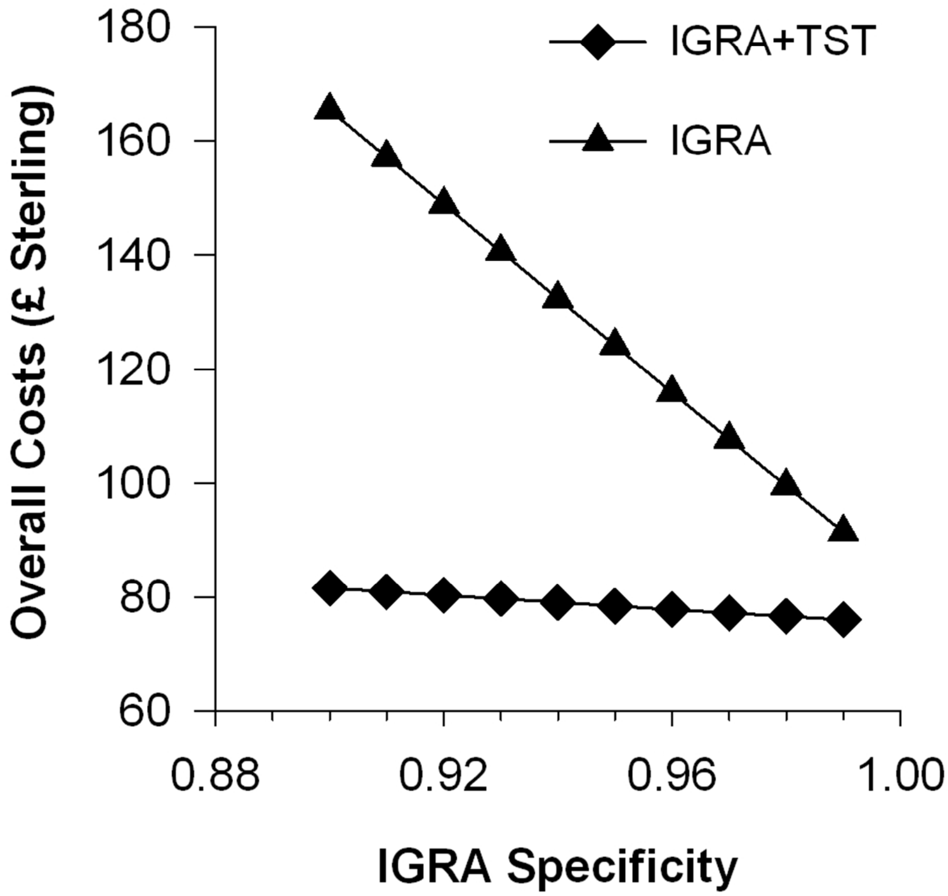

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
a IGRA specificity versus Overall Costs in £ Sterling
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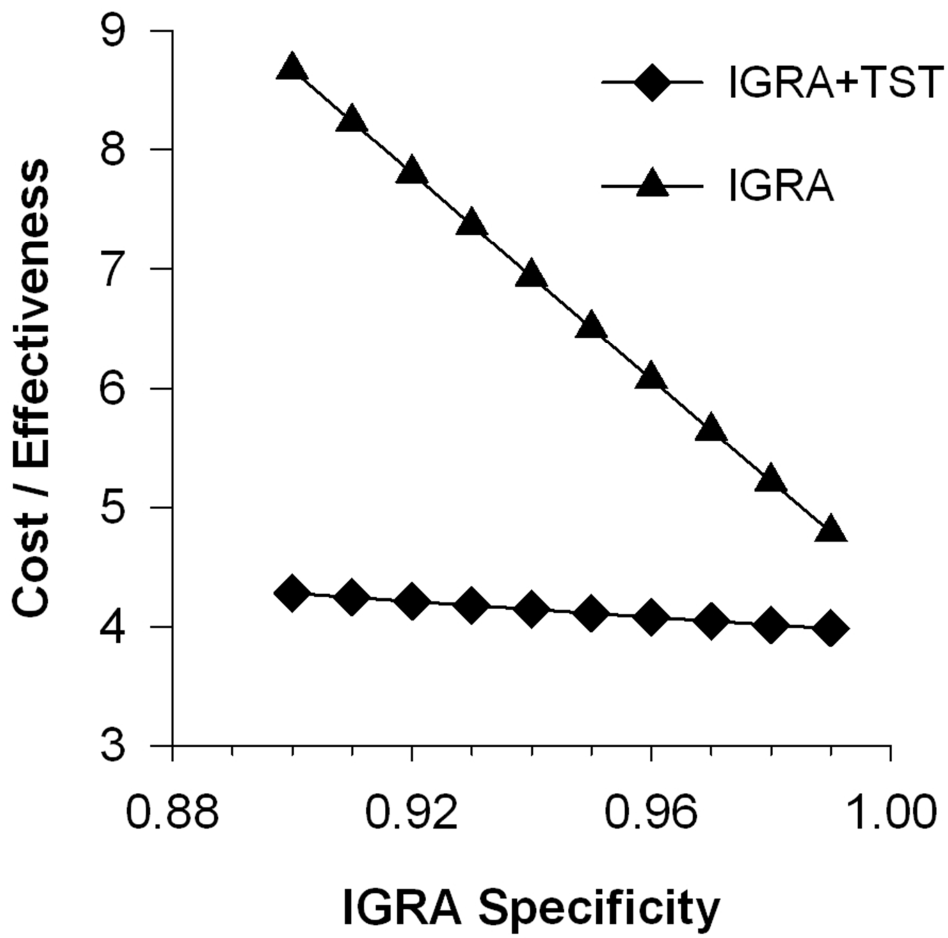

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
b. IGRA specificity versus Cost/Effectiveness
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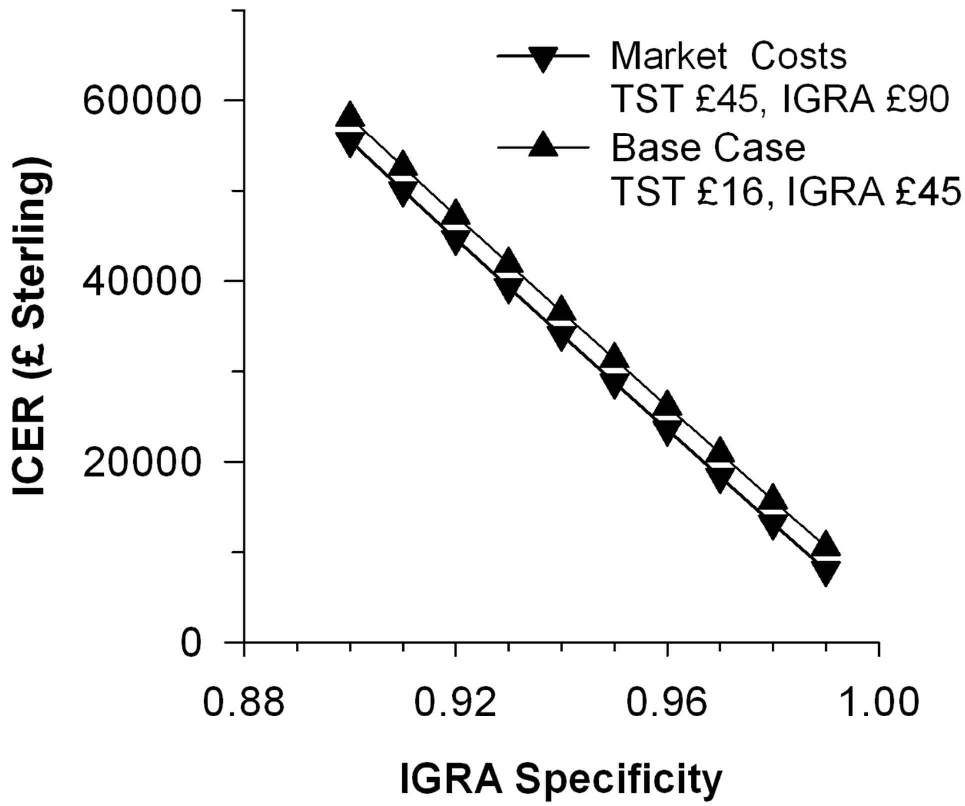

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
c. IGRA Specificity versus ICER, incremental cost per healthy life year gained
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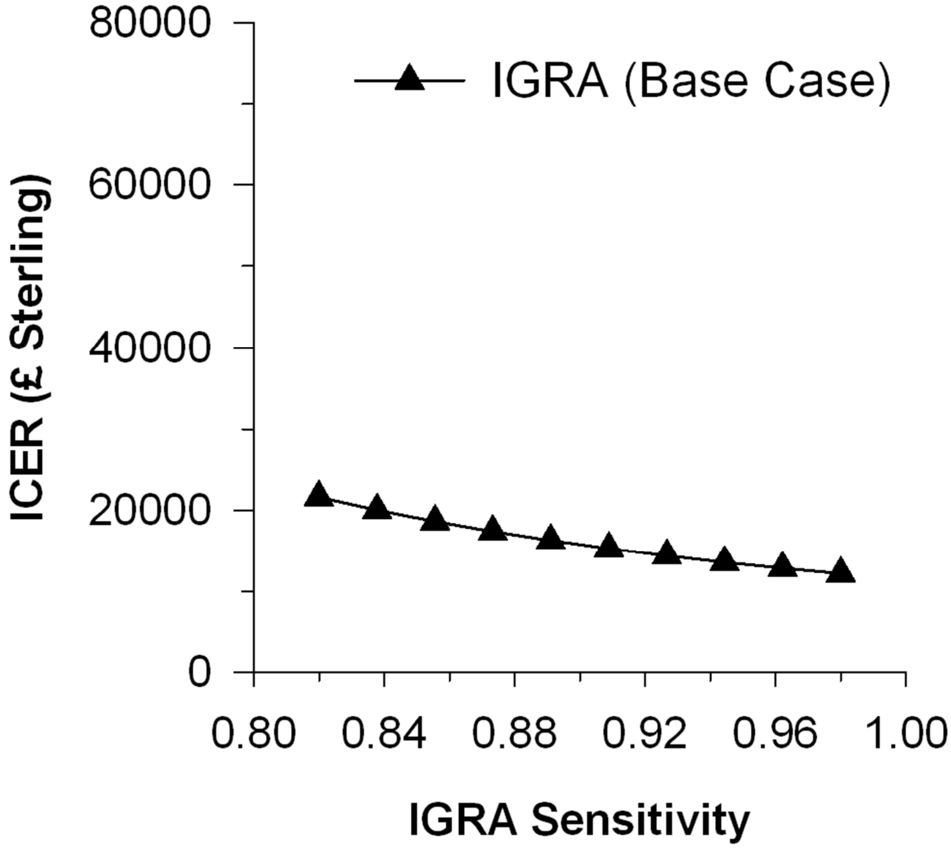

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
d. IGRA sensitivity versus ICER, incremental cost per healthy life year gained, in the base case model
87x80mm (300 x 300 DPI)

