ORIGINAL ARTICLE

Community-based evaluation of immigrant tuberculosis screening using interferon γ release assays and tuberculin skin testing: observational study and economic analysis

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ABSTRACT

Background UK tuberculosis (TB) notifications are rising due to disease in the immigrant population. National screening guidelines have been revised but cost-effectiveness analyses are hampered by the lack of data on the comparative performance of tuberculin skin tests (TSTs) and interferon γ release assays (IGRAs) in immigrants.

Methods Three-way evaluation of TSTs and two IGRAs (QuantiFERON Gold in-tube (QFN-GIT) and T-SPOT.TB) in immigrants aged ≥16 years to quantify test positivity, concordance and factors associated with positivity. Yields were computed at different incidence thresholds and the relative cost-effectiveness of screening was estimated using different latent TB infection (LTBI) screening modalities at varying incidence thresholds with or without port-of-arrival chest x-ray (CXR).

Results 231 immigrants were included; median age 29 (IQR 24–37). TSTs were accepted by 80.9%, read in 93.5% and 30.3% were positive – QFN-GIT and T-SPOT.TB positive in 16.6% and 22.5% respectively. Positive TSTs, QFN-GIT and T-SPOT.TB were independently associated with increasing TB incidence in immigrants' countries of origin (p=0.007, 0.007, 0.037 respectively). Implementing current guidance (threshold 40/100 000 per year) would identify 98–100% of LTBIs (depending on test) but entail testing 97–99% of the cohort; screening at 150/100 000 per year would identify 49–71% of LTBIs but only entail screening half the cohort. The two most cost-effective screening strategies were no port-of-entry chest radiography and screen with single-step QFN-GIT at 250/100 000 per year (incremental cost-effectiveness ratio (ICER)) £21 565.3/case averted); and no port-of-entry CXR and screen with single-step QFN-GIT at 150/100 000 per year (averted additional 7.8 TB cases; ICER £31 867.1/case averted).

Conclusions UK immigrant screening could cost-effectively and safely eliminate mandatory CXR on arrival by emphasising systematic screening for LTBI with single-step IGRA. Intermediate incidence thresholds balance the need to identify as many imported LTBIs as possible against limited service capacity.

Key messages

What is the key question?

- What is the comparative performance, and cost effectiveness, of QuantiFERON Gold in-tube, T-SPOT.TB and tuberculin skin test, with and without chest x-ray (CXR), in the community-based diagnosis of latent tuberculosis (TB) in immigrants in the UK.

What is the bottom line?

- UK immigrant screening could cost effectively and safely eliminate mandatory CXR on arrival by emphasising systematic screening for latent TB with single-step interferon γ release assay in the community. Intermediate screening incidence thresholds balance the need to identify as many cases of imported latent TB as possible against limited service capacity.

Why read on?

- Immigrant TB in developed countries makes up a significant proportion of cases, with most cases arising through the reactivation of latent TB acquired overseas prior to migration. This study is the first three-way comparison, and health economics analysis, of community-based immigrant screening for latent TB with QuantiFERON Gold in-tube, T-SPOT.TB and tuberculin skin test, with and without CXR.

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INTRODUCTION

Tuberculosis (TB) is a public health concern in high-income, low-burden countries where historic reductions in notifications have slowed or reversed, resulting in TB becoming concentrated among foreign-born individuals.[1] The UK has seen TB notifications increase continuously over the past 30 years; between 1998 and 2009 numbers rose by almost 50% to 9040 annual cases. Most of this increase has been among foreign-born individuals, in whom notifications have risen by 98%[2 3]; foreign-born individuals now account for over 70% of UK TB notifications and have a 22-fold higher TB incidence (89 cases/100 000) than UK-born individuals (4 cases/100 000).

Underlying this disproportionate burden is the combination of reactivation of latent tuberculosis

infection (LTBI), acquired prior to migration, and the high levels of migration from high TB burden nations in sub-Saharan Africa and the Indian subcontinent.[4 5] This failure to control TB has reignited debate about immigrant screening.[6]

UK National Institute for Health and Clinical Excellence (NICE) recommendations from 2006 suggested that in addition to chest x-ray (CXR) at port of arrival, LTBI screening in adult immigrants should be restricted to adults from sub-Saharan Africa and other countries with TB incidence >500/100 000, using a dual tuberculin skin test (TST) plus confirmatory interferon γ release assay (IGRA) approach.[7] However, there was a high level of non-adherence to these guidelines with many services using different screening thresholds and diagnostic tools.[8] The health economics analysis underlying the guidelines was weakened by a lack of contemporary data on LTBI prevalence in immigrants, particularly when stratified by different TB incidence thresholds in countries of origin. This has been addressed by a recent UK study which found that screening at the levels that were suggested by NICE would miss most LTBI cases and that a reduced threshold would be more cost effective.[9]

Recently revised guidance now recommends adults from countries with TB incidence >40/100 000 should be screened with TST plus IGRA or single-step IGRA.[10] However, these guidelines continue to be based on scenarios rather than empirical screening data and thus are unable to definitively address key issues, such as which screening strategy is preferred (TST alone, TST plus IGRA or IGRA alone), which of the two commercial IGRAs (QuantiFERON-Gold in-tube (QFN-GIT), Cellestis, Carnegie, Australia and T-SPOT.TB, Oxford Immunotec, Oxford, UK) is more cost effective, and which, if any, incidence threshold may be most cost effective in diagnosing LTBI. In addition, the guidance provides little direction about the system of port-of-arrival CXRs to diagnose active TB which has been in place for over 40 years. The system's high costs and low yields for active disease[11–13] underscore the need for a comprehensive assessment of its cost effectiveness.

We therefore undertook a prospective comparative assessment, in routine care, of TST and both available IGRAs as diagnostic tools for LTBI in new entrants with a specific focus on LTBI prevalence, how this varies by region of origin and the factors associated with LTBI. We also computed the cost effectiveness of LTBI screening using different screening modalities at different incidence thresholds in a primary care setting, with and without CXR screening on arrival at port of entry.

METHODS

Study design and study centre

This prospective assessment of immigrant screening was undertaken in Westminster (London, UK) which has an estimated population of 247 000 people, of whom 53.0% (95% CI 52.8% to 53.2%) are foreign born.[14] Between 2007 and 2009, the 3-year average number of TB notifications per year in this area was 78, while average TB incidence was 33 cases (95% CI 26 to 41) per 100 000 population per year.[15]

Study population and participants

Between October 2008 and June 2010, all foreign-born immigrants registered with one of four participating primary care practices in Westminster were identified and referred to the new-entrant screening service and, if eligible, were invited to participate in TB screening. Eligibility criteria for the study included foreign-born new entrants (arrival within preceding 5 years) aged ≥16 years from all countries (if displaying symptoms of active TB) or from a country with a TB incidence of ≥40/100 000 (if asymptomatic). Country-specific TB incidence figures were based on 2007 WHO figures—the most current at the time the study commenced. Ethical approval was not required because the study utilised fully anonymised observational data collected as part of the routine delivery of a clinical service.

Methods of screening

Eligible immigrants were initially screened with a questionnaire which obtained information on demographics, country of origin, past history of TB, history of TB contact, bacille Calmette Guérin (BCG) vaccination status (ascertained using scar, reliable history or documentary evidence)[16] and clinical symptoms of active TB. Following completion of the questionnaire, screening for LTBI was undertaken (see online supplementary information for details of IGRA and TST screening procedures and criteria for test positivity).

In accordance with UK national guidelines[10] and routine clinical practice, during immigrant screening for LTBI we did not undertake HIV testing of subjects. Instead participants were asked to self-report previous HIV testing and if they knew if they were HIV seropositive.

Management of symptomatic individuals and positive IGRAs

Immigrants who were symptomatic at the initial screening visit and/or had a positive IGRA/TST result were referred for CXR and further clinical assessment to rule out active TB.[7]

For clinical decision-making purposes, immigrants with a positive IGRA (QFN-GIT or T.SPOT.TB) and/or positive TST and normal CXR in the absence of any clinical features suggestive of active TB were defined as having LTBI.[17] Immigrants diagnosed with LTBI aged ≤35 years were offered chemoprophylaxis in accordance with UK guidelines.[7]

Data analysis

Details of the data analysis and health-economic modelling analysis, parameterised by empirical data drawn from the observational study, are presented in the online supplementary information (supplementary methods, supplementary tables 1–8 and supplementary figures 1–5).

RESULTS

Description of the cohort

Study recruitment is outlined in supplementary figure 6. A total of 231 subjects were included in the final analysis (table 1).

Screened immigrants were mainly young adults (74.1%, aged 16–35 years); 64.5% were women and 83.7% had previously been BCG vaccinated. Immigrants in this cohort most commonly originated from Asian countries (excluding the Indian subcontinent) (42.4%) and the Indian subcontinent (21.2%); 61.9% of the cohort had been resident in the UK for ≤2 years.

There were no significant demographic differences between immigrants who were eligible, and screened, versus those who did not attend (table 1).

Uptake and results of screening tests

Supplementary figure 7 outlines the uptake of the three screening tools—TST, QFN-GIT and T-SPOT.TB.

Overall, if the stratified cut-off (≥6 mm and ≥15 mm in BCG-unvaccinated and BCG-vaccinated individuals, respectively) for TST positivity was used, 53 of 175 immigrants (30.3%, 95% CI 23.6 to 37.7%) had a positive TST, whereas if the non-stratified cut-off (≥10 mm) was used, 66 of 175 (37.7%, 95% CI 30.5 to 45.3%) were deemed TST positive. There was no significant difference in size of induration

Table 1 Demographic characteristics of immigrants screened in the study; selected characteristics (when data were available) are compared against those of immigrants who were not screened

Variable	Immigrants who were screened (n=231)	Immigrants who did not attend (n=75)*	p Value
Age categories (years)			
16–25	87 (37.7%)	23 (30.7%)	0.39†
26–35	84 (36.4%)	33 (44.0%)	
36–45	35 (15.2%)	14 (18.7%)	
Over 45	25 (10.8%)	5 (6.7%)	
Gender			
Women	149 (64.5%)	43 (57.3%)	0.27
Men	82 (35.5%)	32 (42.7%)	
World region of origin‡			
Europe, North America	16 (6.9%)	5 (8.9%)	0.57
South America	14 (6.1%)	6 (10.7%)	0.24
Middle East	19 (8.2%)	3 (5.4%)	0.59
Other Africa	5 (2.2%)	3 (5.3%)	0.20
Other Asia	98 (42.4%)	17 (30.4%)	0.13
Indian subcontinent	49 (21.2%)	16 (28.6%)	0.29
Sub-Saharan Africa	30 (12.9%)	6 (10.7%)	0.82
TB incidence in country of origin‡			
0–65	39 (16.9%)	11 (19.6%)	0.70
66–170	105 (45.5%)	33 (58.9%)	0.08
171–300	74 (32.0%)	11 (19.6%)	0.08
>300	13 (5.6%)	1 (1.8%)	0.32
Time since entry to the UK (years)			
<1	38 (15.6%)		
1–2	107 (46.3%)		
3–5	88 (38.1%)		
BCG vaccinated§			
No	37 (16.3%)		
Yes	190 (83.7%)		
History of TB contact¶			
No	216 (94.3%)		
Yes	13 (5.7%)		
Travel to TB endemic country			
No	161 (69.7%)		
Yes	70 (30.3%)		
Employed			
Student	66 (28.6%)		
No/housewife	66 (28.6%)		
Yes	99 (28.6%)		
History of imprisonment			
No	228 (98.7%)		
Yes	3 (1.3%)		
Previous HIV test**			
No	139 (60.2%)		
Yes	85 (36.8%)		
Unsure	7 (3.0%)		
Current smoker			
No	195 (84.4%)		
Yes	36 (15.6%)		
Consumes alcohol			
No	169 (73.2%)		
Yes	62 (26.8%)		

*Selected characteristics (when data were available) are compared against those of immigrants who were not screened.
†p Value refers to overall comparison of age groups between immigrants who were screened and immigrants who did not attend.
‡For immigrants who were not screened, data on world region of origin and TB incidence in country of origin were available for 56 individuals.
§Data available for 227 individuals.
¶Data available for 229 individuals.
**HIV testing was not undertaken in this study but no subjects self-reported themselves as being HIV positive.
BCG, bacille Calmette Guérin; TB, tuberculosis.

between BCG-vaccinated (median 7 mm; IQR 0–15 mm) and unvaccinated (median 6 mm; IQR 0–10 mm) individuals (p=0.51) (supplementary figure 8 and supplementary table 9).

Overall, with QFN-GIT, 38 of 229 individuals (16.6%, 95% CI 12.0 to 22.1%) tested positive and 189 (82.5%, 95% CI 77.0 to 87.2%) were negative; two subjects (0.87%, 95% CI 0.1 to 3.1%) had indeterminate results (supplementary figure 9). T-SPOT.TB results were available in 160 (97.6%) immigrants. Thirty-six individuals (22.5%, 95% CI 16.3 to 29.8%) were positive, 117 (73.1%, 95% CI 65.6 to 79.8%) were negative and 7 (4.4%, 95% CI 1.8 to 8.8%) individuals had an indeterminate result (supplementary figure 9).

Pairwise comparisons revealed that the proportion of immigrants positive by TST was significantly higher than QFN-GIT (p=0.0025 for stratified TST cut-off, p<0.0001 for unstratified 10 mm TST cut-off) and T-SPOT.TB (p=0.02 for stratified TST cut-off, p<0.0001 for unstratified 10 mm TST cut-off). In contrast, there was no difference in the proportion of immigrants positive by QFN-GIT and T-SPOT.TB (p=0.49). However, there was a significantly lower proportion of indeterminate results with QFN-GIT compared with T-SPOT.TB (p=0.02).

Factors associated with positive screening test results

Univariate and multivariate analyses of factors associated with TST and IGRA positivity in the immigrant cohort are shown in table 2. On multivariate analysis, for TST, QFN-GIT and T-SPOT.TB, increasing TB incidence in country of origin and increasing age were independently associated with positive screening test results (table 2).

Concordance between screening tests and impact of prior BCG vaccination

Supplementary results (supplementary information—*Concordance between screening tests and impact of prior BCG vaccination*), figure 1 and supplementary table 10 outline concordance between the different screening tools.

Relationship between screening thresholds and screening test positivity

Table 3 illustrates the outcomes of LTBI immigrant screening stratified by screening test and TB incidence in the migrants' countries of origin. For all three tests (TST, QFN-GIT and T-SPOT.TB) as the incidence threshold at which screening is instigated increases, fewer immigrants within the cohort are eligible to be screened; the number of individuals identified with a positive test result also decreases, although the proportion testing positive remains relatively constant. At each incidence threshold TST, in comparison to both IGRAs, identified a lower proportion of the total positives.

Health economics analyses

The numbers of cases of active TB, and the associated costs, for a hypothetical cohort of 10 000 immigrants over the 20-year time horizon of the health economics model are presented in table 4 with more detailed text in the supplementary results (supplementary information—health economics analysis).