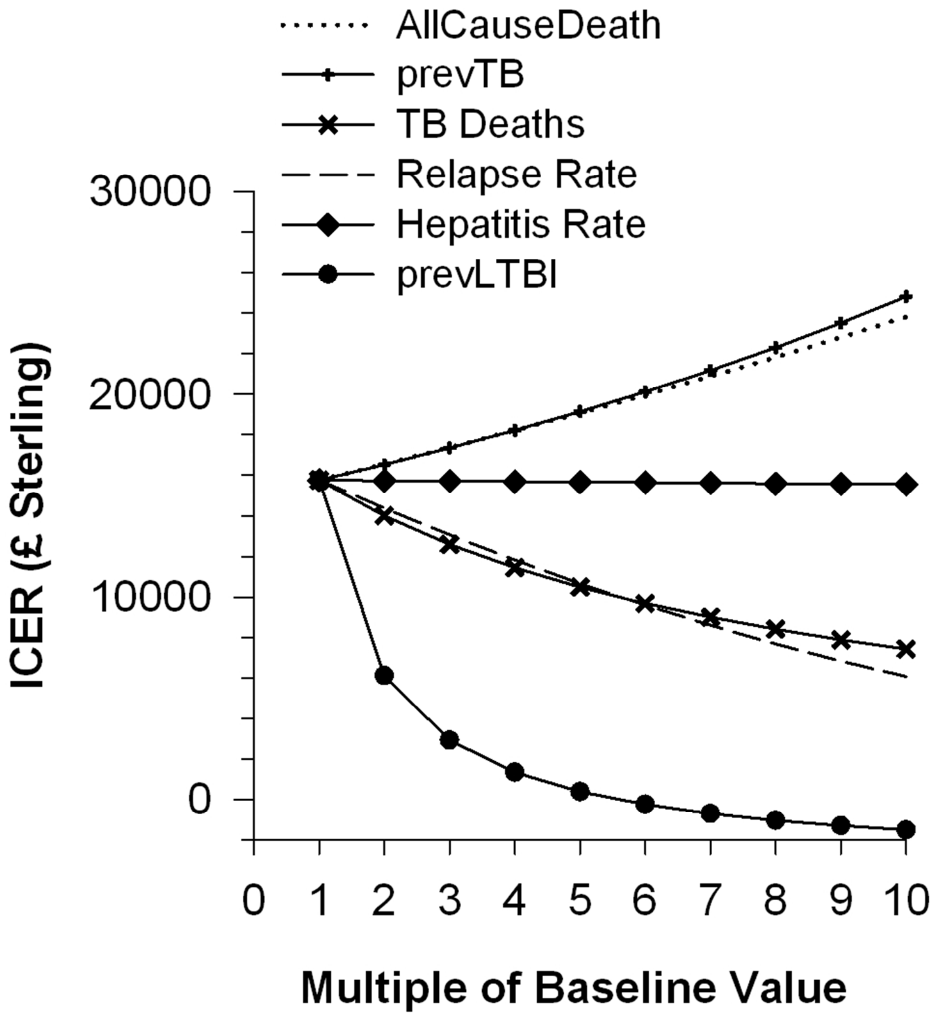

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
e. ICER, incremental cost per healthy life year gained, in the base case model versus Key Disease Parameters inflated ten-fold. Prev prevalence
87x93mm (300 x 300 DPI)

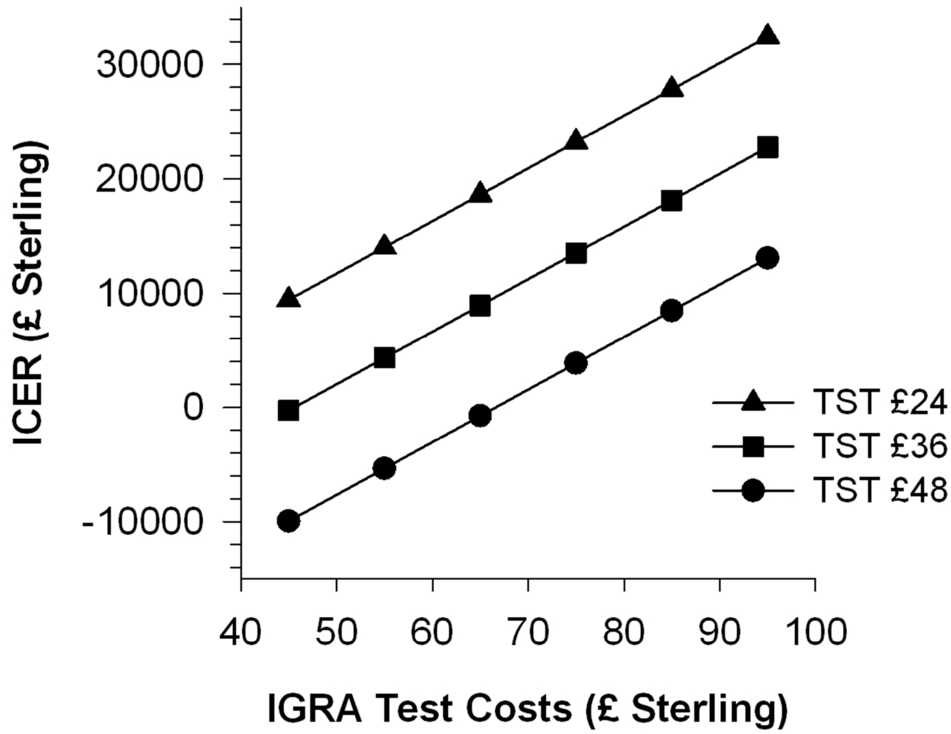

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
f. ICER, incremental cost per healthy life year gained, in the base case model versus TST and IGRA costs
99x80mm (300 x 300 DPI)

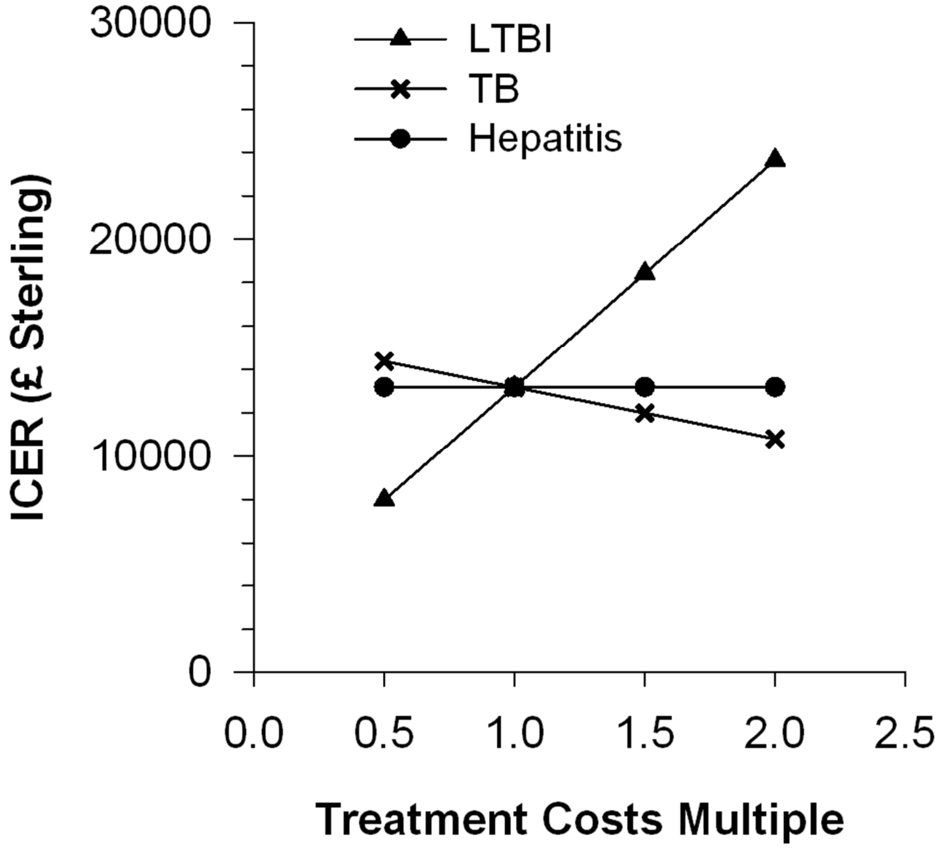

Figure 2: Impact of Wide Differences in Disease and Test Parameters on Cost-Effectiveness
g. ICER, incremental cost per healthy life year gained, in the market cost model versus four-fold variation in treatment costs
87x80mm (300 x 300 DPI)

Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice

Merve Nazli Eralp[1], Stefan Scholtes[1] , Geraldine Martell[2] , Robert Winter[3] , Andrew Robert Exley[4]

Reporting Checklist after Drummond and Jefferson, BMJ Economic Evaluation Working Party, BMJ 1996; 313 : 275 :

STUDY DESIGN
(1) Research question *Yes*
(2) Economic importance of the research question *Yes*
(3) Viewpoint of the analysis *Yes*
(4) Rationale for choosing the alternatives *Yes*
(5) The alternatives being compared *Yes*
(6) The form of economic evaluation *Yes*
(7) Justification of economic evaluation used *Yes*

Data Collection
(8) The sources of effectiveness estimates used *Yes*
(9) Details of the design and results of effectiveness study *Yes*
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) *Yes referenced*
(11) The primary outcome measure(s) for the economic evaluation are clearly stated *Yes*
(12) Methods to value health states and other benefits are stated *Yes*
(13) Details of the subjects from whom valuations were obtained are given *referenced*
(14) Productivity changes (if included) are reported separately *not applicable*
(15) The relevance of productivity changes to the study question is discussed *see discussion*
(16) Quantities of resources are reported separately from their unit costs *Yes*
(17) Methods for the estimation of quantities and unit costs are described *Yes*
(18) Currency and price data are recorded *Yes*
(19) Details of currency of price adjustments for inflation or currency conversion are given *No*
(20) Details of any model used are given *Yes*
(21) The choice of model used and the key parameters on which it is based are justified *Yes*
(21) The choice of model used and the key parameters on which it is based are justified *Yes*
(22) Time horizon of costs and benefits is stated *Yes*
(23) The discount rate(s) is stated *Yes*
(24) The choice of rate(s) is justified *standard rate*
(25) An explanation is given if costs or benefits are not discounted *not applicable*
(26) Details of statistical tests and confidence intervals are given for stochastic data *ranges cited*
(27) The approach to sensitivity analysis is given *Yes*
(28) The choice of variables for sensitivity analysis is justified *Yes*
(29) The ranges over which the variables are varied are stated *Yes*
(30) Relevant alternatives are compared *Yes*
(31) Incremental analysis is reported *Yes*
(32) Major outcomes are presented in a dissaggregated as well as aggregated form *Yes*
(33) The answer to the study question is given *Yes*
(34) Conclusions follow from the data reported *Yes*
(35) Conclusions are accompanied by the appropriate caveats *Yes*

Andrew Exley, on behalf of the authors

Suppl.Table 1

	Treatment costs based on NHS national tariff 2010 - 11		Cost £	Unit rate £	HRG Code	Comment	HCW hours Units	Subtotals
I	**Treatment costs for TB**							
A	Pulmonary TB = 54% cases in UK		£1,276			HPA 2010		£325
B	Extra-pulmonary TB = 46% of cases in UK		£2,062			{3511}		£1,058
	Mean cost		**£1,637**				**HCW**	**£662**
	NB Add health care worker costs, contact tracing costs							
	Total TB treatment costs		**£4,908**					
A	**Pulmonary TB (54% of cases in UK)**							
Path	Positive Test							
1	New patient Respiratory Medicine OPD,CXR etc		£257	£257	340 WF01E	mpc	3	3
1	Six months standard treatment							
1	Respiratory Medicine follow-up OPD			£130	340 WF02A	mpc	2	
1	2, 7 weeks		£260					4
1	4, 6 months		£260					4
2	Admission required, estimate 15%							
	Pulmonary, Pleural or other TB with CC	Hospital Ac	£272	£1,811	DZ14A	Elective		
	Pulmonary, Pleural or other TB without CC	Hospital Admission		£1,618	DZ14B			
	based on 20 hospital days						20	3
3	No sputum, CXR suspicious							
	Bronchoscopy and Lavage , estimate 30%	Day case	£151	£504	DZ07Z	Elective	7.5	2.25
4	CT chest scan required, estimate 20%		£23	£114	RA08Z			
5	after treatment e.g. cavitation							
	Additional OPD x2, in estimate 20%		£52				2	0.8
6	Hepatitis 2.5%					Saukkonen, 2006		
	Additional OPD x3	£9.75				2	*0.15*	
7	Liver failure	Admission	£1	£2,715	GC01Z		20	0
							hrs	17.05
							rate	£19.06
	Subtotal PulTB 1		**£1,276**				**Cost**	**£325**

Key
- HRG health related group
- OPD outpatient attendance
- CXR chest radiograph
- mpc multi-professional clinic
- CC complications

	Treatment costs based on NHS national tariff 2010 - 11		Cost £	Unit rate £	HRG Code	Comment	HCW hours Units	Subtotals
I	**Treatment costs for TB**							
B	**Extra-Pulmonary TB (46% of cases in UK)**							
	Peripheral LN TB (example used)							
Path	Positive Test							
1	New patient Respiratory Medicine OPD + CXR		£257	£257	340 WF01E	mpc	3	3
1	Six months standard treatment							
1	Respiratory Medicine follow-up OPD			£130	340 WF02A	mpc	2	
1	2, 7 weeks		£260					4
1	4, 6 months		£260					4
2	Admission required, estimate 25%							
	Pulmonary, Pleural or other TB with CC	Hospital Ac	£453	£1,811	DZ14A	Elective		
	Pulmonary, Pleural or other TB without CC	Hospital Admission		£1,618	DZ14B			
	based on 20 hospital days						20	5
3	LN excision biopsy							
	Minor thoracic procedure		£616	£616	DZ06Z	Elective	37.5	37.5
4	CT chest scan required, estimate 75%		£86	£114	RA08Z			
5	after treatment							
	Additional OPD x2, in estimate 50%		£130				2	2
6	Hepatitis 2.5%					Saukkonen, 2006		
	Additional OPD x3	£9.75				2	*0.15*	
7	Liver failure	Admission	£1	£2,715	GC01Z		20	0
							hrs	55.5
							Rate	£19.06
	Subtotal ExPulTB 1		**£2,062**			***HCW time***	***Cost***	**£1,058**

	Treatment costs based on NHS national tariff 2010 - 11		Cost £	Unit rate £	HRG Code	Comment	HCW hours Units	Subtotals
II	**Treatment costs for LTBI**							
C	**LTBI , 3 mths INAH + Rifampicin**							
Path	Positive test							
1	New patient Respiratory Medicine OPD,CXR etc		£257	257	340 WF01E	mpc	3	3
1	Six months standard treatment							
1	Respiratory Medicine follow-up OPD			130	340 WF02A	mpc	2	
1	2, 7,12 weeks		£390					6
	Hepatitis risk, 1.77%							
	Additional OPD x3	£7					0.11	
							hrs	9.00
							rate	£19.06
	Subtotal LTBI		**£647**			***HCW time***	***Cost***	**£172**
	total		**£819**					

		Treatment costs based on NHS national tariff 2010 - 11		Cost £	Unit rate £	HRG Code	Comment	HCW hours Units	Subtotals
III		**Contact tracing**							
Path		5 Contacts Traced per case fig 7 {3627}		**£2,132**					**£476**
	1	Initial contact by Telephone		23	£23				
	1	New patient Respiratory Medicine OPD + CXR		257	257	340 WF01E	mpc	3	3
	1	Respiratory Medicine follow-up OPD		130	130	340 WF02A	mpc	2	2
		subtotal CT1		410					5
		1% have active TB		£16				**hrs**	5
								rate	£19.06
		subtotal CT2		**£426**			***HCW time***	***Cost***	**£95**
		5 contacts per case		**£2,608**					

		Treatment costs based on NHS national tariff 2010 - 11		Cost £	Unit rate £	HRG Code	Comment	HCW hours Units	Subtotals
IV		**Hepatitis**							
Path									
	1	Respiratory Medicine follow-up OPD x3		£390	130	340 WF02A	mpc	2	6
		Estimated sick leave per case		£250	£715				
		Note: allocation for liver failure in TB costs						**hrs**	6
		see IA 7						**rate**	£19.06
				£640			***HCW time***	***Cost***	**£114**
			Total	**£755**					

V	**Mantoux test**		
	Test reagents and disposables	*estimate*	£17.25
	Apply and Read Skin Test	2*0.33 hr a	£12.58
	Admin, postage, stationary		£7.50
	Subtotal		£37.33
	Overheads	*30% rate*	£11.20
	Total		**£48.53**

Reference

Saukkonen JJ et al,
An Official ATS Statement:
Hepatotoxicity of Antituberculosis Therapy.
Am.J.Respir.Crit.Care Med. 174 (8):935-952, 2006.

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Suppl.Table 2 Sensitivity Analysis

2a IGRA Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	Incremental Cost-Effectiveness Ratio (ICER) ICER
0.9	IGRA+TST	£81.59	£0.00	19.07438	0	4.27738	£0
0.91	IGRA+TST	£80.95	£0.00	19.07455	0	4.24394	£0
0.92	IGRA+TST	£80.32	£0.00	19.07471	0	4.21058	£0
0.93	IGRA+TST	£79.68	£0.00	19.07487	0	4.17734	£0
0.94	IGRA+TST	£79.05	£0.00	19.07504	0	4.14427	£0
0.95	IGRA+TST	£78.43	£0.00	19.0752	0	4.11142	£0
0.96	IGRA+TST	£77.81	£0.00	19.07536	0	4.07888	£0
0.97	IGRA+TST	£77.19	£0.00	19.07553	0	4.04679	£0
0.98	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.99	IGRA+TST	£76.02	£0.00	19.07585	0	3.9851	£0
0.9	IGRA	£165.39	£83.81	19.07583	0.00144	8.67038	£58,089
0.91	IGRA	£157.13	£76.17	19.07599	0.00145	8.23685	£52,664
0.92	IGRA	£148.86	£68.55	19.07616	0.00145	7.80356	£47,281
0.93	IGRA	£140.60	£60.92	19.07633	0.00145	7.3706	£41,939
0.94	IGRA	£132.35	£53.30	19.07649	0.00145	6.93805	£36,634
0.95	IGRA	£124.11	£45.69	19.07666	0.00146	6.50607	£31,365
0.96	IGRA	£115.89	£38.08	19.07682	0.00146	6.07488	£26,131
0.97	IGRA	£107.69	£30.49	19.07698	0.00146	5.64485	£20,929
0.98	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.99	IGRA	£91.41	£15.39	19.0773	0.00145	4.79137	£10,614

2b IGRA Sensitivity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.82	IGRA+TST	£74.34	£0.00	19.07568	0	3.89697	£0
0.84	IGRA+TST	£74.84	£0.00	19.07568	0	3.92327	£0
0.86	IGRA+TST	£75.34	£0.00	19.07568	0	3.94958	£0
0.87	IGRA+TST	£75.84	£0.00	19.07569	0	3.97589	£0
0.89	IGRA+TST	£76.35	£0.00	19.07569	0	4.00222	£0
0.91	IGRA+TST	£76.85	£0.00	19.07569	0	4.02856	£0
0.93	IGRA+TST	£77.35	£0.00	19.07569	0	4.05492	£0
0.94	IGRA+TST	£77.85	£0.00	19.07569	0	4.08128	£0
0.96	IGRA+TST	£78.36	£0.00	19.07569	0	4.10766	£0
0.98	IGRA+TST	£78.86	£0.00	19.07569	0	4.13405	£0
0.82	IGRA	£98.19	£23.86	19.07679	0.0011	5.14723	£21,589
0.84	IGRA	£98.49	£23.65	19.07687	0.00118	5.16266	£19,999
0.86	IGRA	£98.78	£23.44	19.07694	0.00126	5.17808	£18,602
0.87	IGRA	£99.08	£23.23	19.07702	0.00134	5.1935	£17,366
0.89	IGRA	£99.37	£23.03	19.0771	0.00142	5.2089	£16,264
0.91	IGRA	£99.66	£22.82	19.07718	0.00149	5.2243	£15,276
0.93	IGRA	£99.96	£22.61	19.07726	0.00157	5.23969	£14,384
0.94	IGRA	£100.25	£22.40	19.07734	0.00165	5.25508	£13,576
0.96	IGRA	£100.55	£22.19	19.07742	0.00173	5.27046	£12,840
0.98	IGRA	£100.84	£21.98	19.07749	0.00181	5.28583	£12,166

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Suppl.Table 3

3a Deaths, All causes	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0045	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.009	IGRA+TST	£76.17	£0.00	18.20799	0	4.18356	£0
0.0135	IGRA+TST	£75.77	£0.00	17.38801	0	4.3577	£0
0.018	IGRA+TST	£75.39	£0.00	16.61293	0	4.5379	£0
0.0225	IGRA+TST	£75.02	£0.00	15.88011	0	4.72424	£0
0.027	IGRA+TST	£74.67	£0.00	15.18706	0	4.9168	£0
0.0315	IGRA+TST	£74.34	£0.00	14.53146	0	5.11565	£0
0.036	IGRA+TST	£74.02	£0.00	13.91111	0	5.32085	£0
0.0405	IGRA+TST	£73.71	£0.00	13.32393	0	5.53247	£0
0.045	IGRA+TST	£73.42	£0.00	12.768	0	5.75055	£0
0.0045	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.009	IGRA	£99.23	£23.05	18.20939	0.00139	5.44929	£16,544
0.0135	IGRA	£98.95	£23.18	17.38935	0.00134	5.69038	£17,357
0.018	IGRA	£98.69	£23.30	16.61421	0.00128	5.93999	£18,197
0.0225	IGRA	£98.44	£23.42	15.88134	0.00123	6.19826	£19,063
0.027	IGRA	£98.20	£23.52	15.18824	0.00118	6.46529	£19,955
0.0315	IGRA	£97.97	£23.63	14.53259	0.00113	6.74119	£20,874
0.036	IGRA	£97.75	£23.73	13.91219	0.00109	7.02605	£21,820
0.0405	IGRA	£97.54	£23.82	13.32498	0.00105	7.31996	£22,792
0.045	IGRA	£97.34	£23.92	12.769	0.00101	7.623	£23,791