Applying current UK national guidance (port-of-arrival CXR, screening with single-step IGRA or dual TST plus confirmatory IGRA at 40/100 000) would avert (compared with no screening) between 15.6 and 28.8 cases of active TB and incur additional costs of between £594 956.9 and £1 530 303.0 over 20 years, depending on whether TST plus IGRA or IGRA alone was employed and which specific IGRA was utilised (QFN-GIT was less expensive and less effective than T-SPOT.TB). If

Table 2 Univariate and multivariate analysis of factors associated with tuberculin skin test, QuantiFERON Gold in-tube and T-SPOT.TB positivity

Variable	No. TST positive/total no. tested, n=175	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p	No. QFN-G-IT positive/total no. tested, n=229	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p	No. T.SPOT.TB positive/ total no. tested, n=160	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p
Age (years)												
16–25	16/63 (25.4%)	1	1	0.008	12/86 (14.0%)	1	1	0.003‡	11/63 (17.5%)	1	1	0.03
26–35	23/61 (37.7%)	1.78 (0.82 to 3.83)	2.82 (1.06 to 7.46)		10/84 (11.9%)	0.83 (0.34 to 2.05)	1.49 (0.51 to 4.41)		8/49 (16.3%)	0.92 (0.34 to 2.50)	1.40 (0.42 to 4.69)	
36–45	18/28 (64.3%)	5.29 (2.03 to 13.79)	7.49 (2.31 to 24.31)		8/34 (23.5%)	1.90 (0.70 to 5.16)	2.49 (0.68 to 9.06)		11/30 (36.7%)	2.74 (1.02 to 7.34)	5.76 (1.55 to 21.39)	
>45	9/23 (39.1%)	1.89 (0.69 to 5.19)	4.51 (1.22 to 16.69)		8/25 (32.0%)	2.90 (1.03 to 8.20)	6.23 (1.47 to 26.33)		6/18 (33.3%)	2.36 (0.73 to 7.66)	3.54 (0.72 to 17.33)	
Gender												
Women	33/106 (31.1%)	1	1	0.19	23/147 (15.7%)	1	1	0.72	22/105 (21.0%)	1	1	0.33
Men	33/69 (22.4%)	2.03 (1.08 to 3.79)	1.71 (0.77 to 3.79)		15/82 (18.3%)	1.21 (0.59 to 2.47)	1.19 (0.46 to 3.06)		14/55 (25.5%)	1.29 (0.60 to 2.78)	0.59 (0.20 to 1.72)	
World region of origin†												
Europe, Americas	3/56 (11.5%)	1			0/30 (0.0%)	–			1/16 (6.3%)	1		
Middle East, North Africa	7/19 (36.8%)	4.47 (0.98 to 20.49)			2/24 (8.3%)	1			2/12 (16.7%)	3.00 (0.24 to 37.67)		
Other Asia	36/78 (46.2%)	6.57 (1.82 to 23.70)			20/96 (20.8%)	2.89 (0.63 to 13.36)			20/71 (28.2%)	5.88 (0.73 to 47.52)		
Indian subcontinent	11/32 (34.4%)	4.02 (0.98 to 16.40)			7/49 (14.3%)	1.83 (0.35 to 9.58)			5/42 (11.9%)	2.03 (0.22 to 18.84		
Sub-Saharan Africa	9/20 (45.0%)	6.27 (1.41 to 27.86)			9/30 (30.0%)	4.71 (0.91 to 24.42)			8/19 (42.1%)	10.91 (1.19 to 100.41)		
TB incidence in country of origin (per 100 000 p.a.)†												
≤65	6/30 (20.0%)	1	1	0.007	2/39 (5.1%)	1	1	0.007	2/18 (11.1%)	1	1.75 (0.31 to 9.84)	0.037
66–170	31/84 (36.9%)	2.34 (0.86 to 6.35)	4.50 (1.44 to 14.07)		12/103 (11.7%)	2.44 (0.52 to 11.44)	3.58 (0.69 to 18.62)		12/73 (16.4%)	1.57 (0.32 to 7.76)	6.28 (1.07 to 36.92)	
171–300	27/56 (48.2%)	3.72 (1.32 to 10.5)	10.29 (2.79 to 37.97)		22/74 (29.7%)	7.83 (1.73 to 35.35)	13.92 (2.48 to 78.07)		19/63 (30.2%)	3.45 (0.72 to 16.53)		
>300	2/5 (40.0%)	2.67 (0.36 to 19.71)	5.95 (0.61 to 58.18)		2/13 (15.4%)	3.36 (0.42 to 26.72)	8.07 (0.82 to 79.49)		3/6 (50.0%)	8.00 (0.91 to 70.27)	9.64 (0.77 to 121.31)	
Time since arrival in the UK (years)												
<1	10/25 (40.0%)	1	1	0.11	5/36 (13.9%)	1	1	0.88	5/13 (38.5%)	1	1	0.09
1–2	35/89 (39.3%)	0.97 (0.39 to 2.41)	0.89 (0.31 to 2.56)		15/105 (14.3%)	1.03 (0.35 to 3.08)	0.80 (0.23 to 2.84)		16/81 (19.8%)	0.39 (0.11 to 1.37)	0.22 (0.05 to 1.00)	
3–5	21/61 (34.4%)	0.79 (0.30 to 2.05)	0.37 (0.12 to 1.20)		18/88 (20.5%)	1.59 (0.54 to 4.68)	0.98 (0.27 to 3.59)		15/66 (22.7%)	0.47 (0.13 to 1.65)	0.17 (0.03 to 0.85)	
BCG vaccinated												
No	8/29 (27.6%)	1	1	0.40	7/37 (18.9%)	1	1	0.75	4/25 (16.0%)	1	1	0.57
Yes	57/143 (39.9%)	1.74 (0.72 to 4.20)	1.56 (0.56 to 4.33)		30/188 (16.0%)	0.81 (0.33 to 2.02)	0.84 (0.30 to 2.40)		31/132 (23.5%)	1.61 (0.51 to 5.05)	1.46 (0.40 to 5.28)	

Continued

Table 2 Continued

Variable	No. TST positive/total no. tested, n=175	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p	No. QFN-G-IT positive/total no. tested, n=229	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p	No. T.SPOT.TB positive/ total no. tested, n=160	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p
Travel to TB endemic country												
No	41/121 (33.9%)	1	1	0.18	21/159 (13.2%)	1	1	0.06	21/111 (18.9%)	1	1	0.08
Yes	25/54 (46.3%)	1.68 (0.87 to 3.24)	1.77 (0.77 to 4.06)		17/70 (24.3%)	2.11 (1.03 to 4.30)	2.25 (0.96 to 5.26)		15/49 (30.6%)	1.89 (0.87 to 4.09)	2.37 (0.90 to 6.28)	
TB contact												
No	60/164 (36.6%)	1	1	0.23	33/215 (15.4%)	1	1	0.14	31/148 (21.0%)	1	1	0.07
Yes	6/9 (66.7%)	3.47 (0.84 to 14.36)	2.71 (0.53 to 13.82)		5/13 (38.5%)	3.44 (1.06 to 11.19)	2.93 (0.72 to 12.01)		5/11 (45.5%)	3.15 (0.9 to 10.99)	4.01 (0.92 to 17.48)	
Employment status												
Unemployed	18/51 (35.3%)	1	1	0.55	15/65 (23.1%)	1	1	0.25	11/53 (20.8%)	1	1	0.10
Employed	27/70 (38.6%)	1.15 (0.54 to 2.44)	0.92 (0.36 to 2.37)		13/99 (13.1%)	0.50 (0.22 to 1.14)	0.46 (0.16 to 1.3)		14/63 (22.2%)	1.09 (0.45 to 2.66)	0.96 (0.31 to 2.98)	
Student	21/54 (38.9%)	1.20 (0.50 to 2.60)	1.49 (0.58 to 3.83)		10/65 (15.4%)	0.61 (0.25 to 1.47)	1.06 (0.36 to 3.1)		11/44 (25.0%)	1.27 (0.49 to 3.30)	3.13 (0.94 to 10.4)	
Alcohol												
No	48/131 (36.6%)	1	1	0.79	30/167 (18.0%)	1	1	0.97	27/126 (21.4%)	1	1	0.10
Yes	18/44 (40.9%)	1.20 (0.60 to 2.41)	1.13 (0.46 to 2.78)		8/62 (12.9%)	0.68 (0.29 to 1.57)	1.02 (0.35 to 3.02)		9/34 (26.5%)	1.32 (0.55 to 3.16)	2.78 (0.83 to 9.23)	
Smoker												
No	56/146 (38.4%)	1	1	0.73	34/193 (17.6%)	1	1	0.75	33/136 (24.3%)	1	1	0.75
Yes	10/29 (34.5%)	0.85 (0.37 to 1.95)	1.21 (0.41 to 3.58)		4/36 (11.1%)	0.58 (0.19 to 1.76)	1.25 (0.32 to 4.80)		3/24 (12.5%)	0.45 (0.13 to 1.59)	0.77 (0.15 to 3.88)	
History of imprisonment												
No	65/172 (37.8%)	1	1	0.83	38/226 (16.8%)				35/157 (22.3%)	1	1	0.16
Yes	1/3 (33.3%)	0.82 (0.07 to 9.26)	1.34 (0.09 to 19.49)		0/3 (0.0%)				1/3 (33.3%)	1.74 (0.15 to 19.79)	7.79 (0.46 to 132.76)	

*Models mutually adjusted for the following factors: age, gender, TB incidence in country of origin, time since arrival in the UK, BCG vaccination status, travel to TB endemic country, history of TB contact, employment status, alcohol use, smoking status and history of imprisonment (except for QuantiFERON Gold in-tube).
†World region of origin and TB incidence in country of origin were strongly correlated, so, in the multivariate analysis, world region of origin was dropped.
BCG, bacille Calmette Guérin; QFN, QuantiFERON Gold in-tube; TB, tuberculosis; TST, tuberculin skin test.

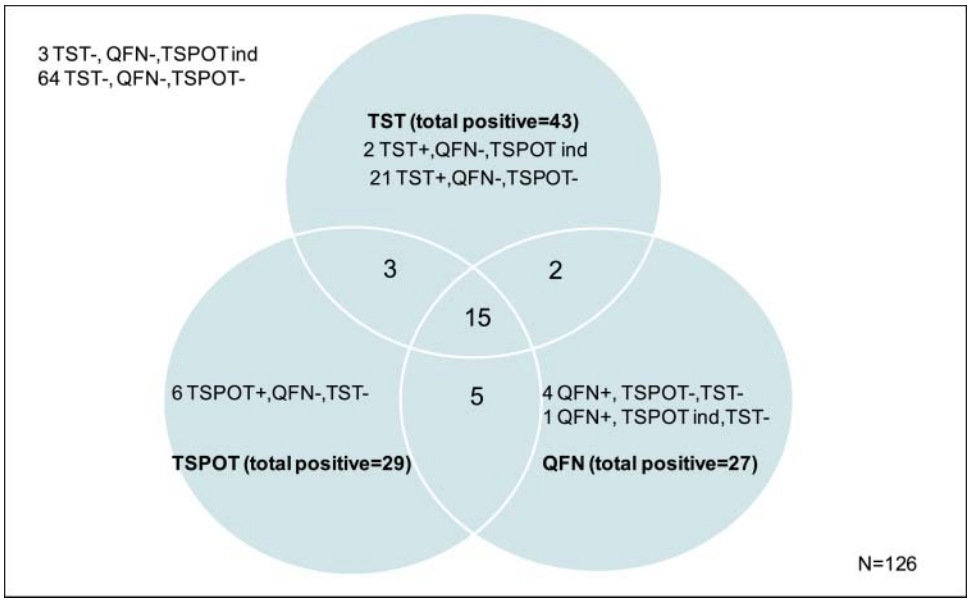

Figure 1 Venn diagram showing test results where all three screening tests were undertaken. Ind, indeterminate; QFN, QuantiFERON; TST, tuberculin skin test.

port-of-arrival CXR screening was removed from national policy then savings of almost £100 000 would be made over 20 years with little impact on the number of TB cases averted. Increasing the screening threshold (eg, to 150/100 000—the Indian subcontinent) but keeping port-of-arrival CXR and using the identical screening tools would avert 58–66% of cases and incur 55–65% of costs compared with screening at 40/100 000.

With dominated options excluded (table 4) five cost-effective strategies remained which, in decreasing order of cost effectiveness, were no port-of-arrival CXR and single-step QFN-GIT at 250/100 000; no port-of-arrival CXR and single-step QFN-GIT at 150/100 000; no port-of-entry CXR and single-step QFN-GIT at 40/100 000; CXR at port-of-arrival and single-step QFN-GIT at 40/100 000; and, finally, CXR at port-of-arrival and single-step T-SPOT.TB at 40/100 000. The associated incremental cost-effectiveness ratios for these strategies were £21 565.3, £31 867.1, £34 753.5, £59 489.1 and £402 421.8 respectively per active TB case averted. The results remained unchanged when analyses were restricted to individuals tested concurrently with all three diagnostic modalities.

The results of the univariate sensitivity analysis are presented in online supplementary tables 11 and 12 with more detailed text in the supplementary results (supplementary information—Sensitivity analysis).

DISCUSSION

This is the first three-way assessment of different screening methods for LTBI in recent immigrants which provides comparative estimates of test performance and positivity stratified by demographic factors and risk factors for LTBI. Consequently we have been able to evaluate, using a decision-analysis model, the cost effectiveness of screening with port-of-arrival CXRs and for LTBI. Our analysis reveals that UK policy could be modified by removing the current requirement for CXR on arrival and concentrating on LTBI testing using single-step IGRA testing targeted at adult immigrants arriving from countries with moderate TB incidence (rather than from countries with TB incidence >40/100 000 as recommended currently).[10]

In this cohort the proportion positive by TST (30.3%; 36.7% with 10 mm cut-off) was significantly higher than with QFN-GIT (16.6%) or T-SPOT.TB (22.5%). Previous studies have assessed LTBI prevalence in immigrants with TST and found that positivity varies from 26% to 72% depending on the setting, type of migrants studied (legal or undocumented immigrants),

Table 3 Yields for test positivity by different screening tests at different screening thresholds

TB incidence screening threshold (/100 000 per year)	No. tested			No. positive			Yield at incidence level, that is, proportion of those tested			Positives identified if threshold set at this level (%)		
	TST	QFN	TSPOT	TST	QFN	TSPOT	TST	QFN	TSPOT	TST	QFN	TSPOT
Screen ≥350	4	11	4	1	1	1	25.0	9.1	25.0	1.9	2.6	2.8
Screen ≥300	5	13	6	1	2	3	20.0	15.4	50.0	1.9	5.3	8.3
Screen ≥250	23	37	28	10	13	12	43.5	35.1	42.9	18.9	34.2	33.3
Screen ≥200	50	75	59	20	19	17	40.0	25.3	28.8	37.7	50.0	47.2
Screen ≥150	71	105	84	26	27	25	36.6	25.7	29.8	49.1	71.1	69.4
Screen ≥100	104	143	110	30	29	28	28.9	20.3	25.5	56.6	76.3	77.8
Screen ≥40*	**170**	**222**	**158**	**52**	**38**	**36**	**30.6**	**17.1**	**22.8**	**98.1**	**100.0**	**100.0**
Screen all	175	229	160	53	38	36	30.3	16.6	22.5	100.0	100.0	100.0

*Current threshold recommended by National Institute for Health and Clinical Excellence guidance is given in bold text.
QFN, QuantiFERON Gold in-tube; TB, tuberculosis; TST, tuberculin skin test.

Table 4 Projected cases of active tuberculosis (TB) and associated costs arising from undertaking immigrant screening using different screening tools at different screening thresholds (arranged in order of increasing effectiveness—ie, fewer cases of active TB) for a hypothetical cohort of 10 000 immigrants over a 20-year time horizon

	Screening for LTBI						
CXR at port of arrival	Screening tool	Screening threshold for immigrants (cases of TB/100 000 per year)	Cases of active TB (over 20 years)	Costs (£, 2010)	Incremental cases of active TB	Incremental costs (£, 2010)	ICER
No	None	None	100.5	659 609.4	Baseline	Baseline	Baseline
No	TST plus QFN	350	100.4	690 521.6	Extended dominance	Extended dominance	Extended dominance
No	TST plus T-SPOT.TB	350	100.3	696 433.4	Extended dominance	Extended dominance	Extended dominance
No	TST	350	100.1	706 478.7	Strict dominance	Strict dominance	Strict dominance
No	TST plus QFN	300	100.0	707 756.2	Strict dominance	Strict dominance	Strict dominance
No	TST plus T-SPOT.TB	300	99.8	715 317.0	Strict dominance	Strict dominance	Strict dominance
No	QFN	350	99.4	701 675.9	Extended dominance	Extended dominance	Extended dominance
No	TST	300	99.4	721 759.0	Extended dominance	Extended dominance	Extended dominance
No	T-SPOT.TB	350	99.3	728 560.7	Strict dominance	Strict dominance	Strict dominance
Yes	None	None	98.9	754 339.9	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus QFN	350	98.8	785 252.0	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus T-SPOT.TB	350	98.7	791 163.9	Strict dominance	Strict dominance	Strict dominance
Yes	TST	350	98.5	801 209.1	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus QFN	300	98.4	802 486.6	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus T-SPOT.TB	300	98.2	810 047.5	Strict dominance	Strict dominance	Strict dominance
No	QFN	300	98.0	723 513.2	Extended dominance	Extended dominance	Extended dominance
Yes	QFN	350	97.8	796 406.3	Strict dominance	Strict dominance	Strict dominance
Yes	TST	300	97.8	816 489.4	Strict dominance	Strict dominance	Strict dominance
No	TST plus QFN	250	97.8	793 192.7	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	300	97.7	751 926.8	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	350	97.7	823 291.1	Strict dominance	Strict dominance	Strict dominance
No	TST plus T-SPOT.TB	250	97.3	813 690.1	Extended dominance	Extended dominance	Extended dominance
Yes	QFN	300	96.4	818 243.7	Extended dominance	Extended dominance	Extended dominance
Yes	TST plus QFN	250	96.2	887 923.2	Strict dominance	Strict dominance	Strict dominance
No	TST	250	96.2	823 749.7	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	300	96.1	846 657.3	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus T-SPOT.TB	250	95.7	908 420.5	Strict dominance	Strict dominance	Strict dominance
No	TST plus QFN	200	95.6	867 394.4	Strict dominance	Strict dominance	Strict dominance
No	TST plus T-SPOT.TB	200	95.0	913 943.4	Strict dominance	Strict dominance	Strict dominance
Yes	TST	250	94.6	918 480.1	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus QFN	200	94.0	962 124.9	Strict dominance	Strict dominance	Strict dominance
No	TST	200	93.8	995 462.9	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus T-SPOT.TB	200	93.4	1 008 673.9	Strict dominance	Strict dominance	Strict dominance
No	TST plus QFN	150	93.0	954 636.7	Strict dominance	Strict dominance	Strict dominance
No	TST plus T-SPOT.TB	150	92.3	1 023 409.3	Strict dominance	Strict dominance	Strict dominance
Yes	TST	200	92.2	1 090 193.4	Strict dominance	Strict dominance	Strict dominance
No	QFN	250	92.1	839 713.7	8.4	180 104.3	21 565.3
No	TST plus QFN	100	91.5	1 018 843.7	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus QFN	150	91.4	1 049 367.2	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	250	91.3	909 426.7	Extended dominance	Extended dominance	Extended dominance
No	TST plus T-SPOT.TB	100	90.7	1 113 644.2	Strict dominance	Strict dominance	Strict dominance
Yes	TST plus T-SPOT.TB	150	90.7	1 118 139.7	Strict dominance	Strict dominance	Strict dominance
No	TST	150	90.6	1 149 671.8	Strict dominance	Strict dominance	Strict dominance