3b TB Deaths	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.018	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.036	IGRA+TST	£76.58	£0.00	19.07496	0	4.01486	£0
0.054	IGRA+TST	£76.57	£0.00	19.07423	0	4.01433	£0
0.072	IGRA+TST	£76.56	£0.00	19.07351	0	4.01381	£0
0.09	IGRA+TST	£76.54	£0.00	19.07278	0	4.01328	£0
0.108	IGRA+TST	£76.53	£0.00	19.07206	0	4.01275	£0
0.126	IGRA+TST	£76.52	£0.00	19.07134	0	4.01223	£0
0.144	IGRA+TST	£76.51	£0.00	19.07062	0	4.0117	£0
0.162	IGRA+TST	£76.49	£0.00	19.0699	0	4.01118	£0
0.18	IGRA+TST	£76.48	£0.00	19.06918	0	4.01066	£0
0.018	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.036	IGRA	£99.51	£22.92	19.0766	0.00164	5.21625	£13,995
0.054	IGRA	£99.50	£22.93	19.07605	0.00182	5.21589	£12,591
0.072	IGRA	£99.49	£22.93	19.07551	0.002	5.21554	£11,444
0.09	IGRA	£99.48	£22.94	19.07497	0.00219	5.21519	£10,491
0.108	IGRA	£99.47	£22.94	19.07443	0.00237	5.21483	£9,686
0.126	IGRA	£99.46	£22.94	19.07389	0.00255	5.21448	£8,997
0.144	IGRA	£99.45	£22.95	19.07335	0.00273	5.21413	£8,401
0.162	IGRA	£99.44	£22.95	19.07281	0.00291	5.21378	£7,880
0.18	IGRA	£99.43	£22.95	19.07227	0.00309	5.21343	£7,420

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3c

Prevalence LTBI	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.035	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.07	IGRA+TST	£116.83	£0.00	19.07038	0	6.12618	£0
0.105	IGRA+TST	£156.98	£0.00	19.06508	0	8.234	£0
0.14	IGRA+TST	£197.08	£0.00	19.0598	0	10.34018	£0
0.175	IGRA+TST	£237.13	£0.00	19.05454	0	12.44492	£0
0.21	IGRA+TST	£277.13	£2.03	19.0493	-0.00873	14.54813	-£233
0.245	IGRA+TST	£317.08	£6.91	19.04407	-0.01014	16.64955	-£682
0.28	IGRA+TST	£356.96	£11.74	19.03887	-0.01152	18.74887	-£1,019
0.315	IGRA+TST	£396.77	£16.49	19.0337	-0.01288	20.84569	-£1,281
0.35	IGRA+TST	£436.51	£21.17	19.02855	-0.01421	22.9395	-£1,490
0.035	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.07	IGRA	£134.75	£17.92	19.07331	0.00293	7.06496	£6,111
0.105	IGRA	£169.88	£12.89	19.06949	0.0044	8.9083	£2,928
0.14	IGRA	£204.96	£7.88	19.06567	0.00586	10.75046	£1,345
0.175	IGRA	£240.04	£2.90	19.06185	0.00731	12.59253	£398
0.21	IGRA	£275.10	£0.00	19.05803	0	14.43492	£0
0.245	IGRA	£310.16	£0.00	19.05421	0	16.27784	£0
0.28	IGRA	£345.22	£0.00	19.05039	0	18.1214	£0
0.315	IGRA	£380.28	£0.00	19.04658	0	19.96564	£0
0.35	IGRA	£415.33	£0.00	19.04276	0	21.8106	£0

3d

Prevalence TB	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
1.00E-04	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
2.00E-04	IGRA+TST	£77.10	£0.00	19.07565	0	4.04193	£0
3.00E-04	IGRA+TST	£77.61	£0.00	19.07561	0	4.06839	£0
4.00E-04	IGRA+TST	£78.11	£0.00	19.07557	0	4.09478	£0
5.00E-04	IGRA+TST	£78.61	£0.00	19.07553	0	4.1211	£0
6.00E-04	IGRA+TST	£79.11	£0.00	19.07549	0	4.14735	£0
7.00E-04	IGRA+TST	£79.61	£0.00	19.07545	0	4.17353	£0
8.00E-04	IGRA+TST	£80.11	£0.00	19.07541	0	4.19964	£0
9.00E-04	IGRA+TST	£80.61	£0.00	19.07537	0	4.22568	£0
0.001	IGRA+TST	£81.10	£0.00	19.07533	0	4.25165	£0
1.00E-04	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
2.00E-04	IGRA	£100.45	£23.35	19.07706	0.00141	5.26539	£16,529
3.00E-04	IGRA	£101.38	£23.77	19.07698	0.00137	5.31406	£17,347
4.00E-04	IGRA	£102.30	£24.19	19.07689	0.00133	5.36263	£18,216
5.00E-04	IGRA	£103.23	£24.61	19.07681	0.00129	5.4111	£19,139
6.00E-04	IGRA	£104.15	£25.04	19.07673	0.00124	5.45945	£20,123
7.00E-04	IGRA	£105.07	£25.46	19.07665	0.0012	5.5077	£21,174
8.00E-04	IGRA	£105.99	£25.88	19.07657	0.00116	5.55585	£22,299
9.00E-04	IGRA	£106.90	£26.30	19.07649	0.00112	5.6039	£23,505
0.001	IGRA	£107.82	£26.72	19.07641	0.00108	5.65184	£24,802

3e Relapse Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0315	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.063	IGRA+TST	£77.72	£0.00	19.07525	0	4.07427	£0
0.0945	IGRA+TST	£78.96	£0.00	19.07476	0	4.13933	£0
0.126	IGRA+TST	£80.33	£0.00	19.07422	0	4.21123	£0
0.1575	IGRA+TST	£81.84	£0.00	19.07361	0	4.29067	£0
0.189	IGRA+TST	£83.51	£0.00	19.07294	0	4.37835	£0
0.2205	IGRA+TST	£85.35	£0.00	19.07219	0	4.475	£0
0.252	IGRA+TST	£87.37	£0.00	19.07136	0	4.58127	£0
0.2835	IGRA+TST	£89.59	£0.00	19.07045	0	4.69774	£0
0.315	IGRA+TST	£92.01	£0.00	19.06944	0	4.82489	£0
0.0315	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.063	IGRA	£100.35	£22.63	19.07682	0.00158	5.2601	£14,365
0.0945	IGRA	£101.26	£22.31	19.07647	0.00171	5.30821	£13,052
0.126	IGRA	£102.28	£21.95	19.07607	0.00186	5.36143	£11,819
0.1575	IGRA	£103.40	£21.56	19.07563	0.00202	5.4203	£10,664
0.189	IGRA	£104.63	£21.13	19.07514	0.0022	5.48537	£9,587
0.2205	IGRA	£106.00	£20.65	19.07459	0.0024	5.5572	£8,589
0.252	IGRA	£107.51	£20.14	19.07399	0.00263	5.63633	£7,668
0.2835	IGRA	£109.16	£19.57	19.07332	0.00287	5.72324	£6,823
0.315	IGRA	£110.97	£18.96	19.07258	0.00313	5.81832	£6,051

3f Hepatitis rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.0177	IGRA+TST	£76.60	£0.00	19.07569	0	4.01539	£0
0.0354	IGRA+TST	£77.23	£0.00	19.07476	0	4.04875	£0
0.0531	IGRA+TST	£77.86	£0.00	19.07383	0	4.08211	£0
0.0708	IGRA+TST	£78.49	£0.00	19.0729	0	4.11548	£0
0.0885	IGRA+TST	£79.13	£0.00	19.07197	0	4.14884	£0
0.1062	IGRA+TST	£79.76	£0.00	19.07105	0	4.18221	£0
0.1239	IGRA+TST	£80.39	£0.00	19.07012	0	4.21559	£0
0.1416	IGRA+TST	£81.02	£0.00	19.06919	0	4.24896	£0
0.1593	IGRA+TST	£81.66	£0.00	19.06826	0	4.28234	£0
0.177	IGRA+TST	£82.29	£0.00	19.06733	0	4.31573	£0
0.0177	IGRA	£99.52	£22.92	19.07714	0.00145	5.2166	£15,757
0.0354	IGRA	£100.15	£22.92	19.07622	0.00146	5.24994	£15,733
0.0531	IGRA	£100.78	£22.92	19.07529	0.00146	5.28328	£15,709
0.0708	IGRA	£101.41	£22.92	19.07436	0.00146	5.31663	£15,685
0.0885	IGRA	£102.04	£22.92	19.07344	0.00146	5.34997	£15,662
0.1062	IGRA	£102.67	£22.91	19.07251	0.00147	5.38332	£15,638
0.1239	IGRA	£103.30	£22.91	19.07159	0.00147	5.41668	£15,615
0.1416	IGRA	£103.94	£22.91	19.07066	0.00147	5.45004	£15,591
0.1593	IGRA	£104.57	£22.91	19.06973	0.00147	5.4834	£15,568
0.177	IGRA	£105.20	£22.91	19.06881	0.00147	5.51676	£15,545

Health Economic Models Inform Screening for Tuberculosis

3g

IGRA Repeat Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.015	IGRA+TST	£75.98	£0.00	19.07569	0	3.98287	£0
0.03	IGRA+TST	£76.46	£0.00	19.07569	0	4.00814	£0
0.045	IGRA+TST	£76.94	£0.00	19.07569	0	4.03344	£0
0.06	IGRA+TST	£77.42	£0.00	19.07569	0	4.05875	£0
0.075	IGRA+TST	£77.91	£0.00	19.07568	0	4.08409	£0
0.09	IGRA+TST	£78.39	£0.00	19.07568	0	4.10945	£0
0.105	IGRA+TST	£78.87	£0.00	19.07568	0	4.13484	£0
0.12	IGRA+TST	£79.36	£0.00	19.07568	0	4.16025	£0
0.135	IGRA+TST	£79.84	£0.00	19.07568	0	4.18568	£0
0.15	IGRA+TST	£80.33	£0.00	19.07568	0	4.21115	£0
0.015	IGRA	£98.64	£22.66	19.07714	0.00146	5.17048	£15,573
0.03	IGRA	£99.32	£22.86	19.07714	0.00145	5.20633	£15,716
0.045	IGRA	£100.01	£23.07	19.07714	0.00145	5.24219	£15,859
0.06	IGRA	£100.69	£23.27	19.07714	0.00145	5.27807	£16,002
0.075	IGRA	£101.38	£23.47	19.07714	0.00145	5.31398	£16,144
0.09	IGRA	£102.06	£23.67	19.07714	0.00145	5.34991	£16,287
0.105	IGRA	£102.75	£23.87	19.07714	0.00145	5.38586	£16,430
0.12	IGRA	£103.43	£24.07	19.07713	0.00145	5.42184	£16,574
0.135	IGRA	£104.12	£24.28	19.07713	0.00145	5.45785	£16,717
0.15	IGRA	£104.81	£24.48	19.07713	0.00145	5.49388	£16,860

3h

TST Repeat Rate	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.025	IGRA+TST	£74.95	£0.00	19.07542	0	3.92919	£0
0.05	IGRA+TST	£75.23	£0.00	19.07546	0	3.94368	£0
0.075	IGRA+TST	£75.50	£0.00	19.07551	0	3.95817	£0
0.1	IGRA+TST	£75.78	£0.00	19.07555	0	3.97267	£0
0.125	IGRA+TST	£76.06	£0.00	19.0756	0	3.98716	£0
0.15	IGRA+TST	£76.33	£0.00	19.07564	0	4.00165	£0
0.175	IGRA+TST	£76.61	£0.00	19.07569	0	4.01615	£0
0.2	IGRA+TST	£76.89	£0.00	19.07573	0	4.03064	£0
0.225	IGRA+TST	£77.16	£0.00	19.07578	0	4.04513	£0
0.25	IGRA+TST	£77.44	£0.00	19.07583	0	4.05962	£0
0.025	IGRA	£99.52	£24.57	19.07714	0.00172	5.2166	£14,242
0.05	IGRA	£99.52	£24.29	19.07714	0.00168	5.2166	£14,462
0.075	IGRA	£99.52	£24.01	19.07714	0.00163	5.2166	£14,695
0.1	IGRA	£99.52	£23.74	19.07714	0.00159	5.2166	£14,942
0.125	IGRA	£99.52	£23.46	19.07714	0.00154	5.2166	£15,202
0.15	IGRA	£99.52	£23.18	19.07714	0.0015	5.2166	£15,479
0.175	IGRA	£99.52	£22.91	19.07714	0.00145	5.2166	£15,773
0.2	IGRA	£99.52	£22.63	19.07714	0.00141	5.2166	£16,085
0.225	IGRA	£99.52	£22.35	19.07714	0.00136	5.2166	£16,419
0.25	IGRA	£99.52	£22.08	19.07714	0.00132	5.2166	£16,776

Health Economic Models Inform Screening for Tuberculosis

Suppl. Table 4
TST, IGRA Costs

TST £24			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
	45 IGRA+TST	£86.07	£0.00	19.07569	0	4.51183	£0
	55 IGRA+TST	£89.71	£0.00	19.07569	0	4.70303	£0
	65 IGRA+TST	£93.36	£0.00	19.07569	0	4.89423	£0
	75 IGRA+TST	£97.01	£0.00	19.07569	0	5.08543	£0
	85 IGRA+TST	£100.66	£0.00	19.07569	0	5.27663	£0
	95 IGRA+TST	£104.30	£0.00	19.07569	0	5.46784	£0
	45 IGRA	£99.75	£13.68	19.07714	0.00145	5.22853	£9,404
	55 IGRA	£110.09	£20.37	19.07714	0.00145	5.7707	£14,006
	65 IGRA	£120.43	£27.07	19.07714	0.00145	6.31287	£18,609
	75 IGRA	£130.77	£33.77	19.07714	0.00145	6.85503	£23,212
	85 IGRA	£141.12	£40.46	19.07714	0.00145	7.3972	£27,815
	95 IGRA	£151.46	£47.16	19.07714	0.00145	7.93937	£32,418

TST £36			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
	45 IGRA+TST	£100.15	£0.41	19.07569	-0.00145	5.25017	-£278
	55 IGRA+TST	£103.80	£0.00	19.07569	0	5.44137	£0
	65 IGRA+TST	£107.45	£0.00	19.07569	0	5.63257	£0
	75 IGRA+TST	£111.09	£0.00	19.07569	0	5.82377	£0
	85 IGRA+TST	£114.74	£0.00	19.07569	0	6.01498	£0
	95 IGRA+TST	£118.39	£0.00	19.07569	0	6.20618	£0
	45 IGRA	£99.75	£0.00	19.07714	0	5.22853	£0
	55 IGRA	£110.09	£6.29	19.07714	0.00145	5.7707	£4,324
	65 IGRA	£120.43	£12.99	19.07714	0.00145	6.31287	£8,927
	75 IGRA	£130.77	£19.68	19.07714	0.00145	6.85503	£13,530
	85 IGRA	£141.12	£26.38	19.07714	0.00145	7.3972	£18,133
	95 IGRA	£151.46	£33.07	19.07714	0.00145	7.93937	£22,736

TST £48			Incremental		Incremental		
IGRA Cost	Strategy	Cost	Cost	Effectiveness	Effectiveness	Cost / Eff	ICER
	45 IGRA+TST	£114.23	£14.49	19.07569	-0.00145	5.98851	-£9,960
	55 IGRA+TST	£117.88	£7.79	19.07569	-0.00145	6.17971	-£5,358
	65 IGRA+TST	£121.53	£1.10	19.07569	-0.00145	6.37092	-£755
	75 IGRA+TST	£125.18	£0.00	19.07569	0	6.56212	£0
	85 IGRA+TST	£128.82	£0.00	19.07569	0	6.75332	£0
	95 IGRA+TST	£132.47	£0.00	19.07569	0	6.94452	£0
	45 IGRA	£99.75	£0.00	19.07714	0	5.22853	£0
	55 IGRA	£110.09	£0.00	19.07714	0	5.7707	£0
	65 IGRA	£120.43	£0.00	19.07714	0	6.31287	£0
	75 IGRA	£130.77	£5.60	19.07714	0.00145	6.85503	£3,848
	85 IGRA	£141.12	£12.29	19.07714	0.00145	7.3972	£8,451
	95 IGRA	£151.46	£18.99	19.07714	0.00145	7.93937	£13,054

Health Economic Models Inform Screening for Tuberculosis

Suppl. Table 5
Market Costs Model
Sensitivity Analysis

5a

IGRA Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.9	IGRA+TST	£132.12	£0.00	19.07438	0	6.92651	£0
0.91	IGRA+TST	£131.48	£0.00	19.07455	0	6.89304	£0
0.92	IGRA+TST	£130.85	£0.00	19.07471	0	6.85966	£0
0.93	IGRA+TST	£130.21	£0.00	19.07487	0	6.8264	£0
0.94	IGRA+TST	£129.58	£0.00	19.07504	0	6.7933	£0
0.95	IGRA+TST	£128.96	£0.00	19.0752	0	6.76043	£0
0.96	IGRA+TST	£128.34	£0.00	19.07536	0	6.72786	£0
0.97	IGRA+TST	£127.73	£0.00	19.07553	0	6.69576	£0
0.98	IGRA+TST	£127.13	£0.00	19.07569	0	6.66433	£0
0.99	IGRA+TST	£126.55	£0.00	19.07585	0	6.63402	£0
0.9	IGRA	£212.17	£80.05	19.07583	0.00144	11.12223	£55,483
0.91	IGRA	£203.90	£72.42	19.07599	0.00145	10.68868	£50,065
0.92	IGRA	£195.63	£64.79	19.07616	0.00145	10.25537	£44,688
0.93	IGRA	£187.38	£57.16	19.07633	0.00145	9.82238	£39,351
0.94	IGRA	£179.12	£49.54	19.07649	0.00145	9.38982	£34,050
0.95	IGRA	£170.89	£41.93	19.07666	0.00146	8.95781	£28,784
0.96	IGRA	£162.66	£34.32	19.07682	0.00146	8.5266	£23,551
0.97	IGRA	£154.46	£26.73	19.07698	0.00146	8.09655	£18,348
0.98	IGRA	£146.29	£19.16	19.07714	0.00145	7.66828	£13,173
0.99	IGRA	£138.18	£11.63	19.0773	0.00145	7.24303	£8,021

5b

TST Specificity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.46	IGRA+TST	£145.44	£0.00	19.07556	0	7.6242	£0
0.5	IGRA+TST	£141.77	£0.00	19.07558	0	7.4322	£0
0.54	IGRA+TST	£138.11	£0.00	19.07561	0	7.2402	£0
0.58	IGRA+TST	£134.45	£0.00	19.07563	0	7.04823	£0
0.62	IGRA+TST	£130.79	£0.00	19.07566	0	6.85627	£0
0.66	IGRA+TST	£127.13	£0.00	19.07569	0	6.66433	£0
0.7	IGRA+TST	£123.47	£0.00	19.07571	0	6.47244	£0
0.74	IGRA+TST	£119.81	£0.00	19.07574	0	6.28059	£0
0.78	IGRA+TST	£116.15	£0.00	19.07576	0	6.08882	£0
0.82	IGRA+TST	£112.49	£0.00	19.07579	0	5.89716	£0
0.86	IGRA+TST	£108.84	£0.00	19.07582	0	5.70571	£0
0.46	IGRA	£146.01	£0.57	19.07717	0.00161	7.65349	£354
0.5	IGRA	£146.05	£4.27	19.07716	0.00158	7.65554	£2,701
0.54	IGRA	£146.09	£7.98	19.07716	0.00155	7.65794	£5,144
0.58	IGRA	£146.15	£11.70	19.07715	0.00152	7.66077	£7,694
0.62	IGRA	£146.21	£15.42	19.07715	0.00149	7.66416	£10,364
0.66	IGRA	£146.29	£19.16	19.07714	0.00145	7.66828	£13,173
0.7	IGRA	£146.39	£22.92	19.07713	0.00142	7.67343	£16,147
0.74	IGRA	£146.51	£26.71	19.07712	0.00138	7.68001	£19,325
0.78	IGRA	£146.68	£30.53	19.0771	0.00134	7.68874	£22,773
0.82	IGRA	£146.91	£34.42	19.07708	0.00129	7.70087	£26,608
0.86	IGRA	£147.25	£38.41	19.07705	0.00124	7.71886	£31,069