Continued

Table 4 Continued

CXR at port of arrival	Screening for LTBI: Screening tool	Screening for LTBI: Screening threshold for immigrants (cases of TB/100 000 per year)	Cases of active TB (over 20 years)	Costs (£, 2010)	Incremental cases of active TB	Incremental costs (£, 2010)	ICER
Yes	QFN	250	90.6	934 444.2	Extended dominance	Extended dominance	Extended dominance
Yes	TST plus QFN	100	89.9	1 113 574.1	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	250	89.7	1 004 157.2	Strict dominance	Strict dominance	Strict dominance
No	QFN	200	89.1	959 014.5	Extended dominance	Extended dominance	Extended dominance
Yes	TST plus T-SPOT.TB	100	89.1	1 208 374.6	Strict dominance	Strict dominance	Strict dominance
No	TST	100	89.0	1 319 841.4	Strict dominance	Strict dominance	Strict dominance
Yes	TST	150	89.0	1 244 402.3	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	200	88.2	1 171 831.5	Strict dominance	Strict dominance	Strict dominance
Yes	QFN	200	87.6	1 053 744.9	Extended dominance	Extended dominance	Extended dominance
Yes	TST	100	87.4	1 414 571.9	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	200	86.6	1 266 562.0	Strict dominance	Strict dominance	Strict dominance
No	TST plus QFN	40	86.5	1 159 835.9	Strict dominance	Strict dominance	Strict dominance
No	TST plus T-SPOT.TB	40	85.5	1 296 089.2	Strict dominance	Strict dominance	Strict dominance
Yes	**TST plus QFN**	**40**	**84.9**	**1 254 566.3**	**Strict dominance**	**Strict dominance**	**Strict dominance**
No	QFN	150	84.3	1 089 176.5	7.8	249 462.8	31 867.1
Yes	**TST plus T-SPOT.TB**	**40**	**83.9**	**1 390 819.6**	**Strict dominance**	**Strict dominance**	**Strict dominance**
No	TST	40	83.3	1 597 273.1	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	150	83.0	1 408 873.0	Strict dominance	Strict dominance	Strict dominance
No	QFN	100	82.8	1 195 634.0	Strict dominance	Strict dominance	Strict dominance
Yes	QFN	150	82.7	1 183 906.9	Extended dominance	Extended dominance	Extended dominance
Yes	TST	40	81.7	1 692 003.5	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	100	81.5	1 666 546.8	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	150	81.4	1 503 603.4	Strict dominance	Strict dominance	Strict dominance
Yes	QFN	100	81.2	1 290 364.5	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	100	79.9	1 761 277.3	Strict dominance	Strict dominance	Strict dominance
No	QFN	40	74.9	1 414 623.3	9.4	325 446.8	34 753.5
Yes	**QFN**	**40**	**73.4**	**1 509 353.7**	**1.6**	**94 730.4**	**59 489.1**
No	T-SPOT.TB	40	73.3	2 095 182.0	Extended dominance	Extended dominance	Extended dominance
Yes	**T-SPOT.TB**	**40**	**71.7**	**2 189 912.4**	**1.7**	**680 558.7**	**402 421.8**

*Ranking different strategies from least effective to most effective (ie, number of cases of active TB predicted to occur) results in the ICERs of most screening options being excluded through extended dominance, which is when the ICER for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis.
†Current National Institute for Clinical Excellence guidance recommends screening with CXR on arrival, using single-step IGRA or dual TST plus confirmatory IGRA at an incidence threshold of 40/100 000 (bold rows).
CXR, chest x-ray; ICER, incremental cost-effectiveness ratio; IGRA, interferon γ release assay; LTBI, latent tuberculosis infection; QFN, QuantiFERON Gold in-tube; TST, tuberculin skin test.

TST cut-off and history of BCG vaccination.[18–22] IGRA performance in diagnosing LTBI in legal (adult) immigrants is poorly studied and has primarily focused on undocumented migrants[19 20] or immigrant contacts of smear-positive cases[23 24] with few studies focusing on legal, documented migrants.[9 25] Nonetheless, in all populations, IGRA positivity (15–60%) has generally been lower than that seen with TST.[19 20 23–26] However, many of these studies have utilised single-step IGRA only[25] or only undertaken IGRA in individuals who have had a positive TST—thereby introducing bias in patient selection.[23]

Positive TST and IGRA were associated with increasing TB incidence in countries of origin and this likely reflects higher degrees of exposure to *Mycobacterium tuberculosis* in these settings. This is in keeping with previous analyses for TST[18 24] and IGRA,[20 24] although there are few data on test positivity in immigrants subcategorised into multiple strata of TB incidence.

Increasing age was also associated with test positivity for all three tests. Previous studies from differing settings and patient groups have shown that TST[18 27] and IGRA[27 28] positivity increase with age. Although this is likely to be due to older immigrants having a higher cumulative probability of TB exposure in their countries of origin, other possibilities include higher cumulative exposure to environmental *Mycobacteria* resulting in false-positive results (for TST) and sub-optimal sensitivity in

younger age groups resulting in false-negative results (for TST and IGRA).[29]

UK national guidance for immigrant TB screening is currently in flux with the prior LTBI screening threshold (adults from sub-Saharan Africa or countries with TB incidence >500/100 000[7]) missing the vast majority of imported latent infections[9] now being revised to an incidence of 40/100 000.[10] While almost all positives in our cohort would be identified using this new recommendation, it would also entail screening most of the immigrant cohort and increase the pressure on already stretched services.[8] In contrast, with an intermediate threshold (such as 150/100 000), just under three-quarters of all positives (with single-step IGRA) would be identified but only half the immigrant cohort would need to be tested thereby offering a balance between diagnostic need and practical service capacity.[8]

Our analysis indicates five screening strategies were cost effective—with three strategies more cost effective than current national guidance. These strategies were no port-of-arrival CXR and single-step QFN-GIT at incidence thresholds of 250/100 000, 150/100 000 or 40/100 000. Introducing port-of-arrival CXR and single-step IGRAs at 40/100 000 was cost effective but at much higher incremental cost-effectiveness ratios. Therefore, while implementing port-of-arrival CXR averts a few additional cases of active TB, it is not highly cost effective (with the findings robust to changes in the prevalence of active TB in immigrants). This finding is consistent with the epidemiology of TB in the UK, where there is little active TB at the time of immigration[11 30] with most cases occurring through reactivation in latently infected foreign-born immigrants after arrival.[2] Therefore, screening with mandatory CXR on arrival for active TB should be reassessed.[11] Other analyses, based on scenarios rather than empirical data, have suggested that CXR screening can be a cost-effective intervention but have assumed very high proportions of the immigrant cohort having prevalent active TB,[31] a very low prevalence of LTBI[32] and a low reactivation rate.[31 32]

UK guidance currently recommends that either dual TST plus IGRA or single-step IGRA can be used in adults[10] but we found that single-step IGRA was the most cost-effective approach. Although previous health economic analyses of immigrant screening were only able to consider TST as a diagnostic modality,[31 33] more recent studies have compared TST and IGRA with varying conclusions—reflecting different modelling techniques and varying estimates of test performance.[25 32] In non-immigrant risk groups, the data are conflicting with some authors concluding that TST plus confirmatory IGRA is superior,[32 34–36] while others that IGRA alone is most cost effective.[37 38] Although all three individuals with active TB in our dataset were IGRA positive, an important caveat to moving to single-step IGRA would be a requirement to supplement testing with a symptom questionnaire (and potentially CXR if any clinical concerns) to avoid missing immigrants with false-negative IGRAs in the setting of active TB—especially if port-of-arrival CXR is withdrawn.

We also found that QFN-GIT is the most cost-effective IGRA, primarily due to the higher unit costs for T-SPOT.TB. Previous economic analyses of IGRAs (including among immigrants) have, in general, only focused on one or other IGRA. Only Pooran *et al* assessed the relative cost effectiveness of QFN-GIT and T-SPOT.TB, but their analysis focused on contacts, only considered a 2-year time horizon, did not include discounting, and most importantly, used now superseded estimates of test performance.[34]

Central to our analysis is the specific threshold at which screening should be instigated: 250/100 000, 150/100 000 and 40/100 000 were all cost-effective thresholds, confirming previous work,[9] and the latter two strategies would include immigrants from the Indian subcontinent who contribute both a large proportion of the individuals migrating to, and a high proportion of the foreign-born active TB cases occurring in, the UK.[2 39] Optimal screening thresholds in different high-income countries may differ due to local patterns of migration and countries should ascertain their specific mix/pattern of migration and prevalence of LTBI to most accurately parameterise health economics models.

Our work had several limitations. The number of participants was relatively small and not all were concurrently screened with all three tests. While the composition of immigrants screened was broadly in keeping with the foreign-born population resident in the UK, other areas of the UK may have slightly higher proportions of immigrants from the Indian subcontinent. As per UK guidelines, HIV testing was not undertaken and thus data on immigrants' HIV status were not available. Consequently we used estimates for this but our work highlights the potential of incorporating testing for bloodborne viruses into community-based screening for TB.

Our health economics model only considered transmission to contacts resulting in secondary cases of active TB and LTBI. Incorporating further generations of transmission would increase the cost effectiveness of screening by increasing the number of cases ultimately averted. However, we assumed relatively high rates of acceptance and completion of chemoprophylaxis which, while broadly in line with the estimates used by NICE,[10] may have overestimated the cost effectiveness of screening (although the results remained broadly unchanged with reductions in completion rates). We only considered incidence thresholds >40/100 000 but future work should ascertain the cost effectiveness, and logistics, of screening immigrants at lower incidence thresholds (such as >20/100 000).

In line with previous published work[31 32 34 37] we elected to assess cost effectiveness by presenting the cost per active TB case averted rather than the cost per quality adjusted life year as there are still limited objective data on utility states for individuals with active and latent TB.

In conclusion, immigrant screening in the UK could cost-effectively remove the requirement for mandatory CXR on arrival and concentrate on screening for LTBI with single-step IGRA at an incidence threshold which balances the need to identify those with LTBI against limited service capacity while still reducing UK TB notifications in the future.

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Contributors The initial study was designed and set up by OMK and MG with input by MP and AL. MB and JS undertook the immigrant screening and entered the data into the databases. SS was in charge of setting up and analysing the IGRA results. MP analysed the data and designed the economic model with input from

OMK, AL and PJW. MP drafted the manuscript with input from all other authors. All authors approved the final version to be published. OMK is the guarantor.

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Competing interests AL is inventor for patents underpinning T-cell-based diagnosis. The ESAT-6/CFP-10 ELISpot was commercialised by an Oxford University spin-out company (Oxford Immunotec, Abingdon, UK) in which Oxford University and Professor Lalvani have a minority share of equity. MP, SS, MB, JS, MG, PJW and OMK have no conflict of interest.

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Online Supplementary information

Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis

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This supplementary information provides further details of the data analysis, decision tree models, the input parameters/probabilities, the estimated costs, the cost-effectiveness analysis and sensitivity analysis.

Supplementary methods

Methods of screening

Peripheral venous blood samples were collected for the two commercially available IGRAs, QuantiFERON Gold in-tube (QFN-GIT), a whole blood ELISA and T-SPOT.TB, an ELISPOT platform. Due to funding and logistic issues, IGRA screening was only available with QFN-GIT for the first 6 weeks of the study although for the remainder of the study period all individuals were concurrently tested using both IGRA platforms. IGRAs were carried out in accordance with the manufacturer's instructions; results were defined as positive, negative or indeterminate depending on the manufacturer's criteria.

Tuberculin skin testing was undertaken at the first visit after blood samples had been collected to avoid the possible boosting effect of TST on the IGRAs.[1] A trained TB nurse performed TST using 2 tuberculin units of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) injected into the forearm following the Mantoux method. Transverse induration (in mm) was measured 48-72 hours later; observers were blind to IGRA results. In general, cut-off for a positive TST was stratified by BCG status ("stratified cut-off") as per national guidelines - ≥6mm and ≥15mm in BCG unvaccinated and vaccinated individuals respectively.[2] In addition, a cut-off of ≥10mm ("non-stratified cut-off") was used to evaluate which factors (including BCG vaccination status) were associated with a positive TST, as this was not predefined/determined by BCG status.

Data analysis

Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as a simple descriptive percentage (with 95% confidence intervals (95% CI)) and comparisons made using Pearson's chi-square test (or Fishers exact test if appropriate). When calculating the proportion of individuals that were IGRA positive, indeterminate results were included in the denominator.

Univariate association of risk factors individually associated with a positive TST (using the "non-stratified cut-off" of ≥10mm), ELISA (QFN-GIT) and ELISpot (T-SPOT.TB) was assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals. To calculate adjusted odds ratios (and 95% CI), three separate multivariate logistic regression models were constructed for each of the screening tools where we mutually adjusted for the following factors: age, gender, TB incidence in country of origin, time since arrival in the UK, BCG vaccination status, history of TB contact, employment status, smoking status, alcohol use and history of imprisonment. Variables were examined for confounding and for effect modification, and the significance of interaction terms was tested.

Concordance between each of the three screening tools (TST with ELISA, TST with ELISpot, and ELISA with ELISpot) was assessed using percentage agreement and Cohen's κ coefficients; strength of agreement was considered 'poor' for $\kappa \leq 0.20$, 'fair' for $0.20 < \kappa \leq 0.40$, 'moderate' for $0.40 < \kappa \leq 0.60$, 'substantial' for $0.60 < \kappa \leq 0.80$ and 'optimal' for $0.80 < \kappa \leq 1.00$.[3] Pairwise comparisons of the proportion of positive results with each screening test were undertaken using McNemar's test.

Assessment of the different incidence screening thresholds was undertaken by calculating individually for TST, the ELISA and ELISpot, at each incidence threshold (increasing from 0/100,000 per year to 350/100,000 per year in increments of 50/100,000 per year), the absolute number of immigrants who would need to be screened, the proportion positive with each screening test and the proportion of individuals with a positive test who would not be detected if screening was undertaken at a particular threshold.

Analyses used STATA 9.2 (StataCorp, College Station, TX). All tests were two tailed; p-value of ≤ 0.05 was considered significant.

Health economic evaluation

A health-economic analysis, conducted from a National Health Service perspective, explored poorly understood areas including the cost-effectiveness of supplementing chest radiography at port-of-entry with immigrant screening for LTBI with different strategies/tools at different incidence thresholds.

We developed new, complex decision-tree models (supplementary figures 1-5), additionally incorporating HIV infection and drug resistance, parameterised by empirical data on test positivity (and thus LTBI prevalence), the proportion of individuals eligible for screening at different incidence thresholds and test acceptance, in those immigrants aged 35 years and under, from the observational study described above to simulate the clinical (numbers of active TB cases) and economic outcomes of screening a hypothetical cohort of 10,000 recently arrived immigrants (aged ≤ 35 years) for active TB (at port-of-entry) and LTBI over a 20-year time horizon. One important exception to this was HIV status. Given the lack of data on HIV infection in our cohort (and immigrants in general) we used HIV prevalence figures from the

World Health Organisation to estimate HIV prevalence at each screening threshold which were used to parameterise the economic analysis. Five distinct screening strategies were considered: TST alone, T-SPOT.TB alone, QFN-GIT alone, TST plus confirmatory T-SPOT.TB if TST positive, and TST plus confirmatory QFN-GIT if TST positive). For each of these strategies, we evaluated the impact of varying the incidence screening threshold (in the immigrants' country of origin) at which immigrants became eligible for screening from a minimum of 40/100,000 per year (in other words immigrants from all high-burden countries would be eligible for screening) to a maximum of 350/100,000 per year. At each threshold, we evaluated the number of immigrants who would be eligible for screening, the number of true positive individuals with LTBI and the number of individuals with LTBI that would be missed relative to screening the whole cohort. Model assumptions are outlined in supplementary table 1. A detailed description of the model, discussion of the model parameters, costs (in 2010 UK pounds sterling) and sensitivity analyses are presented in next section of this. The decision tree was constructed, and analysed, using Microsoft Excel 2007 (Microsoft, USA) and TreeAge Pro 2011 (Tree Age Software, Inc., Williamstown, MA).

General modelling approach

The modelling approach builds on previous work by utilising empirical immigrant screening data obtained from a prospective three-way comparison of tuberculin skin test (TST), QuantiFERON Gold in-tube (QFN-GIT) and T-SPOT.TB. The current work is distinct from earlier studies as it incorporates both HIV infection and TB drug-resistance amongst the immigrant cohort – thereby enhancing the realism of the model.

Screening strategies and incidence thresholds considered in health-economic analysis

In this cost-effectiveness analysis, we first considered that immigrants arriving in the UK could either be screened with chest radiography (CXR) at port-of-entry or, in an alternative scenario, that this initial CXR would not be undertaken. Subsequently immigrants could be screened for LTBI with one of five strategies (TST alone, T-SPOT.TB alone, QFN-GIT alone, TST followed by confirmatory T-SPOT.TB if TST positive and TST followed by confirmatory QFN-GIT if TST positive) at seven different incidence thresholds (screening at ≥40/100,000, ≥100/100,000, ≥150/100,000, ≥200/100,000, ≥250/100,000, ≥300/100,000, ≥350/100,000) based on empirical data from the observational study described in the main manuscript; screening at incidence thresholds <40/100,000 was not considered due to the lack of data in the observational study on immigrants at these lower incidence levels. This resulted in 70 potential active TB and LTBI screening policies (see supplementary table 2) which were included in the current analysis with the primary aim being to understand which screening policy/policies would be most cost-effective for the United Kingdom (UK).

Description of the decision models

All decision models (see supplementary figures 1-5) considered a hypothetical cohort of 10,000 immigrants, aged ≤35 years, who had recently arrived in the UK.

Chest radiography at port-of-entry

Amongst those immigrants arriving in the UK, a proportion will have originated from countries with a TB incidence of ≥40/100000 per year. As per UK national policy, these individuals are subject to immigration control measures which require that if they are intending to stay in the UK for >6 months they should undergo CXR on arrival.[4] In the model port-of-entry screening is explored through two scenarios. In scenario one, we assume a proportion of those immigrants (from countries with TB incidence ≥40/100000 per year) are screened with CXR on arrival in the UK; the remainder either refuse or are not appropriately identified for, and thus miss, CXR screening. In contrast those who come from countries with a TB incidence <40/100000 per year do not undergo CXR screening. In scenario two we assume that there is no port-of-entry screening system in place and therefore immigrants do not undergo CXR screening on arrival in the UK.

Amongst those immigrants who do, and do not, undergo chest radiography a fixed proportion (in keeping with meta-analytical and national data) will be diagnosed with active TB – with a fixed proportion of these cases being caused by drug sensitive and drug-resistant strains of *Mycobacterium tuberculosis*. However the model makes an important distinction between those immigrants actively diagnosed with active TB (through port-of-entry CXR screening) and those individuals who are passively diagnosed after presenting with symptoms (in other words those individuals who have not been screened at port-of-entry with CXR). Actively diagnosed individuals are

assumed to be infectious for a shorter duration than passively diagnosed individuals with the model assuming a 50% reduction in the number of their close contacts becoming latently infected or developing active TB.

All individuals diagnosed with active TB are assumed to accept and complete treatment; as a simplifying assumption we assume that there is a 100% cure rate. Immigrants who have been cured of active TB cannot be re-infected during the course of the 20-year model so they have no further sequelae in the model.

Immigrants who have not been diagnosed with active TB at this initial stage, but have arrived from countries with a TB incidence of ≥40/100000, represent the cohort that will be targeted, depending on the specific incidence threshold at which screening is to be instigated (see ***Screening strategies and incidence thresholds considered in health-economic analysis*** above), for LTBI screening. On the other hand, in keeping with national guidelines, immigrants who have arrived from countries with a TB incidence of <40/100000 are not eligible to be screened for LTBI. However, it is important to note that this does not mean they have no further sequelae in the model. In fact a proportion of this subgroup will actually have LTBI and therefore remain at risk of progressing to active TB over the time course of the model and this eventuality is included in the model.

Screening strategies for latent tuberculosis infection

The five screening strategies/tools (TST alone, T-SPOT.TB alone, QFN-GIT alone, TST followed by confirmatory T-SPOT.TB if TST positive and TST followed by confirmatory QFN-GIT if TST positive) were encapsulated in three related, but distinct, decision models.

Model 1 considers the TST only screening approach (supplementary figure 2), model 2 the IGRA only approach (either single-step testing with QuantiFERON Gold in-tube (QFN-GIT) or T-SPOT.TB – supplementary figure 3) and model 3 considers a scenario where TST is followed by a confirmatory IGRA – if the TST is positive (supplementary figure 4). For models 2 and 3, although the actual model flows are identical, both IGRAs, QFN-GIT and T-SPOT.TB were considered independently, with unique input parameter values (such as test sensitivity and specificity).

In many respects the three models overlap although the initial flows which deal with acceptance of the screening tests do differ as set out below.

Eligibility for testing and acceptance of screening test

Depending on the specific incidence threshold at which immigrant screening is to be instigated, a proportion of migrants will be eligible to be screened for LTBI (data drawn from the observational study described in the main manuscript) and will thus be offered initial testing with either TST (which applies to model 1 the TST only approach and model 3 the TST plus confirmatory IGRA approach) or IGRA (which applies to model 2 the IGRA only approach). Immigrants who are ineligible for screening are not offered appointments and if they have LTBI (which can be caused by either a drug-sensitive or drug-resistant strain *M. tuberculosis*) they remain at risk of progressing to active TB over the twenty-year time horizon of the model at a rate which is determined by their HIV status – with HIV-positive individuals experiencing a higher annual progression rate than HIV-negative individuals. As highly active anti-retroviral therapy (HAART) coverage is high in the UK, and would render HIV positive individuals immunocompetent, we assumed that their pattern of disease (in terms of disease-types) would be similar to the rest of the, HIV-negative, cohort.

Amongst those eligible immigrants who are offered testing with TST, a proportion will accept (data on this parameter drawn from the observational study described in the main manuscript) and have the Mantoux test administered at this first visit. If TST testing is not accepted, the immigrant will be discharged from clinical care. Forty-eight to seventy-two hours following administration of TST, a proportion of immigrants will return to have the size of induration read/measured (data on this parameter drawn from the observational study described in the main manuscript). If the immigrant does not return to have the TST reaction read, they are also discharged from clinical care.

In the IGRA only approach, a proportion of those individuals offered testing with the IGRA will accept and have blood drawn at this first visit (data on this parameter drawn from the observational study described in the main manuscript). Those who decline the screening test are discharged from clinical care. In contrast to TST testing, no further visits are required (we assume that all results are determinate and no repeat IGRA testing is required).

Confirmation of positive TST in dual TST plus confirmatory IGRA testing model

In contrast to models 1 (TST only approach) and 2 (IGRA only approach) where clinical decisions are made solely on the basis of one test result, model 3, the TST plus confirmatory IGRA approach, has an additional step. Immigrants who have had the initial TST will return to have the reaction read. If it is negative, they will be discharged. However if the immigrant is found to have a positive TST, then further, confirmatory, testing is offered with an IGRA (we separately consider both QFN-GIT and T-SPOT.TB). If IGRA testing is accepted by the immigrant, blood is drawn for the IGRA whilst those who refuse are discharged from clinical care.

Assessment and confirmation of positive screening tests

As a result of reading the TST (in the TST only model), or obtaining the IGRA result from the laboratory (in the IGRA only and TST plus confirmatory IGRA models), immigrants will be classified positive or negative. Of these individuals who test positive or negative, fixed proportions are assumed to be HIV positive and negative respectively (*see section* ***Input parameters and probabilities – HIV prevalence*** for details***)***.

Depending on the HIV status of the individual, and the performance of the screening tests (which can be adversely affected by HIV infection[5]), subjects with a positive test result can either be classified true positive (determined by the positive predictive value of the test) or false positive (1-positive predictive value of the test); conversely if the test is negative subjects can be true negative (which is determined by the negative predictive value of the test) or false negative (1-negative predictive value of the test). Amongst those individuals with LTBI (in other words those who test true positive or false negative) it is assumed that fixed proportions are latently infected with a drug-resistant strain with the remainder a drug-sensitive strain. However, it should be noted in routine clinical practice there is no way of being able to differentiate these individuals and therefore their subsequent management (including drug therapy) will be identical.

Individuals who are TST or IGRA positive (both true and false) will go on to be assessed for active TB with chest radiography. As a simplification, in the current model it is assumed that there are no prevalent cases of active TB in the immigrant cohort at the time of screening. In reality, however, a very small proportion of migrants will have active TB although this is extremely rare and in most cases, the chest radiograph/assessment for active TB will be normal.

Uptake of chemoprophylaxis by individuals who test positive

All TST and IGRA positive (both true and false) individuals, where active TB has been excluded, are assumed to have LTBI and so will be offered chemoprophylaxis with three months of rifampicin and isoniazid. Identical proportions of these true positive and false positive individuals will accept therapy with the remainder, who refuse treatment, being discharged. However, the potential outcomes are different. If an immigrant with a true positive LTBI screening test refuses therapy, they can either remain in the LTBI state or progress to active TB disease over the 20 year time horizon of the model; the actual drug sensitivity of the active TB case will depend on the whether the reactivating strain is drug-sensitive or drug-resistant. On the other hand if a false positive individual refuses therapy, as they are actually uninfected with TB, there are no further sequelae.

Drug-induced liver injury amongst individuals who commence chemoprophylaxis

Amongst those individuals who commence chemoprophylaxis, a fixed proportion develop drug-induced liver injury (DILI) even though this is relatively rare (approximately 0.2%[6]) in the age-group we considered (immigrants ≤35 years). In those immigrants who develop DILI, extra costs in the form of additional clinic visits, blood tests and, in a proportion, inpatient admission are required. In a small proportion of those with DILI, there is no resolution of symptoms and the chemoprophylaxis will be discontinued. It is assumed that these individuals will have only completed four weeks of therapy and so chemoprophylaxis is assumed to have no efficacy. Therefore these individuals remain latently infected and thus at future risk of progressing to active TB disease. In most cases, however, the DILI will usually improve and liver function tests will return to normal.

Completion of chemoprophylaxis and efficacy in preventing progression from LTBI to active TB disease

In those individuals where drug-induced liver injury has resolved, or does not occur at all, fixed proportions will complete and not complete the chemoprophylactic regimen.

Complete treatment is 65% efficacious in preventing progression from LTBI to active TB - in those individuals who are truly infected with a drug-sensitive strain.[7] This means that there will be some patients (with drug-sensitive LTBI) who complete therapy but in whom the drug regimen has been ineffectual. As an added layer of complexity it is assumed that the proportion of true-positive immigrants (with drug-sensitive LTBI) in whom DILI has resolved but do not complete therapy will have completed 50% of the drug regimen (ie. 6 weeks) and, based on data suggesting equivalence of 3 months of rifampicin and isoniazid and 6 months isoniazid, we assume, in keeping with previous authors,[8 9] that this reduces the risk of reactivation by 21%.[7] Therefore ineffective therapy, either if treatment has been fully or partially completed, in true positive individuals with drug sensitive LTBI, means that they will remain as true positive, uncured, drug-sensitive LTBI and therefore at risk of progression, over the 20-year time horizon of the model, to active TB disease.

It should be noted that the preceding discussion focuses on the situation where the immigrant is latently infected with a drug-sensitive strain of *Mycobacterium tuberculosis*. However in the model a proportion of those individuals with a true-positive screening test will actually have drug-resistant LTBI. In these individuals although identical proportions either fully or partially complete chemoprophylaxis, it is assumed that the drug regimen has no efficacy in reducing the risk of progressing from LTBI to active TB.

Outcomes for negative screening tests

Immigrants who test negative with TST or IGRA are discharged from clinical care. For true negative individuals no further costs or health effects are incurred. Individuals who are false negative actually have LTBI, either drug-sensitive or drug-resistant, and are at risk of progressing to drug-sensitive or drug-resistant active TB disease (with its attendant costs) respectively over the 20-year time horizon of the model.

Groups at risk of progressing from latent TB to active TB

In the three decision models there are a number of different immigrant groups with LTBI who remain at risk of progressing to active TB disease over the time horizon of the model (see supplementary table 3). It is important to note that the outcomes of these groups are incorporated into the cost-effectiveness models.

Modelling progression of latently infected individuals to active TB

Certain individuals, in the model, with LTBI (supplementary table 3) remain at risk of progressing to active TB disease. We assume that as many of the immigrants will have been remotely infected that the rate of progression from LTBI to active TB disease occurs at a constant hazard (in other words risk per unit time). In the subset of immigrants who are HIV positive a higher annual rate of progression is applied as compared to those immigrants with LTBI who are HIV negative.[10]

In those immigrants with LTBI a proportion will be caused by a drug-sensitive strain whilst the remainder will be due to a drug-resistant strain. The relevance of this is that if, and when, an individual progresses from LTBI to active TB disease, the

resulting active TB disease will either be drug-sensitive or drug-resistant (depending on the original LTBI strain). The development and diagnosis of active TB will result in TB services initiating contact tracing procedures as per national guidance.[2] As a consequence, a fixed number of contacts will be identified amongst whom a fixed number of secondary active TB cases and latent infections will be diagnosed. One area of ongoing controversy is whether drug-resistant TB strains are as transmissible as drug-sensitive strains or whether drug-resistance imparts a fitness cost which reduces their onward transmissibility to close contacts. As there is no consensus on this, in the base case model we adopt the approach taken by Dye[11] and others[12 13] in assuming that drug-resistance imparts little/no fitness cost (in other words the same number of secondary active TB cases and latent infections will be diagnosed in contacts of drug-resistant cases as drug sensitive cases) although in our sensitivity analysis we consider a fitness cost of up to 50%. Secondary cases of LTBI, identified through contact tracing, are managed according to whether the index case was drug-sensitive or drug-resistant. If the index case was drug-sensitive, then latently infected contacts are managed/treated in an identical manner (with identical input parameters) to latently infected immigrants identified through screening. However, as per UK guidelines, latently infected contacts of drug-resistant index cases are not offered chemoprophylaxis.[14] Instead these individuals are closely monitored for clinical features of active TB – at which point appropriate treatment for drug-resistant tuberculosis will be initiated.[14]

A proportion of those individuals who develop active TB disease, either as a result of reactivation from LTBI or as a consequence of being a contact of an index case, will require inpatient management with the remainder treated as outpatients. It is assumed that all subjects with active TB (both drug-sensitive and drug-resistant)

accept treatment and that treatment will be undertaken as per national guidelines.[2] An important consideration is that drug-resistant cases of active TB require a significantly longer duration of treatment and much higher treatment costs.[2 15] As a simplification, compliance with, and cure from, anti-tuberculous therapy were fixed at 100% for both drug-sensitive and drug-resistant cases of active TB. Once an individual has been treated for active TB we assume they will not be re-infected during the course of the 20-year model. In view of the low mortality rate from TB in the UK it is assumed that there is no TB/background mortality during the 20-year horizon of the model.

Input parameters and probabilities

Parameters for the health economic model were drawn from the published literature and the current three-way assessment of LTBI screening methods (see supplementary tables 4 and 5). However, as UK guidelines only recommend treatment for latently infected immigrants aged ≤35 years,[2] specific input parameters (such as the prevalence of LTBI) were only obtained from the subset of tested immigrants who were aged ≤35 years.

HIV prevalence

The model builds on previous work[16] by incorporating the fact that a proportion of the immigrant cohort is assumed to be HIV infected. HIV prevalence data were based on country-specific 2007 UNAIDS/WHO figures (in adults aged 15-49 years).[17] However we did not simply assume that there was an average proportion infected across the whole cohort. Instead, we first stratified countries, and their HIV prevalence, by the TB incidence thresholds considered in the health-economic model. This allowed us to calculate, at each TB incidence threshold, the median HIV

prevalence for those eligible, and not eligible, for LTBI screening (see supplementary table 5). This does, of course, in the absence of empirical data, depend on the assumption that migrants have the same prevalence of HIV as the general population in their countries of origin.

The importance of including HIV infection is that it allows one to model:

1. The differential performance of screening tests (TST and both commercial IGRAs) in HIV infected individuals.
2. The differential progression rate from LTBI to active TB in HIV infected individuals

Drug-resistant tuberculosis

The multiple forms of drug-resistance, including mono-, multi- and extensive-, make it difficult/complex to include all aspects of these subtypes. Therefore we made a simplifying assumption that all drug-resistance is in the form of multi-drug resistance, as this has the most important implications for health outcomes, treatment, and costs. This means that a proportion of the active TB cases identified through port-of-entry screening will be MDR-TB and that a fixed proportion of immigrants with LTBI are infected with a multi drug-resistant strain of *Mycobacterium tuberculosis* where chemoprophylaxis has no effect. If these latently infected individuals progress to active TB, multi-drug resistant active tuberculosis will result – with significantly greater management costs than drug-sensitive TB.

Performance of screening tests

Estimates for the performance (in other words sensitivity and specificity) of the screening tools for LTBI, stratified by HIV seropositivity, were obtained from

contemporary meta-analyses. Importantly, many of these studies based their pooled estimates on culture-confirmed active TB as the reference standard (particularly with respect to sensitivity).

In HIV negative individuals, three recent analyses have concluded that tuberculin skin test sensitivity is 70%, 77% and 65%;[18-20] in the base-case model we used the highest of these estimates (77%) to be conservative with respect to the relative benefits of IGRA vs TST, although we explored a suitably wide range in the sensitivity analyses. In HIV positive individuals TST has reduced sensitivity.[21] However, in the absence of reliable meta-analytical estimates for TST sensitivity in HIV positive individuals, we used the lower bound of the 95% confidence interval for TST sensitivity in HIV negative subjects (71%) from Pai et al[20] as our estimate.

TST specificity, in both HIV negative and positive individuals, is reduced by bacilli Calmette Guerin (BCG) vaccination and cross-reactivity with environmental *Mycobacteria*.[21] A meta-analysis estimated TST specificity is 59% (range 46%-73%) in BCG vaccinated individuals, but significantly higher (97%) in BCG unvaccinated individuals.[20] More recently, Sester and colleagues calculated a lower TST specificity of 75% (95% CI 72-78%).[19] In the current immigrant cohort, most individuals had been BCG vaccinated and therefore TST specificity is likely to have been adversely affected. However we felt that the estimate for BCG vaccinated subjects (59%) from Pai and colleagues was too low whereas the estimate in unvaccinated individuals was too high (97%).[20] In addition, there is the possibility that the effect of BCG vaccination may have waned with age in the immigrants and we therefore elected to use a "middle-ground" estimate of 78% from Sester and colleagues[19] in our base-case model – although, again, a wide range was explored in the sensitivity analyses.