5c

TST Sensitivity	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
0.65	IGRA+TST	£127.84	£0.00	19.07536	0	6.70169	0
0.66	IGRA+TST	£127.70	£0.00	19.07543	0	6.69422	0
0.67	IGRA+TST	£127.55	£0.00	19.07549	0	6.68675	0
0.68	IGRA+TST	£127.41	£0.00	19.07556	0	6.67928	0
0.69	IGRA+TST	£127.27	£0.00	19.07562	0	6.6718	0
0.7	IGRA+TST	£127.13	£0.00	19.07569	0	6.66433	0
0.71	IGRA+TST	£126.98	£0.00	19.07575	0	6.65686	0
0.72	IGRA+TST	£126.84	£0.00	19.07582	0	6.64939	0
0.73	IGRA+TST	£126.70	£0.00	19.07588	0	6.64192	0
0.74	IGRA+TST	£126.56	£0.00	19.07594	0	6.63445	0
0.65	IGRA	£146.29	£18.46	19.07714	0.00178	7.66849	£10,385
0.66	IGRA	£146.29	£18.60	19.07714	0.00171	7.66845	£10,859
0.67	IGRA	£146.29	£18.74	19.07714	0.00165	7.66841	£11,369
0.68	IGRA	£146.29	£18.88	19.07714	0.00158	7.66837	£11,921
0.69	IGRA	£146.29	£19.02	19.07714	0.00152	7.66833	£12,520
0.7	IGRA	£146.29	£19.16	19.07714	0.00145	7.66828	£13,173
0.71	IGRA	£146.29	£19.30	19.07714	0.00139	7.66824	£13,885
0.72	IGRA	£146.29	£19.44	19.07714	0.00133	7.6682	£14,667
0.73	IGRA	£146.29	£19.59	19.07714	0.00126	7.66816	£15,529
0.74	IGRA	£146.29	£19.73	19.07714	0.0012	7.66812	£16,484

Suppl. table 6

Treatment Costs

LTBI	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£410	IGRA+TST	£113.97	£0.00	19.07569	0	5.97446	£0
£820	IGRA+TST	£127.16	£0.00	19.07569	0	6.66602	£0
£1,230	IGRA+TST	£140.35	£0.00	19.07569	0	7.35758	£0
£1,640	IGRA+TST	£153.54	£0.00	19.07569	0	8.04914	£0
£410	IGRA	£125.55	£11.58	19.07714	0.00145	6.58118	£7,963
£820	IGRA	£146.34	£19.18	19.07714	0.00145	7.67094	£13,185
£1,230	IGRA	£167.13	£26.78	19.07714	0.00145	8.7607	£18,408
£1,640	IGRA	£187.92	£34.38	19.07714	0.00145	9.85046	£23,631

TB	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£2,454	IGRA+TST	£120.59	£0.00	19.07569	0	6.32187	£0
£4,908	IGRA+TST	£127.13	£0.00	19.07569	0	6.66433	£0
£7,362	IGRA+TST	£133.66	£0.00	19.07569	0	7.0068	£0
£9,816	IGRA+TST	£140.19	£0.00	19.07569	0	7.34926	£0
£2,454	IGRA	£141.49	£20.89	19.07714	0.00145	7.41647	£14,361
£4,908	IGRA	£146.29	£19.16	19.07714	0.00145	7.66828	£13,173
£7,362	IGRA	£151.09	£17.43	19.07714	0.00145	7.9201	£11,984
£9,816	IGRA	£155.90	£15.70	19.07714	0.00145	8.17191	£10,796

Hepatitis	Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Eff	ICER
£378	IGRA+TST	£126.81	£0.00	19.07569	0	6.64749	£0
£755	IGRA+TST	£127.13	£0.00	19.07569	0	6.66433	£0
£1,133	IGRA+TST	£127.45	£0.00	19.07569	0	6.68118	£0
£1,510	IGRA+TST	£127.77	£0.00	19.07569	0	6.69802	£0
£378	IGRA	£145.97	£19.16	19.07714	0.00145	7.65148	£13,173
£755	IGRA	£146.29	£19.16	19.07714	0.00145	7.66828	£13,173
£1,133	IGRA	£146.61	£19.16	19.07714	0.00145	7.68509	£13,172
£1,510	IGRA	£146.93	£19.16	19.07714	0.00145	7.70189	£13,172

Health Economic Models Inform Screening for Tuberculosis

Suppl. Table 7 Monte Carlo Probability Sensitivity Analysis

Variable	Distribution	Minimum	Peak/Mode	Maximum	Average Value	Reference	No.
1. TB prevalence	Triangular	0.0001	0.0004	0.0010	0.0005	HPA 2010	21
2. LTBI prevalen	Triangular	0.010	0.035	0.100	0.0483	Schablon 2	20
3. TST specificity	Triangular	0.46	0.66	0.86	0.66	Menzies 20	15
4. IGRA specifici	Triangular	0.950	0.980	0.998	0.976		17, 30
5. IGRA cost	Triangular	£30.00	£90.00	£120.00	£80.00	see text	
6. TST cost	Triangular	£16.00	£45.00	£64.00	£41.67	see text	
7. TB treatment c	Triangular	£2,454.00	£4,908.00	£9,816.00	£5,726.00	see text	
8. LTBI treatmen	Triangular	£409.50	£819.00	£1,638.00	£955.50	see text	
9. TST sensivity	Triangular	0.65	0.71	0.74	0.70	Menzies 20	15
10. IGRA sensitiv	Triangular	0.86	0.9	0.93	0.897	Pai 2008	5
11. TST repeat ra	Triangular	0.07	0.175	0.35	0.215	see text	
12. IGRA repeat	Triangular	0.017	0.035	0.070	0.040	see text	

Screening of Health Care Workers for Tuberculosis: Development and Validation of a New Health Economic Model to Inform Practice

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Key words: Tuberculosis; delivery of health care; cost-benefit analysis; tuberculin test; interferon gamma

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TreeAge Pro file available from corresponding author

ABSTRACT

Background: Methods for determining ~~the~~ cost-effectiveness of different treatments are well established, unlike ~~the~~ appraisal of non-drug interventions, including novel diagnostics and biomarkers

Objective: We develop and validate a new health economic model by comparing ~~the~~ cost-effectiveness of tuberculin skin test, TST; blood test, IGRA; and TST followed by ~~then~~ IGRA in conditional sequence, in screening health care workers for latent or active TB. ~~We test the impact of key variables to inform health care provision.~~

Design: We focus on healthy life years gained as the benefit metric, rather than quality adjusted life years (QALYs) given limited data to estimate quality-adjustments of life years with TB and complications of treatment~~its complementary diseases~~, like ~~such as~~ hepatitis. Healthy life years gained refers to the number of TB or ~~complementary~~ hepatitis cases avoided, and the increase in life expectancy. We incorporate disease and test ~~variables~~parameters informed by systematic meta-analyses and clinical practice. Health and economic outcomes of each strategy are modelled as a decision tree in Markov chains, representing different health states informed by epidemiology. Cost and effectiveness values are generated as the individual is cycled through 20 years of the model. Key parameters undergo one-way and Monte Carlo probabilistic sensitivity analyses.

Setting: Screening health care workers in secondary and tertiary care.

Results: IGRA is the most effective strategy, with ~~an~~ incremental costs per healthy life year gained of £10,614 - £20,~~6,5~~929, ~~to £12,532 at~~ base case, £8,021 - ~~and~~ £189,34~~96~~8, ~~to £5,882 for~~ market costs~~,~~ TST £45, IGRA £90, ~~with~~ IGRA specificities of 99% - 97%; mean (5%, 95%), £12,060 (£4,137 - £38,418) by Monte Carlo analysis ~~- 99%~~.

Conclusions: Incremental costs per healthy life year gained, a conservative estimate of benefit, are comparable to the £20,000~~-~~ - £30,000 NICE band for IGRA alone, across wide differences in disease and test ~~variables~~parameters. Health gains justify IGRA costs, even if IGRA tests cost~~s~~ three times TST ~~costs~~. This health economic model offers a powerful tool for appraising non-drug interventions in the market and under development. (300 words)

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What this paper adds

1. What is already known and why this study is required

- Methods for determining the cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analyses and clinical practice, testing key disease and test ~~variables~~parameters by one-way and Monte Carlo probabilistic sensitivity analyses

2. What this study adds

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- Screening with IGRA appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- These findings are robust for wide differences in disease and test ~~variables~~parameters, even if IGRA test costs are three times TST costs suggesting this health economic model is a powerful tool for appraising non-drug interventions

ARTICLE SUMMARY

Article focus

- Methods for determining cost-effectiveness of different treatments are well established unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers
- We develop and validate a new health economic model by comparing cost-effectiveness of tuberculin skin test, TST and / or a TB blood test, IGRA, in screening health care workers for latent or active TB
- We investigate gains in healthy life years, without TB or hepatitis, in a comprehensive model informed by epidemiology, meta-analysis and clinical practice, testing~~ key~~ disease and test ~~variables~~parameters by one-way and Monte Carlo probabilistic sensitivity analyses

Key messages

- IGRA is the most effective strategy when screening health care workers for latent or active TB
- IGRA screening has an incremental cost per healthy life year gained of £10,614 - £20,929, base case, £8,021 - £18,348, market costs, TST £45, IGRA £90, IGRA specificities 99% -97%; mean (5%, 95%), £12,060 (£4,137 - £38,418) by Monte Carlo analysis ~~£19,968 to £5,882 at standard market costs, TST £45, IGRA £90, for IGRA specificities of 97% - 99% respectively~~
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Strengths and limitations of this study

- Screening with IGRA alone appears cost effective since incremental costs per healthy life year gained, a conservative estimate of benefit, are at the lower end of the £20,000 to £30,000 NICE band
- Neither TST not IGRA differentiate latent ~~LTBI~~ from active TB, and the specificity of IGRA is inferred from studies in populations at low risk of TB

- These findings are robust for wide differences in disease and test ~~variables~~parameters, including IGRA test costs three times TST costs, suggesting this health economic model is a powerful tool for appraising non-drug interventions in the market and under development

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INTRODUCTION

Economic evaluation is a recognised approach to optimising national health care provision within a limited budget but informed choice requires transparent analysis highlighting key assumptions and critical factors[1]. Methods for determining the cost-effectiveness of different treatments are well established [2],[3], unlike the appraisal of non-drug interventions, including novel diagnostics and biomarkers. We develop and validate a new health economic model by focusing on whether a tuberculin skin test, TST, and / or a blood test for tuberculosis, IGRA, is more cost-effective in screening health care workers for latent or active tuberculosis, TB. The screening of health care workers for tuberculosis has economic importance given the impact of disease transmission in each case together with the large number of NHS employees at risk, 1.7 million personnel and 80,000 new employees per annum (National Health Service, 2010). We inform the health economic model by applying insight from epidemiology, meta-analysis, and clinical practice including knowledge of market costs to compare the cost-effectiveness of new technology supporting or replacing established practice. The analysis is from the NHS and societal perspective.