Test performance of the IGRAs was obtained from recent meta-analyses, although many of these studies have come to widely differing conclusions about IGRA performance. In HIV negative individuals, meta-analyses have calculated that the sensitivity of QuantiFERON Gold in-tube and T-SPOT.TB is in the range of 67-84% and 81-89% respectively.[18-20] In the base-case model we used sensitivity estimates from Diel and colleagues who calculated QFN-GIT and T-SPOT.TB sensitivity to be 84% and 89% respectively.[18] In HIV positive individuals, fewer studies have been conducted. However, a recent systematic review and meta-analysis from Cattamanchi et al estimated that in HIV positive individuals, QFN-GIT sensitivity was 61% (95% CI 47-75%) whilst T-SPOT.TB sensitivity was 72% (95% CI 62-81);[22] in view of the prevailing opinion that IGRAs have a superior sensitivity to TST in HIV positive individuals we elected to use the upper bound of the 95% confidence intervals in the base-case model although we explored a wide range in the sensitivity analysis.

IGRAs have been found in most meta-analyses to have greater specificity than TST.[18 20] and seem to be less adversely affected by prior BCG vaccination.[21] In the base-case model we used specificity values of 99% and 86% for QFN-GIT and T-SPOT.TB respectively.[18] However, in view of ongoing debate about the specificity of IGRAs we examined a suitably wide range in the sensitivity analysis.

Prevalence of LTBI

One of the key, but also most poorly understood, model parameters is the prevalence of LTBI in immigrants. Whilst previous authors have estimated an overall prevalence of infection when undertaking economic modelling, this does not take account of differences by TB burden in the countries of origin. In the current analysis we base

the estimates for LTBI prevalence (stratified by the threshold at which screening is instigated) on empirical data from the immigrant cohort that we have studied.

In order to avoid overestimating LTBI prevalence, we based all prevalence estimates only on those immigrants who were aged ≤35 years of age (excluding immigrants aged >35 years and had been tested in parallel with either all three screening tools (in other words TST, QFN-GIT and T-SPOT.TB) or two screening tools (in other words TST/QFN-GIT or QFN-GIT/T-SPOT.TB – no subjects were actually tested with TST/T-SPOT.TB). We defined "actual positives" as the following:

1. Individuals who tested positive with all three screening tools where all three had been undertaken.
2. Individuals who tested positive with two out of three screening tools where all three had been undertaken.
3. Individuals who tested positive with both screening tools where two had been undertaken.

The results for these 148 individuals, stratified by TB incidence screening thresholds, are set out in supplementary table 6.

Using estimates on HIV prevalence we estimated the proportion of the tested cohort (at each incidence threshold) that was HIV positive/negative. We could therefore calculate (at each incidence threshold) the proportion of individuals that screened positive (as defined in points 1-3 above) stratified by whether they were HIV negative and positive. However it is incorrect to simply conclude that the proportion positive at each incidence threshold is the actual prevalence of LTBI as this assumes

that the screening tools used are 100% sensitive and 100% specific. As the proportion positive is the result of an algorithm using two or three screening tools the sensitivity and specificity of the algorithm using multiple tests in parallel will be different than if a single test was used (and will also differ according to HIV status as the screening tools are acknowledged to perform differently in HIV positive and HIV negative individuals).

At each incidence threshold it is easiest to consider that there are three separate groups (those triple tested with TST/QFN-GIT/T-SPOT.TB, those dual tested with TST/QFN-GIT and those dual tested with QFN-GIT/T-SPOT.TB – all stratified by HIV status) in whom LTBI prevalence needs to be calculated separately.

To calculate LTBI prevalence we must first define the sensitivity and specificity of the diagnostic algorithm using screening tools in parallel. Amongst those individuals who were tested with all three screening tools (TST/QFN-GIT/T-SPOT.TB), we defined actual positives to be those individuals who were triple or dual positive – separately for HIV negative and positive individuals. The sensitivity of this algorithm, that requires two or three of three test results to be positive to regard the overall result as positive, is defined in equation 1.

$$Sensitivity_{triple\_tested} = (Sens_{TST} \times Sens_{QFN\text{-}GIT}) + (Sens_{TST} \times Sens_{TSPOT.TB}) + (Sens_{QFN\text{-}GIT} \times Sens_{TSPOT.TB}) - 2(Sens_{TST} \times Sens_{QFN\text{-}GIT} \times Sens_{TSPOT.TB}) \quad \text{(Equation 1)}$$

The specificity of an algorithm that requires two or three of three test results to be positive to regard the overall result as positive is defined in equation 2.

$$Specificity_{triple\ tested} = (Spec_{TST} \times Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) + (Spec_{TST} \times Spec_{QFN\text{-}GIT}) + (Spec_{TST} \times Spec_{T\text{-}SPOT.TB}) + (Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) - 3(Spec_{TST} \times Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) \quad \text{(Equation 2)}$$

In those individuals who were tested with two screening tools (TST/QFN-GIT or QFN-GIT/T-SPOT.TB), where actual positives were defined as those individuals who were dual positive, the combined sensitivity of an algorithm that requires both test results to be positive to regard the overall result as positive can be represented by equations 3 (for those individuals tested by both TST and QFN-GIT) and 4 (for those individuals tested by both QFN-GIT and T-SPOT.TB). [23]

$$Sensitivity_{dualtestedTSTandQFN\text{-}GIT} = (Sens_{TST} \times Sens_{QFN\text{-}GIT}) \quad \text{(Equation 3)}$$

$$Sensitivity_{QFN\text{-}GITandT\text{-}SPOT.TB} = (Sens_{QFN\text{-}GIT} \times Sens_{T\text{-}SPOT.TB}) \quad \text{(Equation 4)}$$

The specificity of this algorithm (which requires both test results to be positive to regard the overall result as positive) regards individuals who test negative by one/both tools to be classified negative (see equations 5 and 6).

$$Specificity_{dualtestedTSTandQFN\text{-}GIT} = Spec_{TST} + Spec_{QFN\text{-}GIT} - (Spec_{TST} \times Spec_{QFN\text{-}GIT}) \quad \text{(Equation 5)}$$

$$Specificity_{dualtestedQFN\text{-}GITandT\text{-}SPOT.TB} = Spec_{QFN\text{-}GIT} + Spec_{T\text{-}SPOT.TB} - (Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) \quad \text{(Equation 6)}$$

Now the sensitivities and specificities of the algorithms have been defined, the next step is to separately calculate the prevalence of LTBI for each of the three groups

(those triple tested with TST/QFN-GIT/T-SPOT.TB, those dual tested with TST/QFN-GIT and those dual tested with QFN-GIT/T-SPOT.TB) at each incidence screening threshold. For those individuals who were triple, and dual, tested the prevalence of LTBI (at each incidence threshold) was calculated using equations 7, 8 and 9 respectively.

$$\text{PrevalenceofLTBI}_{\text{tripletested}} = \frac{\text{Proppositiveresult}_{\text{dualortriplepositiveintripletested}} - (1\text{-Specificity}_{\text{tripletested}})}{\text{Sensitivity}_{\text{tripletested}} - (1\text{-Specificity}_{\text{tripletested}})} \quad \text{(Equation 7)}$$

$$\text{PrevalenceofLTBI}_{\text{dualtestedQFN-GITandT-SPOT.TB}} = \frac{\text{Proppositiveresult}_{\text{dualpositiveindualtestedQFN-GITandT-SPOT.TB}} - (1\text{-Specificity}_{\text{dualtestedQFN-GITandT-SPOT.TB}})}{\text{Sensitivity}_{\text{dualtestedQFN-GITandT-SPOT.TB}} - (1\text{-Specificity}_{\text{dualtestedQFN-GITandT-SPOT.TB}})} \quad \text{(Equation 8)}$$

$$\text{PrevalenceofLTBI}_{\text{dualtestedTSTandQFN-GIT}} = \frac{\text{Proppositiveresult}_{\text{dualpositiveindualtestedTSTandQFN-GIT}} - (1\text{-Specificity}_{\text{dualtestedTSTandQFN-GIT}})}{\text{Sensitivity}_{\text{dualtestedTSTandQFN-GIT}} - (1\text{-Specificity}_{\text{dualtestedTSTandQFN-GIT}})} \quad \text{(Equation 9)}$$

Following calculation of LTBI prevalence for each of the three groups separately as outlined above, we then calculated, at each incidence threshold, a combined weighted prevalence. The weighted LTBI prevalence, at each incidence threshold, was the prevalence that we used for the remainder of the analysis when exploring the impact of screening with different diagnostic tests.

In the single screening approaches (in other words TST alone, QFN-GIT alone and T-SPOT.TB alone) we used the weighted prevalence of LTBI (at each incidence threshold) to calculate the probability of a positive result (at each incidence threshold) for each screening test using equations 10a, 10b and 10c.

$$\text{Probability of positive result}_{\text{QFN-GIT}} = \text{Sens}_{\text{QFN-GIT}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{QFN-GIT}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10a)}$$

$$\text{Probability of positive result}_{\text{T-SPOT.TB}} = \text{Sens}_{\text{T-SPOT.TB}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{T-SPOT.TB}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10b)}$$

$$\text{Probability of positive result}_{\text{TST}} = \text{Sens}_{\text{TST}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{TST}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10c)}$$

The proportion of those who test positive by these screening tests who are actually truly infected (the positive predictive value) is given by equations 11a, 11b and 11c:

$$\text{Probability of true positive result}_{TST} = \frac{\text{Sens}_{TST} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{TST}} \quad \text{(Equation 11a)}$$

$$\text{Probability of true positive result}_{QFN\text{-}GIT} = \frac{\text{Sens}_{QFN\text{-}GIT} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{QFN\text{-}GIT}} \quad \text{(Equation 11b)}$$

$$\text{Probability of true positive result}_{T\text{-}SPOT.TB} = \frac{\text{Sens}_{T\text{-}SPOT.TB} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{T\text{-}SPOT.TB}} \quad \text{(Equation 11c)}$$

The probability of a negative result for each of the screening tests is given by equations 12a, 12b and 12c:

$$\text{Probability of negative result}_{TST} = \text{Spec}_{TST} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{TST}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12a)}$$

$$\text{Probability of negative result}_{QFN\text{-}GIT} = \text{Spec}_{QFN\text{-}GIT} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{QFN\text{-}GIT}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12b)}$$

$$\text{Probability of negative result}_{T\text{-}SPOT.TB} = \text{Spec}_{T\text{-}SPOT.TB} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{T\text{-}SPOT.TB}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12c)}$$

Of those individuals who test negative, the proportion who are truly uninfected – the negative predictive value – is given by equations 13a, 13b and 13c:

$$\text{Probability of true negative result}_{TST} = \frac{\text{Spec}_{TST} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{TST}} \quad \text{(Equation 13a)}$$

$$\text{Probability of true negative result}_{QFN\text{-}GIT} = \frac{\text{Spec}_{QFN\text{-}GIT} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{QFN\text{-}GIT}} \quad \text{(Equation 13b)}$$

$$\text{Probability of true negative result}_{T\text{-}SPOT.TB} = \frac{\text{Spec}_{T\text{-}SPOT.TB} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{T\text{-}SPOT.TB}} \quad \text{(Equation 13c)}$$

Testing all patients with more than one test is not the same as testing patients with one test and then confirming positive results with a second, different, test. In the two-step strategies (TST followed by confirmatory QFN-GIT or T-SPOT.TB if TST positive) it is important to note that the prevalence of infection is not the weighted prevalence but the proportion who test true positive by TST (positive predictive value) amongst all TST positives. The probability of positive IGRA results (in the two-step strategy where TST is positive) is given by equations 14a and 14b (for QFN-GIT and T-SPOT.TB respectively) and the probability of negative IGRA results by equations 15a and 15b (for QFN-GIT and T-SPOT.TB respectively).

$$\text{Probability of positive result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Sens}_{\text{QFN-GIT}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}} + (1\text{-Spec}_{\text{QFN-GIT}}) \times (1\text{- Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 14a)

$$\text{Probability of positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Sens}_{\text{T-SPOT.TB}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}} + (1\text{-Spec}_{\text{T-SPOT.TB}}) \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 14b)

$$\text{Probability of negative result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Spec}_{\text{QFN-GIT}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}}) + (1\text{-Sens}_{\text{QFN-GIT}}) \times (\text{Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 15a)

$$\text{Probability of negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Spec}_{\text{T-SPOT.TB}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}}) + (1\text{-Sens}_{\text{T-SPOT.TB}}) \times (\text{Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 15b)

From the probability of positive and negative results, we can then calculate the positive and negative predictive values for QFN-GIT and T-SPOT.TB (for the dual step screening approach) (equations 16a, 16b, 17a and 17b):

$$\text{Probability of true positive result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Sens}_{\text{QFN-GIT}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}}$$

$$\text{Probability of positive result}_{\text{confirmatoryQFN-GITifTSTpositive}} \qquad \text{(Equation 16a)}$$

$$\text{Probability of true positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Sens}_{\text{T-SPOT.TB}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}}$$

$$\text{Probability of positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} \qquad \text{(Equation 16b)}$$

$$\text{Probability of true negative result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Spec}_{\text{QFN-GIT}} \times (\text{1-Prevalence of LTBI}_{\text{TSTpositive}})$$

$$\text{Probability of negative result}_{\text{confirmatoryQFN-GITifTSTpositive}} \qquad \text{(Equation 17a)}$$

$$\text{Probability of true negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Spec}_{\text{T-SPOT.TB}} \times (\text{1-Prevalence of LTBI}_{\text{TSTpositive}})$$

$$\text{Probability of negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} \qquad \text{(Equation17b)}$$

Progression rate from latent tuberculosis infection to active tuberculosis disease

One of the most poorly understood parameters is the rate at which latently infected immigrants progress to active TB disease. Immigrants from high-TB-burden countries with LTBI may be similar to recently infected contacts of smear-positive tuberculosis index cases in terms of having a high rate of progression, as they are likely to have been repeatedly exposed, and potentially infected, by infectious individuals. Literature reports are conflicting: a study of a cohort of Southeast Asian refugees arriving in Australia found a relatively low progression rate of 6.7% over 40 years[24] whereas a more recent UK study, predominantly of immigrants from the Indian Subcontinent, calculated that over 13% of TST positive, untreated, immigrants developed active TB over a 10-year period.[25]

A detailed review of progression rates (albeit based on TST data) has been conducted by Horsburgh.[10] In this seminal paper he estimated that in 16-35 year-olds with a non-recently converted TST of >15mm that the annual risk of reactivation was 0.19%.[10] If the skin test was >15mm and there was recent conversion then the annual risk of reactivation would increase to 0.56%.[10] We therefore, conservatively, assumed that 5% of the HIV negative cohort with LTBI, in the absence of chemoprophylaxis, would progress to active TB over the 20 year time horizon of the model, i.e. the progression rate is approximately 0.0026 per year (using the formula $-ln\ (1-p)/t$ where p is the proportion that progress over time t (in years). By contrast, HIV-positive individuals have impaired cell-mediated immunity and therefore experience a much higher rate of progression to active TB disease. In the Horsburgh review, the lifetime risk for an individual aged 16-35 with HIV infection is 73-83% (equating to an annual rate of 0.024 – assuming a further 55 years of life) and the relative risk of HIV infected (versus HIV uninfected) individuals progressing to active TB was

approximately 10 (per year). Therefore in the base case analysis we assumed that the annual rate of progression for immigrants with HIV infection was approximately 0.026 per year which equates to an estimated 40% of HIV positive immigrants progressing from LTBI to active TB over a 20 year time horizon. This figure takes account, to some degree, of HAART mitigating progression in the HIV-positive cohort. However, we fully acknowledge that there is a lack of consensus on progression rates (in both HIV negative and positive individuals) and thus assessed a suitably wide range of progression rates in the sensitivity analysis.

Costs

Component costs considered were primarily direct costs obtained from economic evaluations conducted for the UK NICE TB guidelines,[1] and its forthcoming update, uplifted to 2010 prices (see supplementary tables 7 and 8 for costs) using the Consumer Prices Index. In the present analysis, indirect costs such as transportation and loss of earnings by patients were not considered. Both costs and non-monetary health effects were discounted at an annual rate of 3.5%, which reflects UK Treasury and NICE recommendations.[2 26]

Effects

The main effects considered in the model were the number of cases of active tuberculosis that would be predicted to occur over the 20-year time horizon and the number needed to treat (the number of individuals with LTBI that need to be treated) to prevent one case of active TB.

Cost-effectiveness

As recommended by the Panel of Cost-effectiveness in Health and Medicine, the comparative performance of the different screening protocols was measured using the Incremental Cost-Effectiveness Ratio (ICER – see equation 18) which quantifies the trade-offs between switching from one competing, mutually-exclusive, intervention to another.[27] The higher the ICER, the less cost-effective the intervention is.

$$ICER = \frac{Cost_{screeningprotocolA} - Cost_{screeningprotocolB}}{Effectiveness_{screeningprotocolA} - Effectiveness_{screeningprotocolB}} \quad \text{(Equation 18)}$$

Sensitivity analysis

Parameter uncertainty can potentially affect the results of the cost-effectiveness analysis. A one-way sensitivity analysis was therefore undertaken to explore the impact that changes in all key parameters and costs had on the number of cases of active TB occurring over 20 years, the costs and the associated ICERs.