Established practice is for trained occupational health staff to administer a TST using cheap readily available reagents injected intradermally at an initial visit. The skin test reaction is measured at a second clinic visit 48 – 72 hours later[4]. The need for two visits is operationally inefficient, and the test itself is limited both by specificity and sensitivity. TST has a low specificity in subjects exposed to BCG vaccination or environmental non-tuberculous mycobacteria (NTM) and moderate sensitivity resulting in false negatives [54], [65]. A new technological approach requires a single clinic visit to draw a blood sample which is transferred to the laboratory for analysis in a TB specific interferon-gamma release assay, IGRA[76]. The approach is operationally efficient and the assay has a high specificity and sensitivity, although simple costs per test are greater than the TST. In principle the advantages of old and new might be combined using TST for all and then applying IGRA

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blood testing to TST positive cases to exclude false positive TST after previous exposure to NTM including BCG immunisation. ~~This third approach depends on each test having a similar sensitivity or false negative rate, so the impact of this parameter is subjected to further analysis.~~ Following earlier work,[8~~7~~] this study has focused on healthy life years gained as the benefit metric, rather than ~~the more common~~ quality adjusted life years. The reason is the lack of robust data to estimate quality-adjustments of life years with TB and complications of treatment~~its complementary diseases,~~ such as hepatitis. Health life years gained refers to the number of TB or ~~complementary~~ hepatitis cases avoided, and the associated increase in life expectancy.

This study adds to the literature[9~~8~~], [8~~7~~], [10~~9~~], [11~~10~~] in four key areas by incorporating:

1. Healthy life years to avoid the assumptions inherent in estimating QALYs
2. Key disease ~~variables~~parameters in a comprehensive model of all relevant health states informed by epidemiology including

   i. The impact of LTBI Tuberculosis treatment side effects[12~~11~~]

   ii. The higher relapse rate of active TB within the first three years of treatment in comparison to the years thereafter[13~~12~~]

3. Key test ~~variables~~parameters relevant to clinical practice including

   i. The inability of screening tests to differentiate between active and latent TB[6~~5~~]

   ii. The sensitivity and specificity of IGRA and TST independently of each other

   iii. Operational inefficiencies of TST prompting repeat testing[14~~13~~]

4. And we provide a powerful methodology for appraising the cost-effectiveness of non-drug interventions to inform health care policy, including sensitivity analyses of key ~~variables~~parameters

METHODS

The health and economic outcomes of the three alternatives testing strategies are modelled as a decision tree, representing the health outcomes of each of the strategies as Markov chains over twenty years. The model incorporates economic, medical, epidemiological and operational factors in the analysis. This approach lends itself to the clinical setting where the risks are continuous over time, key events may be repeated, and operational factors may interact with other key variablesparameters to influence the base case result.

Data collection

The test, population, and outcome characteristics (**table 1**) include data from the meta-analyseis by Menzies 2007 [15] and Pai 2008 [54]. In the absence of a gold standard for latent tuberculosis infection, LTBI, active TB is used as a surrogate to determine assay sensitivity [15]. Specificity for LTBI is derived by testing populations at low risk of TB [54], [1614], [1715] to determine the rate of false positives. The analysis is guided by our clinical and market experience with the T-Spot TB test, applying an an IGRA specificity of 98% [17] for the base case. We then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model. We apply an IGRA specificity of 98% [15] for the base case analysis guided by our clinical and market experience with T-Spot TB, and then examine the impact of IGRA specificity in the sensitivity analyses of the cost-effectiveness model. The operational characteristics of the three alternative approaches include repeat test rates due to test failure and failure to attend for skin test reading. Direct and indirect costs are shown (**table 2)** drawing on data supplied by NICE *(see appendix 6)* [1816], the Cambridge TB service, and the NHS National tariff 2010 [19] with costs adjusted to the 2010-2011 financial year (**suppl. table 1**). The impact of regional or national differences in disease parametersvariables and costs are examined in one-way sensitivity analyses. The impact of uncertainty within multiple parameters is then examined using Monte Carlo probabilistic sensitivity analysis.

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Model construction

We built a decision analysis model, which incorporates the health outcomes as Markov chains over twenty years, to analyze three different diagnostic approaches to LTBI. This model only considers the initial screening for newly hired personnel; the annual testing is beyond the scope of this model. The model is coded and composed using the decision analysis software TreeAge Pro Suite 2009, 2011. The states of the Markov chains represent the health conditions of the individuals; following a LTBI diagnosis test and possible interventions. Each Markov state length is one year. The decision is made at the first node of the decision tree between three diagnosis options: TST, IGRA, and a combined sequential testing strategy. The alternatives are assessed according to their cost and effectiveness values over twenty years; in which the costs are direct and indirect monetary costs and their effectiveness is measured by total number of healthy years. The Markov chain is implemented through 20 years, related cost and effectiveness values due to different health states are recorded as the individual is cycled through the model. All future costs are discounted at 5% per year.

Table 1: Base Case Data for Test, Population and Outcomes Parameters

Parameter	Base-case values	Range Tested	Reference
1. Test characteristics			
Tuberculin skin test (TST)			
Specificity	0.66~~59~~	0.46 – 0.86	~~4~~15
Sensitivity	0.70~~7~~	0.65 – 0.74	~~4~~15
Probability a second TST is placed	0.1737	0.025 – 0.25 *	14~~13~~
~~Repeat due to operational inefficiency~~	~~0.324~~		~~Martell 2010~~
TB specific IFNgamma release assay (IGRA)			
Specificity	0.98	0.90 – 0.99	17~~15~~
Sensitivity	0.90	0.82 – 0.98	54
Probability a second IGRA is required	0.0343	0.015 – 0.15 *	14~~13~~
~~Repeat due to operational inefficiency~~	~~0~~		~~Martell 2010~~
2. Population characteristics			
Age range	20 – 30		
Occupation	Healthcare worker		
BCG vaccination rates	52.8%		20~~17~~
Nationality of majority	English		
Prevalence of LTBI	0.035	0.035 – 0.35 *	20~~17~~
Prevalence of TB	0.0001	0.0001 – 0.001 *	21~~18~~
Probability of all causes of death	0.0045	0.0045 – 0.045 *	Office for National Statistics 2008
3. Probability of Outcomes			
Efficacy of LTBI treatment	0.65		22~~19~~
Risk of hepatitis caused by treatment	0.0177	0.0177 – 0.177 *	12~~11~~

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Risk of activation of LTBI	0.01		65
Probability of relapse of TB	0.0315	0.0315 – 0.315 *	1312
Probability of death due to TB	0.018	0.018 – 0.18 *	2118
Probability of death due to hepatitis	0		Assumption

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Key

* Ten-fold range tested in sensitivity analyses to highlight potential impact on incremental cost per healthy life year gainedMartell 2010: Martell G, Robinson M-J 2010, Inefficiencies and delays in healthcare worker screening for Mycobacterium tuberculosis – an audit of medical student screening. 3rd HPA Pointers (Prevention of Occupational Infections, Treatment and Exposure Reporting Strategies for Healthcare Workers) Conference, London Dec 2010. Sensitivity analyses test the impact of regional or national differences in disease variables.

Table 2: Costs

Parameter	Base-case values	Range tested
4. Cost of Interventions		
	NICE [18~~16~~]	
TST	£16	£16 - £64
IGRA	£44.78	£30 - £120
Chest radiograph (CXR)	£28	
	Cambridge TB Service 2010 NHS National Tariff [19]	
TB Treatment	£1,637 ~~[16]~~	0.5 – 2 times
Contact tracing	£4263	0.5 – 2 times
LTBI Treatment	£647	0.5 – 2 times
Hepatitis Treatment	£64025	0.5 – 2 times
5. Healthcare worker costs	**Cambridge TB Service 2010** NHS Pay 2/2010 [23] ~~**NHS National Tariff**~~ ~~***Midpoint band 6 with on costs 2010***~~	
Time to attend for~~for~~ TB treatment	£6632	0.5 – 2 times
Time to attend for Contact tracing	£95	0.5 – 2 times
Time to attend for LTBI treatment	£1762	0.5 – 2 times
Time for Hepatitis treatment	£11408	0.5 – 2 times
6. Discount rate	0.05	

Key

TB treatment costs are derived from the NHS National Tariff 2010-11 [19] applied to the ~~discussions with NICE 2010 and~~ Cambridge TB service. Healthcare worker costs are derived from the NHS Pay Circular (AforC) 2/2010 [23], point 26 £30,460, plus 22% overheads £37,161 per annum, applied to the Cambridge TB service. Total model costs for TB treatment are TB treatment, plus contact tracing x5 contacts per case [22], plus health care worker time costs, £4908; for LTBI, LTBI treatment plus health care worker time costs, £819; for Hepatitis, Hepatitis treatment plus health care worker time costs, £755, (**suppl. table 1**). ~~Sensitivity analyses examine the impact of four fold variation in costs.~~

Model construction

This Markov model assumes

i. Each health state is taken as a time periods of one year, can not be left earlier and can only last longer if the return probability is greater than zero.

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ii. All patients with positive results for LTBI accept treatment, consistent with conditions of employment in the NHS. The impact of limited compliance is allowed for within the efficacy of LTBI treatment [22].

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iii. Standard Isoniazid and Rifampicin treatment for LTBI lasts three months and all treatments are completed.

iv. Diagnostic tests are repeated once only as required to achieve a result

v. The repeat rate for diagnostic tests is further No diagnostic tests are repeated due to operational inefficiencies; this variable is addressed in the sensitivity analyseis

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vi. The probability that LTBI generates a positive result is assumed to be the same as the probability that active TB generates a positive result, as there is no gold standard for LTBIThe conditional probability of a positive test result in LTBI is the same as for TB

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vii. The risk of active TB in cases with false negative results is proportional to the prevalence rates of latent and active TB

viii. The result of the second test is independent of the first in two stage testing

ix. The effects of TB and Hepatitis are the simple sum, rather than synergistic

x. All cases with positive TST or IGRA will have a CXR that identifies all cases of active TB. All positive CXRs are active TB

xi. The relapse rate of TB is higher than the prevalence rate in the general population for the first three years after recovery [1312]

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xii. The probability of continuing to have TB after standard TB treatment is the probability of relapse

xiii. All TB is diagnosed and treated on time. The effect of late diagnosis of latent or active TB in cases with false negative results is neglected.

xiv. An equal number of males and females make up new NHS healthcare workers

xv. Death of an employee has no monetary cost for NHS.

xvi. Transmission of TB to the community is modeled as a constant monetary cost for contact tracing, including screening the close contacts of the patient, and their treatment in the case of positive Tuberculosis findings.

xvii. All employees are employed for 20 years

The comprehensive decision tree consists of 985 nodes including three similar sub-trees with different probability and cost parameters (**figure 1**). The initial analysis was then subjected to one-way sensitivity analysies applied to key variablesparameters including IGRA sensitivity and specificity; prevalence rates of TB and LTBI, all causes death rates; test repetition rates; market rates for TST and IGRA tests; and treatment costs for TB, LTBI, and hepatitis. We tested the impact of variation in multiple parameters by first generating triangular distributions using minimum, mode or peak, and maximum values for key parameters.[24]. Probabilistic sensitivity analysis was then carried out by Monte Carlo simulation using 100, 000 iterations to estimate the total impact of uncertainty on the model, TreeAge Pro 2011.

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RESULTS

Base case analysis indicates the incremental cost of IGRA alone is offset by the increased effectiveness of this approach over the two stage sequential approach of TST followed by IGRA for positive TST results (**table 3a**). IGRA is the most effective strategy with an incremental effectiveness of 0.0015 and an incremental cost-effectiveness ratio, ICER, of £19,54515,757 per healthy life year gained. The strategy of TST alone is clearly inferior by all criteria. We therefore focused on further analysis of variablesparameters affecting the relative efficacy of TST + IGRA versus IGRA alone.