Supplementary results

Concordance between screening tests and impact of prior BCG vaccination

Figure 1 outlines the results amongst those subjects who were tested with all three screening tools whilst supplementary table 10 illustrates the pair-wise analysis of test results. In general, test agreement between TST and both IGRAs was fair to moderate. Using the stratified (κ 0.30, 95% CI 0.15-0.46, p<0.0001) and unstratified (κ 0.29, 95% CI 0.15-0.42, p<0.0001) TST cut-offs, levels of concordance between TST and QFN-GIT were fair. Likewise, agreement between TST and T-SPOT.TB was fair at the stratified TST cut-off (κ 0.29, 95% CI 0.11-0.47, p=0.0002) but improved using the unstratified cut-off (κ 0.38, 95% CI 0.23-0.54, p<0.0001).

When subdivided by BCG vaccination status, agreement at the unstratified 10mm TST cut-off with both IGRAs was higher for BCG unvaccinated (κ 0.55, 95% CI 0.17-0.74, p=0.0014 for QFN-GIT and κ 0.41, 95% CI 0.11-0.65, p=0.02 for T-SPOT.TB) than BCG vaccinated individuals (κ 0.26, 95% CI 0.17-0.35, p=0.0001 for QFN-GIT and κ 0.39, 95% CI 0.28-0.50, p<0.0001 for T-SPOT.TB). Discordancy, in the BCG vaccinated cohort, most commonly took the form of TST positive/IGRA negative results (TST positive/QFN-GIT negative in 39 of 45 discordant pairs; TST positive/T-SPOT.TB negative in 26 of 29 discordant pairs).

In contrast, overall agreement between QFN-GIT and T-SPOT.TB was higher (κ 0.58, 95% CI 0.51-0.67, p<0.0001) although it was interesting to note that concordance appeared to be lower for BCG unvaccinated (κ 0.43, 95% CI 0.16-0.68, p=0.008) than BCG vaccinated (κ 0.60, 95% CI 0.47-0.70, p<0.0001 individuals.

Health-economic analysis

Strategies which supplemented screening for LTBI with port-of-entry chest radiography for immigrants arriving from countries with TB incidence >40 cases per 100,000 prevented a modest number of additional cases of active TB but also incurred substantial extra costs as compared to those strategies which only employed screening for LTBI (in other words no chest radiography undertaken at port-of-entry).

Although having no LTBI screening in place was less expensive than any screening strategy for LTBI, it also resulted in more cases of active TB over the time course of the model. With reference to the specific LTBI screening tools used, at any screening threshold, single-step T-SPOT.TB was consistently the most expensive screening protocol followed by TST only and single-step QFN-GIT – both of which had relatively similar overall costs. However, single-step T-SPOT.TB was also the most effective strategy, resulting in the fewest cases of active TB, followed by QFN-GIT and then TST, which was the least effective of the single testing protocols due to T-SPOT.TB having the highest sensitivity. By contrast the dual TST plus confirmatory IGRA (QFN-GIT or T-SPOT.TB) approaches were the least expensive protocols (TST plus QFN-GIT less expensive than TST plus T-SPOT.TB) but resulted in the most cases of active TB (TST plus T-SPOT.TB prevented more cases than TST plus QFN-GIT), due to the low sensitivity of TST.

For all screening tools, irrespective of whether port-of-entry CXR was undertaken or not, costs increased as the threshold at which immigrants were eligible to be screened shifted downwards (table 3) although, in general, there was also a concomitant increase in the number of cases prevented (as compared to no screening).

Sensitivity analysis

Varying several parameters affected the ICER estimates for each of the strategies although, in general, the order of most cost-effective strategies remained relatively unaffected (supplementary tables 11 and 12). Natural history parameters which particularly impacted on ICER values and the order of the most cost-effective strategies were the cohort prevalence of LTBI and HIV as well as the progression rate of latently infected individuals to active TB. Higher values for all of these parameters reduced ICER values (in other words increased cost-effectiveness) and made it more cost-effective to screen at lower TB incidences (40/100000 per year) with single-step QFN-GIT remaining the most cost-effective tool.

The test characteristic which particularly affected the outputs of the cost-effectiveness model was the diagnostic specificity of the different screening tests. Reductions in specificity resulted in higher ICER estimates and, for QFN-GIT, actually resulted in the test becoming a dominated strategy and replaced by single-step T-SPOT.TB at an incidence of 250/100000 per year as the most cost-effective screening option. Programmatic factors, such as the proportion of immigrants commencing, and completing, chemoprophylaxis also affected cost-effectiveness – with reductions in both parameters increasing ICER estimates (in other words making screening less cost-effective). In terms of cost parameters, ICER estimates were most sensitive to changes in the costs of screening for LTBI or evaluating those who screened positive with reductions significantly reducing ICER values (i.e. increasing cost-effectiveness).

Supplementary table 1. Model assumptions of the health-economic model

Assumption
Immigrants are screened for LTBI once at the start of the time horizon
Tuberculin skin test positivity is classified as per UK guidelines (≥6mm in BCG unvaccinated and ≥15mm in BCG vaccinated
All IGRA results are determinate and no repeat testing is required
The proportion of immigrants with HIV is reflective of the HIV prevalence in their country of origin
A proportion of immigrants with latent tuberculosis infection are infected by a resistant strain of *Mycobacterium tuberculosis*
A proportion of active tuberculosis cases are drug-resistant
Amongst those individuals identified with LTBI and treated with chemoprophylaxis, a three month course of rifampicin and isoniazid is considered to have equivalent efficacy to six months of isoniazid[28]
Individuals who commence chemoprophylaxis and subsequently develop drug-induced liver injury which does not resolve are assumed to only complete 4 weeks of therapy which affords no reduction in the risk of progressing from LTBI to active TB
No individuals who develop drug induced liver injury die due to this adverse effect
Equal proportions of HIV negative and positive immigrants develop drug-induced liver injury from chemoprophylaxis
Chemoprophylaxis will have no efficacy in those immigrants who have a resistant strain causing their LTBI
An individual with LTBI who has completed successful chemoprophylaxis is assumed to have cleared the infection with *Mycobacterium tuberculosis* and will not experience any further outcomes during the time course of the model (such as reinfection)
An individual who does not have LTBI on arrival in the UK does not become infected during the time-period considered by the model.
Drug sensitive and drug resistant strains are assumed to be equally transmissible (in other words drug resistance does not result in any fitness cost)
There is no HIV acquisition within the cohort during the time horizon of the model
Data on the test performance of the IGRA was based on the most recent meta-analysis obtained from meta-analyses where sensitivity was calculated using culture-confirmed active TB as the reference standard whilst specificity was calculated from BCG-vaccinated individuals at low risk of infection.[29]
Point estimates for test sensitivity were assumed to be different for HIV positive individuals
All individuals diagnosed with drug-sensitive active tuberculosis are assumed to accept treatment for active TB and to complete the 6 month course of drugs
All individuals diagnosed with drug-resistant active tuberculosis are assumed to accept treatment for active TB and to complete the course of drugs

Supplementary table 2. Screening tools and thresholds considered in the health economic analysis

Chest radiography undertaken at port of entry	Screening for latent tuberculosis infection	
	Screening tool	Screening threshold for immigrants (number of cases of TB per 100,000 per year)[1]
Yes	Tuberculin skin test	40
Yes	Tuberculin skin test	100
Yes	Tuberculin skin test	150
Yes	Tuberculin skin test	200
Yes	Tuberculin skin test	250
Yes	Tuberculin skin test	300
Yes	Tuberculin skin test	350
No	Tuberculin skin test	40
No	Tuberculin skin test	100
No	Tuberculin skin test	150
No	Tuberculin skin test	200
No	Tuberculin skin test	250
No	Tuberculin skin test	300
No	Tuberculin skin test	350
Yes	T-SPOT.TB	40
Yes	T-SPOT.TB	100
Yes	T-SPOT.TB	150
Yes	T-SPOT.TB	200
Yes	T-SPOT.TB	250
Yes	T-SPOT.TB	300
Yes	T-SPOT.TB	350
No	T-SPOT.TB	40
No	T-SPOT.TB	100
No	T-SPOT.TB	150
No	T-SPOT.TB	200
No	T-SPOT.TB	250
No	T-SPOT.TB	300
No	T-SPOT.TB	350
Yes	QuantiFERON Gold in-tube	40
Yes	QuantiFERON Gold in-tube	100
Yes	QuantiFERON Gold in-tube	150
Yes	QuantiFERON Gold in-tube	200
Yes	QuantiFERON Gold in-tube	250
Yes	QuantiFERON Gold in-tube	300
Yes	QuantiFERON Gold in-tube	350
No	QuantiFERON Gold in-tube	40
No	QuantiFERON Gold in-tube	100
No	QuantiFERON Gold in-tube	150
No	QuantiFERON Gold in-tube	200
No	QuantiFERON Gold in-tube	250
No	QuantiFERON Gold in-tube	300
No	QuantiFERON Gold in-tube	350
Yes	Tuberculin skin test + T-SPOT.TB	40
Yes	Tuberculin skin test + T-SPOT.TB	100
Yes	Tuberculin skin test + T-SPOT.TB	150
Yes	Tuberculin skin test + T-SPOT.TB	200
Yes	Tuberculin skin test + T-SPOT.TB	250
Yes	Tuberculin skin test + T-SPOT.TB	300
Yes	Tuberculin skin test + T-SPOT.TB	350
No	Tuberculin skin test + T-SPOT.TB	40
No	Tuberculin skin test + T-SPOT.TB	100
No	Tuberculin skin test + T-SPOT.TB	150
No	Tuberculin skin test + T-SPOT.TB	200
No	Tuberculin skin test + T-SPOT.TB	250
No	Tuberculin skin test + T-SPOT.TB	300
No	Tuberculin skin test + T-SPOT.TB	350
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	40
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	100
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	150
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	200
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	250
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	300
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	350
No	Tuberculin skin test + QuantiFERON Gold in-tube	40
No	Tuberculin skin test + QuantiFERON Gold in-tube	100

No	Tuberculin skin test + QuantiFERON Gold in-tube	150
No	Tuberculin skin test + QuantiFERON Gold in-tube	200
No	Tuberculin skin test + QuantiFERON Gold in-tube	250
No	Tuberculin skin test + QuantiFERON Gold in-tube	300
No	Tuberculin skin test + QuantiFERON Gold in-tube	350

Footnote

[1]Where the tuberculin skin test and IGRA are shown, the IGRA is used to confirm a positive result

Supplementary table 3. Description of immigrant groups in the model who have LTBI and are at risk of progressing to active TB disease

Groups with latent TB infection who remain at risk of progressing to active TB disease	Applies to which models
Immigrants with LTBI who are not eligible to be screened as they originate from a country with a TB incidence which does not meet the screening criteria	1,2,3
Immigrants with LTBI who are eligible to be screened but refuse the TST screening test	1,3
Immigrants with LTBI who are eligible to be screened but refuse the IGRA screening test (where it is used as the only screening tool)	2
Immigrants with LTBI who are eligible to be screened, have had the initial TST administered and read but refuse the confirmatory IGRA	3
Immigrants with LTBI who are screened by TST but do not return to have the size of induration read	1,3
Immigrants with LTBI who screen true positive with TST or IGRA but decline to commence chemoprophylaxis	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, fully complete therapy but it is not effective	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, partially complete therapy but it is not effective	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, start chemoprophylaxis but develop drug-induced liver injury which does not resolve and so they must stop the therapy (which is assumed to have no efficacy in this short period of time)	1,2
Immigrants with LTBI but who actually test false-negative with TST	1,3
Immigrants with LTBI but who actually test false-negative with IGRA (where it is used as the only screening tool)	2
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA but decline to commence chemoprophylaxis	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, fully complete therapy but it is not effective	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, partially complete therapy but it is not effective	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, start chemoprophylaxis but develop drug-induced liver injury which does not resolve and so they must stop the therapy (which is assumed to have no efficacy in this short period of time)	3
Immigrants with LTBI but who actually test false-negative with the confirmatory IGRA after the initial TST is positive	3

Supplementary table 4. Parameters used as input values in the decision model

Parameter	Base case	Range explored	References
Proportion of immigrants ≤35 with latent tuberculosis	0.13	0.1-0.4	Current study
Prevalence of HIV infection	Varies (supplementary table 5)	Varies (supplementary table 5)	17
Proportion undergoing screening	Varies (supplementary figures 6 and 7)	Varies (supplementary figures 6 and 7)	Current study
Prevalence of multi-drug resistant tuberculosis	0.01	0.005-0.02	30
Specificity of tuberculin skin test in HIV negative individuals	0.78	0.70-0.90	19
Sensitivity of tuberculin skin test in HIV negative individuals	0.77	0.65-0.82	19 20
Specificity of QuantiFERON Gold in-tube in HIV negative individuals	0.99	0.75-1.0	18 29
Sensitivity of QuantiFERON Gold in-tube in HIV negative individuals	0.84	0.75-0.87	18 19
Specificity of T-SPOT.TB in HIV negative individuals	0.86	0.72-0.95	18 29
Sensitivity of T-SPOT.TB in HIV negative individuals	0.89	0.78-0.91	18 19
Specificity of tuberculin skin test in HIV positive individuals	0.78	0.70-0.90	19
Sensitivity of tuberculin skin test in HIV positive individuals	0.71	0.61-0.75	19 20
Specificity of QuantiFERON Gold in-tube in HIV positive individuals	0.99	0.75-1.0	18 29
Sensitivity of QuantiFERON Gold in-tube in HIV positive individuals	0.75	0.61-0.78	18 22
Specificity of T-SPOT.TB in HIV positive individuals	0.86	0.72-0.95	18-20
Sensitivity of T-SPOT.TB in HIV positive individuals	0.81	0.62-0.83	18 22
Proportion of new-entrants from countries with TB incidence >40/100000 p.a. undergoing chest-radiography at port-of entry	0.4	0.3-0.6	31-33
Proportion of new-entrants from countries with TB incidence <40/100000 p.a. undergoing chest-radiography at port-of entry	0.0	Fixed	32
Proportion of new-entrants from countries with TB incidence >40/100000 p.a. with pre-existing active TB (ie. prevalent cases)	0.0035	0.001-0.005	31-33
Proportion of new-entrants from countries with TB incidence <40/100000 p.a. with pre-existing active TB (ie. prevalent cases)	0.0010	0.0005-0.005	31 33
Proportion of new-entrants accepting tuberculin skin test administration	0.81	0.6-1.0	Current study
Proportion of new-entrants returning to have tuberculin skin test read	0.94	0.6-1.0	Current study
Proportion of new-entrants accepting QuantiFERON Gold in-tube	0.99	0.6-1.0	Current study
Proportion of new-entrants accepting QuantiFERON Gold in-tube	0.99	0.6-1.0	Current study
Proportion of IGRA positive new entrants accepting chemoprophylaxis	0.95	0.3-1.0	14
Proportion of IGRA positive new entrants completing chemoprophylaxis	0.85	0.3-1.0	14
Duration of chemoprophylaxis with rifampicin and isoniazid (course completed)	3 months	3 months	2
Duration of chemoprophylaxis with rifampicin and isoniazid (course partially completed)	1.5 months	1.5 months	Assumed
Efficacy of 3 months of Rifampicin and Isoniazid	0.65	0.5-0.8	7 34
Efficacy of 1.5 months of Rifampicin and isoniazid (partial chemoprophylaxis)	0.21	0.1-0.3	7
Efficacy of chemoprophylaxis in immigrants with drug-resistant latent tb infections	0.0	Fixed	Assumed
Proportion of immigrants receiving chemoprophylaxis who develop drug-induced liver injury	0.002	0.001-0.003	6
Proportion of TST or IGRA positive, untreated, HIV negative individuals progressing to active TB (post-exposure TB) over 20 years	0.05	0.025-0.15	10
Proportion of TST or IGRA positive, untreated, HIV positive individuals progressing to active TB (post-exposure TB) over 20 years	0.40	0.20-0.80	10
Proportion of individuals with active TB accepting treatment	1.0	Fixed	Assumed
Proportion of individuals with active TB completing therapy	1.0	Fixed	Assumed
Proportion of individuals with active TB cured	1.0	Fixed	Assumed
Annual discount rate	0.035	0.035	26

Supplementary table 5. Median HIV prevalence amongst immigrants eligible and not eligible for screening at each TB incidence threshold

Screening threshold for immigrants (number of cases of TB/100,000 per year)[1]	HIV prevalence amongst immigrants eligible to be screened at this TB incidence threshold	HIV prevalence amongst immigrants not eligible to be screened at this TB incidence threshold
All[2]	0.004	0
40	0.008	0.002
100	0.013	0.002
150	0.018	0.002
200	0.021	0.002
250	0.031	0.002
300	0.041	0.002
350	0.041	0.003

Footnotes

[1]Refers to TB incidence in the country of origin

[2]Data shown for illustrative/comparative purposes as this threshold was not included in the economic analysis

Supplementary table 6. Test results for immigrants aged ≤35 years who were tested with either all three or two out of three screening tools

Screening threshold	Individuals who were triple tested					Individuals who were dual tested only					
	TST plus QFN plus T-SPOT.TB undertaken					TST plus QFN		TST plus T-SPOT.TB[1]		QFN plus TSPOT	
	Number tested	Number triple positive	Number dual positive: TST plus QFN	Number dual positive: TST plus T-SPOT.TB	Number dual positive: QFN plus T-SPOT.TB	Number tested	Number dual positive: TST plus QFN	Number tested	Number dual positive: TST plus T-SPOT.TB	Number tested	Number dual positive: QFN plus T-SPOT.TB
Screen all	86	7	1	2	3	37	3	0	0	25	3
40	84	7	1	2	3	35	3	0	0	25	3
100	61	6	1	1	2	18	1	0	0	21	3
150	44	6	1	0	2	9	1	0	0	17	3
200	29	4	0	0	1	6	1	0	0	12	3
250	10	3	0	0	1	3	1	0	0	5	2
300	2	0	0	0	0	2	0	0	0	3	2
350	2	0	0	0	0	2	0	0	0	2	1

Footnotes

[1]There were no immigrants aged ≤35 years who were dual-tested with TST and T-SPOT.TB.

Supplementary table 7. Costs (2010 pounds sterling) associated with diagnosis and treatment of active TB

Active TB cases	Base case	Range[1]	Reference(s)
Contact tracing			
Contact tracing per contact (£)	482	241-723	[14]
Mean number of contacts examined per primary case	6.5	3.25-10	[14]
Mean number of secondary active TB cases per index case (drug sensitive and drug resistant)	0.24	0.1-0.3	[35 36]
Mean number of latent infections per primary case of active TB disease (drug sensitive and drug resistant)	0.18	0.09-0.27	[36]
Proportion reduction in mean number of secondary active TB cases per index case (if identified through chest x-ray screening)	0.5	0.25-0.75	[37]
Proportion reduction in mean number of latent infections per primary case of active TB disease (if identified through chest x-ray screening)	0.5	0.25-0.75	[37]
Inpatient care (drug sensitive tuberculosis)			
Cost of inpatient episode for acute TB (£ per episode)	4012.97 (2006.5-6019.46)	2006.5-6019.5	[38 39]
Proportion of patients with acute TB who are admitted	0.53 (0.265-0.795)	0.25-0.75	[14]
Cost of inpatient care (£ per active case)	2126.87		Calculated
Cost of tests (drug sensitive tuberculosis)			
Costs of culture test (£ per test)	10		[14 38]
Costs of chest X-ray (£ per X-ray)	28		[14 38]
Costs of liver functions tests (£ per test)	1		[14 38]
Culture tests per case treated (number)	4		[14 38]
Chest X-ray per case treated (number)	2		[14 38]
Liver functions tests per case treated (number)	4		[14 38]
Total cost of tests (£ per TB case treated)	100[2]		Calculated
Cost of chemotherapy (drug sensitive tuberculosis)			
Rifampicin (£ per month)	10.76		[14 38]
Isoniazid (£ per month)	17.87		[14 38]
Pyrazinamide (£ per month)	6.88		[14 38]
Ethambutol (£ per month))	18.48		[14 38]
Duration of rifampicin (months)	6		[14]
Duration of isoniazid (months)	6		[14]
Duration of pyrazinamide (months)	2		[14]
Duration of ethambutol (months)	2		[14]
Total cost of drugs (drug sensitive TB)	222	111-333	Calculated
Outpatient care (drug sensitive tuberculosis)			
Cost of outpatient consultation (first visit)	230		Local tariff
Cost of outpatient consultation (follow-up visit)	104		[14 38]
Cost of TB Nurse home visit	22		[14 38 40]
Number of outpatient clinic visits per case treated	4		[14 38]
Visits from TB Nurse per case treated	6		[14 38]
Total costs of non-drug outpatient care (£ per case treated)	674[2]		Calculated
Total cost of diagnosis, management and follow-up of drug resistant tuberculosis case	32299	16,150.0-48,450.0	[14 38]

Footnotes

[1]Refers to the range explored in the univariate sensitivity analysis
[2]In the sensitivity analysis the costs of outpatient care for an active TB case and the tests required were considered together (total = 774, range explored 387-1161).

Supplementary table 8. Costs (2010 pounds sterling) associated with diagnosis and treatment of latent TB infection

	Base case (range)	Range[1]	Reference(s)
Cost of screening for single-step strategies			
Tuberculin skin test	34.22	17.11-51.33	[14 38]
QuantiFERON (test kit, consumables and phlebotomy)	52	26-78	Local laboratory cost
T-SPOT.TB	82	41-123	Local laboratory cost
Cost of confirmatory IGRA testing in dual-step strategies			
QuantiFERON (test kit, consumables and phlebotomy)	41	20.5-61.5	Local laboratory cost
T-SPOT.TB	71	35.5-106.5	Local laboratory cost
Cost of evaluating positive LTBI screening tests (or tests if dual step strategy used)			
Cost of outpatient consultation: first visit (£ per visit)	230		Local tariff
CXR	28		[14 38]
LFT	1		[14 38]
Number of outpatient consultation	1		[14 38]
Number of CXR	1		[14 38]
Number of LFT	1		[14 38]
Total cost of evaluating positive QuantiFERON	259	130-389	Calculated
Cost of follow-up and chemoprophylactic therapy for positives undergoing treatment			
Follow up via TB nurses	22		[40]
Rifampicin (£ per month)	10.76		[14 38]
Isoniazid (£ per month)	17.87		[14 38]
Number of TB Nurses appointments	2		[14 38]
Duration of rifampicin (months)	3		[14 38]
Duration of isoniazid (months)	3		[14 38]
Total cost of chemoprophylaxis (£ per course) plus TB nurse follow-up	130	65-195	Calculated
Cost of managing a case of chemoprophylaxis induced liver injury			
Cost of additional clinic visits and blood tests	362	181-1362	[41]
Cost of inpatient stay	1000		[41]

Footnote

[1]Refers to the range explored in the univariate sensitivity analysis

Supplementary table 9. Size of tuberculin skin test response stratified by BCG status (pink shaded area is classed negative and blue shaded area is positive – as per the stratified threshold recommended by UK guidelines)

TST (mm)	Non BCG vaccinated (n=29)	BCG vaccinated (n=143)	BCG status unsure (n=3)
<6	14 (48.3%)	61 (42.7%)	2 (66.7%)
6-9	7 (24.1%)	25 (17.5%)	0 (0.0%)
10-14	2 (6.9%)	20 (14.0%)	0 (0.0%)
≥15	6 (20.7%)	37 (25.9%)	1 (33.3%)

Supplementary table 10a. Concordance between TST (using different cut-offs) and both IGRAs

IGRA	Result/agreement	Tuberculin skin test (using stratified cut-off[1])		Tuberculin skin test (using non-stratified cut-off[2])	
		Negative	Positive	Negative	Positive
QuantiFERON Gold in-tube	Negative	107	33	97	43
	Positive	12	20	9	23
	Indeterminate	1	0	1	0
	Agreement (%)	73.4		69.4	
	Kappa (95% CI)	0.30 (0.15-0.46)		0.29 (0.15-0.42)	
T.SPOT.TB	Negative	68	23	64	27
	Positive	11	18	5	24
	Indeterminate	4	2	3	3
	Agreement (%)	68.3		69.8	
	Kappa (95% CI)	0.29 (0.11-0.47)		0.38 (0.23-0.54)	

Footnotes

[1]TST positive if induration ≥6mm (in BCG unvaccinated) and ≥15mm (in BCG unvaccinated)

[2]TST positive if induration ≥10mm (irrespective of BCG status)

Supplementary table 10b. Concordance between QuantiFERON Gold in-tube and T-SPOT.TB

		QuantiFERON Gold in-tube		
		Negative	Positive	Indeterminate
T.SPOT.TB	Negative	110	7	0
	Positive	11	25	0
	Indeterminate	6	1	0
	Agreement (%)	84.4		
	Kappa (95% CI)	0.58 (0.51-0.67)		

Supplementary table 11. Univariate sensitivity analysis of probabilities and proportions used as input variables in the decision model

Model parameter			Screening protocols for latent tuberculosis infection (stratified by chest radiography at port of entry; screening tools; and screening incidence, cases per 100,000 per year)[1]							
	Point Estimate	Range	No CXR QFN-GIT only >250	No CXR T-SPOT.TB only >250	CXR T-SPOT.TB only >250	No CXR QFN-GIT only >150	CXR T-SPOT.TB only >150	No CXR QFN-GIT only >40	CXR QFN-GIT only >40	CXR T-SPOT.TB only >40
Prevalence of latent tuberculosis infection	0.13	0.1	22,871.7	ED	SD	40,812.9	SD	45,585.8	59,489.1	533,781.1
		0.4	SD[2]	ED[3]	SD	ED	SD	16,520.5	59,489.1	115,523.1
Prevalence of HIV	0.004	0.002	17,620.0	ED	SD	32,950.4	SD	38,732.2	59,489.1	417,409.7
		0.01	SD	ED	SD	ED	SD	26,122.6	59,489.1	363,151.4
Prevalence of multi-drug resistant tuberculosis	0.01	0.005	21,248.5	ED	SD	31,695.1	SD	34,634.9	59,631.5	400,332.2
		0.02	22,214.7	ED	SD	32,216.1	SD	34,993.4	59,204.3	406,666.1
Proportion accepting TST	0.81	0.6	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
		1	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
Proportion TST read	0.94	0.6	21,565.3	ED	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		1	21,565.3	ED	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Proportion accepting QFN-GIT testing	0.99	0.6	ED	ED	31,863.8	ED	SD	32,113.8	ED	74,578.3
		1	21,390.6	ED	SD	31,889.7	SD	34,857.1	59,489.1	477,815.5
Proportion accepting T-SPOT.TB	0.99	0.6	21,565.3	SD	SD	31,867.1	SD	34,753.5	59,489.1	ED
		1	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	349,020.9
Sensitivity of QFN-GIT in HIV-negative	0.84	0.75	21,432.8	ED	ED	33,214.2	SD	35,936.2	59,489.1	149,541.2
		0.87	21,589.2	ED	SD	31,472.1	SD	34,396.3	59,489.1	875,064.3
Sensitivity of TST in HIV-negative	0.77	0.65	20,611.4	ED	SD	31,433.0	SD	32,531.7	59,489.1	372,124.3
		0.82	21,934.4	ED	SD	32,048.1	SD	35,607.3	59,489.1	414,163.7
Sensitivity of T-SPOT.TB in HIV-negative	0.89	0.78	20,431.4	SD	SD	30,714.6	SD	34,187.8	59,489.1	SD

		0.91	21,768.2	ED	SD	32,069.2	SD	34,851.8	59,489.1	301,351.4
Sensitivity of QFN-GIT in HIV-positive	0.75	0.61	27,182.4	ED	SD	31,382.7	SD	32,641.1	59,489.1	301,251.5
		0.78	20,716.3	ED	SD	31,971.5	SD	35,177.2	59,489.1	428,998.4
Sensitivity of TST in HIV-positive	0.71	0.61	22,241.0	ED	SD	31,494.6	SD	34,622.0	59,489.1	408,700.2
		0.75	21,347.2	ED	SD	31,981.4	SD	34,803.3	59,489.1	400,159.5
Sensitivity of T-SPOT.TB in HIV-positive	0.81	0.62	23,648.3	SD	SD	30,988.5	SD	33,800.6	59,489.1	686,342.1
		0.83	21,418.1	ED	SD	31,922.0	SD	34,832.8	59,489.1	386,673.4
Specificity of QFN-GIT	0.99	0.75	ED	30,595.7	59,489.1	ED	175,719.7	SD	SD	392,557.9
		1	21,201.6	ED	SD	29,844.3	SD	32,271.1	59,489.1	412,426.3
Specificity of TST	0.78	0.7	21,764.5	ED	SD	33,182.7	SD	37,459.5	59,489.1	425,885.4
		0.9	21,285.0	ED	SD	30,212.7	SD	31,567.6	59,489.1	372,344.9
Specificity of T-SPOT.TB	0.86	0.72	22,118.2	SD	SD	36,206.2	SD	42,842.0	59,489.1	772,301.4
		0.95	21,248.5	SD	SD	29,874.0	SD	31,407.8	59,489.1	221,514.0
Proportion HIV negative progressing from latent to active TB (over 20 years)	0.05	0.025	ED	ED	SD	ED	SD	ED	65,734.0	745,855.7
		0.10	5,315.9	ED	SD	13,070.0	SD	16,110.2	59,487.2	202,851.6
Proportion HIV positive progressing from latent to active TB (over 20 years)	0.40	0.20	17,229.9	ED	SD	33,078.3	SD	39,287.3	59,489.1	419,095.8
		0.80	ED	ED	SD	ED	SD	27,097.2	59,489.1	368,659.4
Number of contacts	6.5	3.25	23,131.8	ED	SD	33,433.6	SD	36,320.0	61,055.6	403,988.3
		10	19,878.3	ED	SD	30,180.1	SD	33,066.5	57,802.1	400,734.8
Efficacy of completed chemoprophylaxis (risk reduction proportion)	0.65	0.5	36,853.3	ED	SD	41,713.0	SD	42,764.8	59,342.8	518,747.6
		0.8	14,284.3	ED	SD	25,378.6	SD	28,996.6	59,636.0	328,347.2
Efficacy of partial chemoprophylaxis (risk reduction proportion)	0.21	0.1	22,903.3	ED	SD	32,907.1	SD	35,639.3	59,470.1	414,481.5
		0.3	20,558.7	ED	SD	31,056.6	SD	34,056.2	59,504.6	393,058.2
Proportion starting chemoprophylaxis	0.95	0.3	SD	SD	SD	SD	SD	ED	109,522.6	1,165,096.7
		1	19,679.1	ED	SD	30,315.4	SD	33,427.2	59,520.0	385,466.6
Proportion completing chemoprophylaxis	0.85	0.3	ED	ED	SD	ED	SD	56,449.5	59,236.9	660,994.7
		1	17,677.4	ED	SD	28,561.9	SD	31,889.0	59,558.3	365,814.8

Number of secondary active TB cases per index case (drug sensitive)	0.24	0.12	25,056.5	ED	SD	36,370.8	SD	39,285.2	148,336.7	448,254.4
		0.36	19,100.2	ED	SD	28,510.1	SD	31,148.6	37,840.6	366,409.7
Number of secondary active TB cases per index case (drug resistant)	0.24	0.12	21,530.9	ED	SD	31,871.0	SD	34,770.5	59,962.2	402,414.9
		0.36	21,599.7	ED	SD	31,863.3	SD	34,736.6	59,020.7	402,428.8
Number of secondary latent TB cases per index case (drug sensitive)	0.18	0.09	21,596.2	ED	SD	31,906.2	SD	34,794.8	59,801.9	402,760.1
		0.27	21,534.4	ED	SD	31,828.2	SD	34,712.3	59,178.9	402,084.2
Number of secondary latent TB cases per index case (drug resistant)	0.18	0.09	21,565.2	ED	SD	31,867.2	SD	34,753.5	59,490.0	402,421.8
		0.27	21,565.4	ED	SD	31,867.1	SD	34,753.5	59,488.2	402,421.9
Proportion of active TB cases admitted as inpatient	0.53	0.25	22,695.9	ED	SD	32,990.1	SD	35,874.3	60,601.6	403,545.7
		0.75	20,676.9	ED	SD	30,984.8	SD	33,872.9	58,615.0	401,538.8
Proportion of immigrants having CXR on arrival	0.4	0.3	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
		0.6	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
Prevalence of active TB in immigrants from countries with TB incidence >40/100000	0.0035	0.001	21,570.0	ED	SD	31,869.0	SD	34,763.4	224,786.7	402,421.8
		0.005	21,562.5	ED	SD	31,866.0	SD	34,747.5	39,653.4	402,421.8
Prevalence of active TB in immigrants from countries with TB incidence <40/100000	0.001	0.0005	21,564.4	ED	SD	31,866.8	SD	34,751.5	59,489.1	402,421.8
		0.005	21,572.8	ED	SD	31,870.1	SD	34,769.4	59,489.1	402,421.8
Proportion reduction in number of secondary active cases for actively diagnosed active TB	0.5	0.25	21,565.3	ED	SD	ED	SD	33,439.3	124,449.8	402,421.8
		0.75	21,565.3	ED	ED	31,867.1	SD	34,753.5	37,597.7	402,421.8
Proportion reduction in number of secondary latent infection for actively diagnosed active TB	0.5	0.25	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,802.8	402,421.8
		0.75	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,178.0	402,421.8
Proportion receiving chemoprophylaxis developing hepatotoxicity	0.002	0.001	21,532.3	ED	SD	31,841.3	SD	34,730.0	59,489.1	402,039.5
		0.003	21,598.4	ED	SD	31,893.0	SD	34,777.0	59,489.1	402,804.3

Footnotes

[1]Only non-dominated options are presented - the figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness

[2]Strict dominance (SD): This is the situation where a particular screening threshold is both less effective and more expensive than the next most effective screening threshold

[3]Extended dominance (ED): This is the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

Supplementary table 12. Univariate sensitivity analysis of costs used as input variables in the decision model