Table 3 Incremental Costs Per Healthy Life Year Gained (ICER) of IGRA or TST

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost / Effectivene
a. Base Case					
IGRA+TST	£76.60£77.12	£0.00£0.00	19.0756919.07609	00.00000	4.024.04
IGRA	£99.52£97.85	£22.92£20.73	19.0771419.07715	0.0014550.00106	5.225.13
TST	£333.42£387.11	£233.90£289.26	19.0708819.07000	-0.00626-0.00715	17.4820.3(
b. Market Costs					
IGRA+TST	£127.13£130.92	£0.00£0.00	19.075719.07609	00.00000	6.666.86

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IGRA	£146.29£144.62	£19.16£13.70	19.077119.07715	0.001450.00106	7.677.58	£13,173£12,915
TST	£367.45£421.15	£221.16£276.52	19.070919.07000	-0.0063-0.00715	19.2722.08	-£35,324-£38,663 *(Dominated)*

Base case, TST £16, IGRA £45; market costs TST £45, IGRA £90.

Sensitivity analyses of disease and test variablesparameters

Sensitivity analysis of the base case model indicates that the ICER for IGRA ranges from £20,6,5929 to £102,614532 per healthy life year gained for test specificities of 97% - 99% (**figure 2a-c, suppl. table 12**). Assay sensitivity has a much smaller impact on the ICER (**figure 2d**).

The superior cost-effectiveness of IGRA was not threatened when base case values were inflated by up to ten fold increases for in all cause death rates; TB death rates; prevalence of LTBI or TB; relapse rates and hepatitis rates (**figure 2e, suppl. table 2a3a-f**).

TST repeat rates were estimated using the 17.4% rate of failure to achieve a TST result in a UK study of routine practice [14]. This compares with 53%, 35/66, of medical students who failed to attend their first Mantoux appointment [25] and a 12% failure rate to read the 1st TST [11]. Varying the IGRA repeat rate from 1.5% to 15% or TST repeat rate from 2.5% to 25% had little impact on the ICER which increased from £15,5739,346 to £16,86020,744 and £147,242991 to £16,77620,591 per healthy life year gained respectively (**suppl. table 2g3g, h**).

The cost of TST testing was investigated by eliciting costs from five private medical service providers, was a median of £65 per test, range £45 to £75, and by £48.50 using estimated itemized costings from Cambridge Occupational Health (**suppl. table 1.V**), total cost £48.53. We used £45 as a market cost for TST and tested the impact of test costs on ICER. Market costs for TST significantly enhance the ICER for IGRA alone across a range of IGRA costs (**figure 2f**, **suppl. table 43a**). In particular, the market standard test costs of £45 per TST and

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£90 per IGRA generate an ICER of £13,1732,915 per healthy life year gained (**table 3b3b**). A threshold value of £30,000 per healthy life year gained is still achieved when IGRA test costs are three-times TST test costs.

Examining the impact of assay specificity and sensitivity, this market standard model generates a range of £18,349,968 to £5,8,0821 per healthy life year gained for an IGRA specificity of 97% - 99%. Sensitivity analysis for TST test characteristics specificity [4] over a wide range of ,0.46 – 0.86 for specificity, and 0.65 – 0.74 for sensitivity,[15]73, suggests IGRA remains the optimal strategy with costs of £351,455 to £31,069, and £10, 385 - £16, 484 28,455 per healthy life year gained respectively. (**suppl. table 53b**).

The calculation and apportionment of treatment costs is likely to vary between centres, but a four fold variation, 0.5 times – 2 times baseline, in treatment costs for LTBI, TB, or hepatitis is also accommodated by the market standard model (**figure 2g**, **suppl. table 64**).

Probabilistic sensitivity analysis by Monte Carlo simulation was carried out with uncertainty in each of 12 key parameters defined as triangular distributions (**suppl. table 7**). Mean incremental cost per healthy life year gained was £12,060, with 5% and 95% values of £4,137 and £38, 418 respectively.

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DISCUSSION

The methodology for determining the cost-effectiveness of different treatments is well established [2], [3], [1] in contrast to the analysis of non-drug interventions. Our health economic model suggests a methodology to appraise the host of novel diagnostics [76] and biomarkers generated by clinical science. Healthy life years, despite being a conservative benefit metric, may be particularly useful in evaluating novel screening and monitoring tests by avoiding the assumptions inherent in generating quality adjusted life years [2620], [1], [87], [1110], [2721]. This approach, allied to the use of multiple disease states supported by epidemiological data, is far more powerful than standard comparisons since the IGRA strategy will overcome a two – three fold excess of simple test costs.

In our study wWe compare the effectiveness of the diagnostic procedures by focusing on healthy life years gained, [1], [87] rather than quality adjusted life years [2620], [1110], [1816]. The reason is there are limited data to base estimates of quality adjusted life years for each of the health states applicable to latent or active TB and its treatment [2822]. The additional costs of IGRA alone appear justified by the health gains at £19,5,7457 per healthy life year gained, falling to £13,1732,915 per healthy life year when applying market costs where blood tests cost twice as much as skin tests. Our estimates are conservative in that they only take a healthy life year as a benefit (i.e. years without tuberculosis or hepatitis). Since the calculated ratio is at the lower end of the NICE band of £20,000 - £30,000, IGRA is cost-effective, even at the current NICE threshold which may or may not be conservative [2], [3]. These findings are supported by the probabilistic sensitivity analysis of multiple disease and test parameters. There is no validated instrument for determining quality of life with tuberculosis [2923], but when such data are available it is likely that additional health gains we would be identified, further improvinge the cost/benefit ratio.

The health economic model is sensitive to IGRA specificity, which is derived from estimates of false positives in populations at low risk of TB [3024] [2721], [1715]. An IGRA specificity of 98% is conservative by current literature [30~~24~~] [27~~21~~], [17~~15~~] but higher than analyses potentially confounded by data from studies in populations at intermediate rather than low risk of TB [5~~4~~], [16~~14~~], [18~~16~~]. Our model accommodates substantial enhancement of TST specificity greater than expected in BCG-vaccinated populations or mixed populations including non-BCG vaccinated health care workers [15]. T~~, but t~~he outcome may be different in non-BCG vaccinated populations with low NTM infection rates [5~~4~~] but ~~-~~NTM infection is an increasing problem in adults [31]. Studies testing children prior to BCG immunisation have revealed false positive TST rates of 14% in SE England [32] and 79% in Norway [33]. It seems likely therefore that previous infection with NTM has a significant role in reducing the specific of TST. The study's findings ~~also~~ accommodate wide regional or national differences in disease ~~variables~~parameters, although health gains are enhanced by a relative increase in the prevalence of LTBI and hampered by doubling costs for the treatment of LTBI.

Studies including the relative risk of progression to active TB suggest additional limits to TST specificity, reviewed recently [34]. IGRA positive cases with LTBI are more likely to progress to active TB than TST positive cases. In particular, IGRA positive cases showed a 19% greater chance of progression to active TB than expected solely from the increased specificity of IGRA over TST [10]. This advantage would lead to further domination of TST only approaches, by sequential TST then IGRA and IGRA alone strategies.

The one-stop approach of IGRA alone has additional, operational advantages which are likely to enhance the value of this strategy. Testing at a single visit boosts compliance whilst minimising consumption of resources to achieve a test result and the risk of loss to follow up. The health economic model does not include an allowance for health care workers time to attend for testing, but these staff costs would be ~~are~~ greater when two – three visits are required for TST then IGRA further limiting cost-effectiveness of strategies incorporating TST. Efficiency is enhanced by combining IGRA with other screening blood tests, although a blood sample is more invasive than TST. Blood testing may offer more flexibility than TST with

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blood sampling facilities widely available in primary care and hospital settings. In contrast, carrying out a TST requires registered nurses with proven competence and recent training or administration of TSTs [4], which is more expensive than phlebotomy and ~~there is a premium on the skills and training required to accurately place and measure TST which~~ may be limiting during peaks in demand such as in contact tracing. An IGRA strategy transfers costs from the clinic to the laboratory, where cost pressures are intense but responsive to focusing expertise and optimising staffing structures. Critical aspects of blood sampling are defined including the impact of the test population and sampling conditions on the performance characteristics of IGRA [1413], [3525], [3626], [3727]. An IGRA strategy also avoids the possibility of TST boosting TST responses after repeat testing [65] or IGRA responses if follow-up testing is delayed [3626]. The relative merits of different IGRA tests are controversial [2721], [1715], [54] but where there is a consensus on the assay characteristics this model should allow further investigation.

Our study suggests health gains justify IGRA costs when screening health care workers for latent or active TB. These findings are robust for wide differences in key disease and test ~~variables~~parameters including IGRA test costs three times TST costs, whilst maintaining cost-effectiveness at the lower end of the £20,000 - £30,000 NICE band. We suggest this health economic model incorporating healthy life years gained, epidemiology, meta-analyses and clinical practice provides a powerful tool for assessing the potential impact of new technology on established practice.

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Figures

Figure 1: The Decision Tree

Health and economic outcomes of TST and / or IGRA modeled as a decision tree in Markov chains representing different health states informed by epidemiology: TB, active tuberculosis; LTBI, LTBI1, latent tuberculosis, with treatment; D, Death; S, S1, healthy, with unnecessary treatment for LTBI ; H, H+TB, H+LTBI, hepatitis, and TB, or LTBI; T1, T2, T1H, T2H, transition states indicating relapse rates within three years of treatment and thereafter, with hepatitis; A – E, node points repeated as Clone A - Clone E. X, Y are probabilities, p, X = pLTBI / (pLTBI + pTB), Y = pTB /(pLTBI + pTB)

Figure 2:
Impact of Wide Differences in Disease and Test ~~Variables~~Parameters on Cost-Effectiveness

a – c IGRA specificity versus **a** overall costs in £ Sterling, **b** cost / effectiveness, **c** ICER, incremental cost per healthy life year gained. **d - f** ICER in the base case model versus **d** IGRA sensitivity, **e** key disease ~~variables~~parameters increased times ten, prev prevalence, **f** TST and IGRA costs. **g** ICER in the market case model versus four fold variation in treatment costs.

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Competing Interests

MNE has no competing interests; SS has no competing interests; GM has no competing interests; RW has no competing interests. ARE is the director of the specialist Immunology Laboratory at Papworth Hospital NHS Foundation Trust which provides a supra-regional service for interferon-gamma release assays using the T-Spot TB test (Oxford Immunotech).

Contributor Statement

ARE & RW conceived the study. SS and MNE developed the economic model with additional clinical data from GM, ARE, RW. MNE, SS, ARE, tested and revised the economic model. All authors contributed to the interpretation of the results and approved the final version of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

The economic model run on TreeAge Pro is available from the corresponding author.

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