Parameter	Point estimate	Range	Screening protocols for latent tuberculosis infection (stratified by chest radiography at port of entry, screening tools and screening incidence)[1]								
			No CXR QFN-GIT only >250	No CXR T-SPOT.TB only >250	CXR T-SPOT.TB only >250	No CXR QFN-GIT only >200	No CXR QFN-GIT only >150	CXR T-SPOT.TB only >150	No CXR QFN-GIT only >40	CXR QFN-GIT only >40	CXR T-SPOT.TB only >40
Cost of initial screening (using single-step TST)	34.22	17.11	21,565.3	ED	SD[2]	ED[2]	31,867.1	SD	34,753.5	59,489.1	402,421.8
		51.33	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of initial screening (using single-step QuantiFERON-Gold in-tube)	52	26	17,956.3	ED	SD	ED	20,744.1	SD	21,521.2	59,489.1	545,003.0
		78	ED	ED	SD	SD	33,794.1	SD	47,985.8	59,489.1	259,840.7
Cost of initial screening (using single-step T-SPOT.TB)	82	41	ED	ED	ED	ED	26,549.6	SD	34,753.5	59,489.1	177,582.3
		123	21,565.3	SD	SD	ED	31,867.1	SD	34,753.5	59,489.1	627,261.4
Cost of confirmatory IGRA screening in dual-step strategy (using QuantiFERON-Gold in-tube)	41	20.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		61.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of confirmatory IGRA screening in dual-step strategy (using T-SPOT.TB)	71	35.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		106.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of evaluating of new-entrants who test positive for TST/IGRA	259.0	130.0	14,521.3	ED	SD	ED	26,383.4	SD	29,709.7	59,489.1	318,265.4
		389.0	28,663.9	ED	SD	ED	37,393.4	SD	39,836.4	59,489.1	487,230.7
Cost of treating new-entrants	130.0	65.0	18,707.5	ED	SD	ED	29,644.0	SD	32,709.3	59,527.8	368,194.7
		195.0	24,423.2	ED	SD	ED	34,090.3	SD	36,797.7	59,450.5	436,649.0
Cost of active drug sensitive TB OP follow-up	774.0	387.0	21,954.7	ED	SD	ED	32,253.9	SD	35,139.5	59,872.3	402,808.9
		1,161.0	21,175.9	ED	SD	ED	31,480.4	SD	34,367.5	59,106.0	402,034.8
Cost of active drug sensitive TB OP drugs	222.0	111.0	21,677.0	ED	SD	ED	31,978.1	SD	34,864.2	59,599.0	402,532.9
		333.0	21,453.6	ED	SD	ED	31,756.2	SD	34,642.8	59,379.2	402,310.8
Cost of active TB inpatient treatment	4,013.0	2,006.5	22,635.4	ED	SD	ED	32,930.0	SD	35,814.3	60,542.0	403,485.5

		6,019.5	20,495.2	ED	SD	ED	30,804.3	SD	33,692.7	58,436.2	401,358.2
Cost of contact tracing	482.0	241.0	23,131.8	ED	SD	ED	33,433.6	SD	36,320.0	61,055.6	403,988.3
		723.0	19,998.8	ED	SD	ED	30,300.6	SD	33,187.0	57,922.6	400,855.3
Cost of treatment for drug resistant active TB	32,299.0	16,150.0	21,464.5	ED	SD	ED	31,876.6	SD	34,793.8	59,649.6	402,419.2
		48,450.0	21,666.1	ED	SD	ED	31,857.7	SD	34,713.2	59,328.6	402,424.5
Cost of Hepatotoxicity with chemoprophylaxis	362.0	181.0	21,525.8	ED	SD	ED	31,836.4	SD	34,725.2	59,489.1	401,949.6
		1,862.0	21,575.7	ED	SD	ED	31,875.2	SD	34,760.9	59,489.1	402,545.8

Footnotes

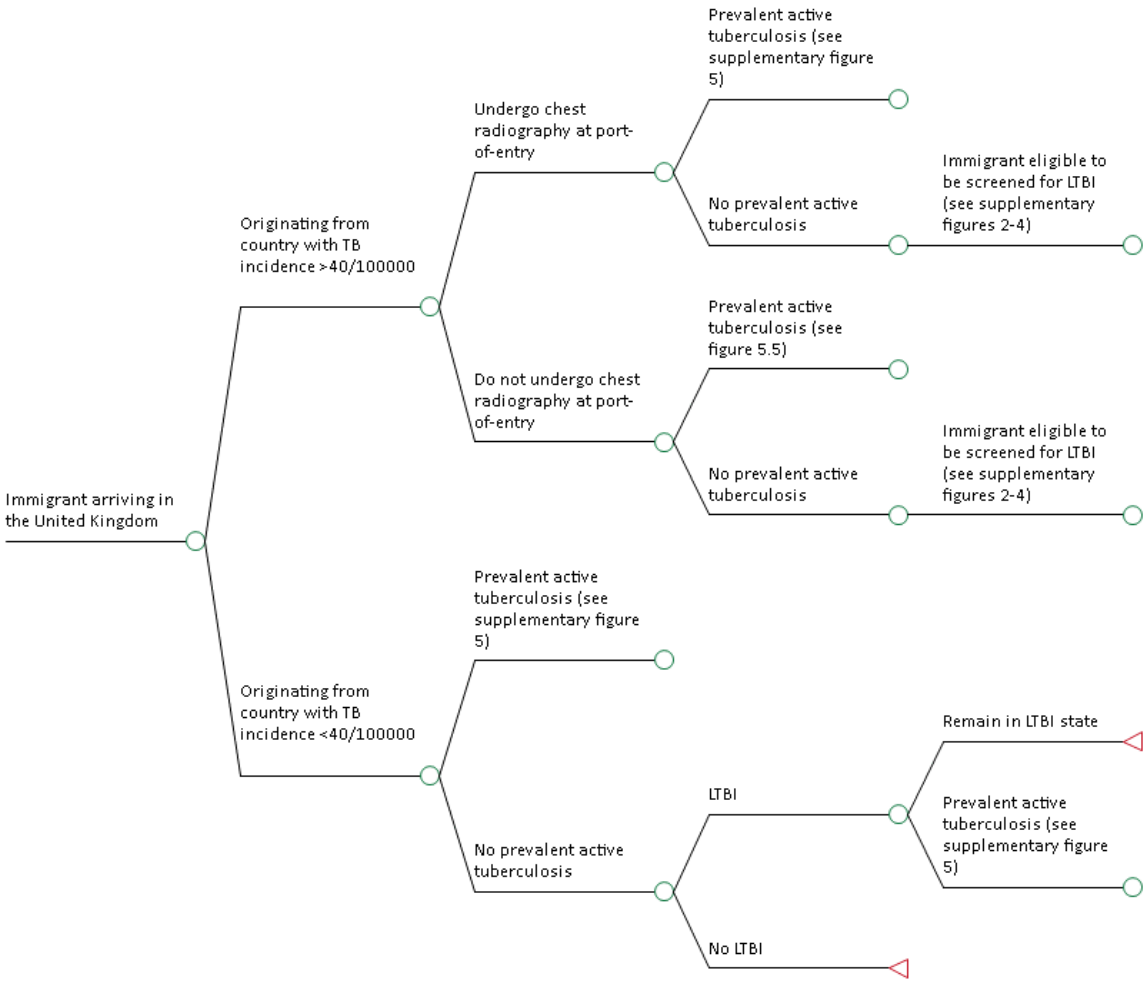
[1]Only non-dominated options are presented - the figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness

[2]Strict dominance (SD): This is the situation where a particular screening threshold is both less effective and more expensive than the next most effective screening threshold

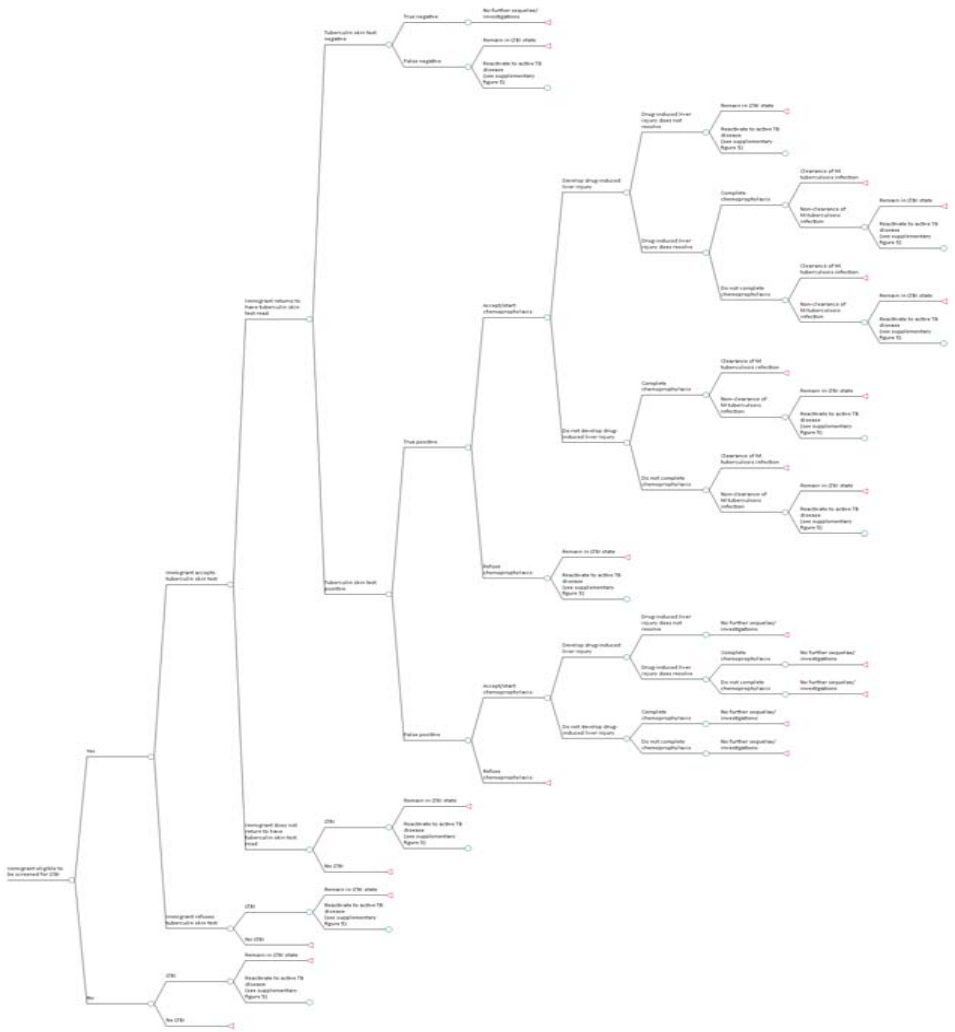
[3]Extended dominance (ED): This is the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

Figures

Supplementary figure 1. Decision tree outlining the potential screening outcomes (particularly with respect to chest radiography) at port-of-entry for immigrants arriving in the United Kingdom from overseas (for clarity all (prevalent active tuberculosis" and "reactivate to active TB subtrees" are shown in supplementary figure 5 below)


Immigrant arriving in the United Kingdom
Originating from country with TB incidence >40/100000
Undergo chest radiography at port-of-entry
Prevalent active tuberculosis (see supplementary figure 5)
No prevalent active tuberculosis
Immigrant eligible to be screened for LTBI (see supplementary figures 2-4)
Do not undergo chest radiography at port-of-entry
Prevalent active tuberculosis (see figure 5.5)
No prevalent active tuberculosis
Immigrant eligible to be screened for LTBI (see supplementary figures 2-4)
Originating from country with TB incidence <40/100000
Prevalent active tuberculosis (see supplementary figure 5)
No prevalent active tuberculosis
LTBI
Remain in LTBI state
Prevalent active tuberculosis (see supplementary figure 5)
No LTBI

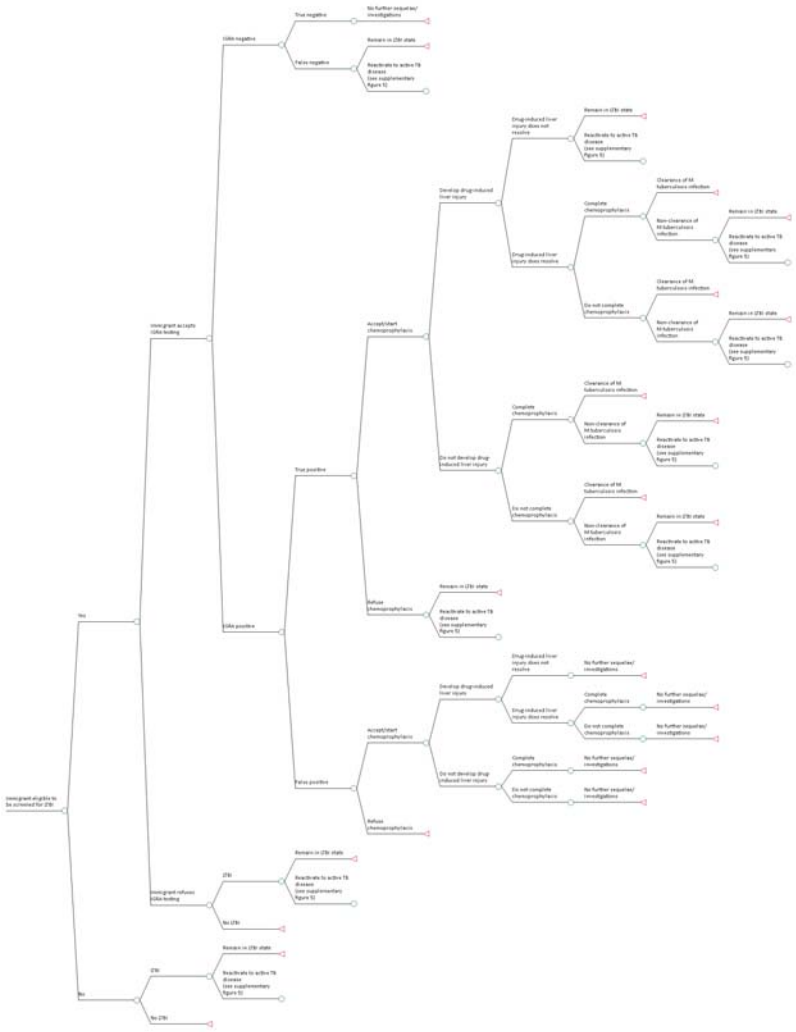
Supplementary figure2. Decision tree used for the health economic analysis of immigrant screening with tuberculin skin test for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity/space restrictions HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram.
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node).
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future.
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB.
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes.

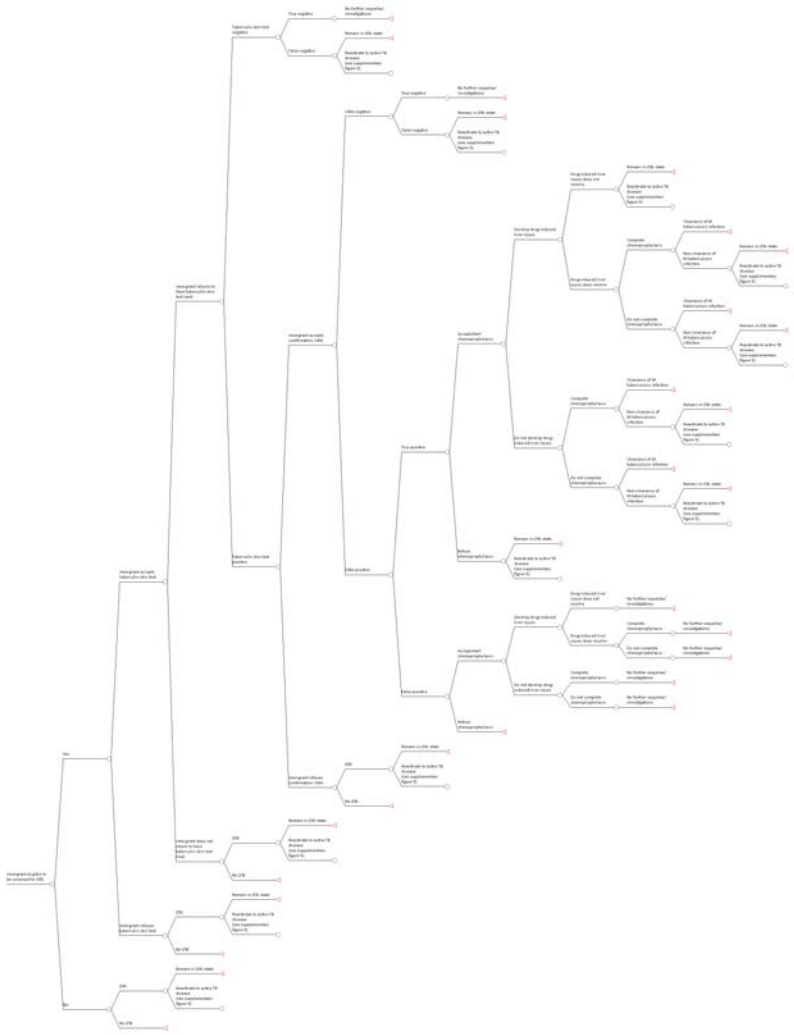
Supplementary figure 3. Decision tree used for the health economic analysis of immigrant screening with interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity/space restrictions HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram.
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node).
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future.
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB.
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes.

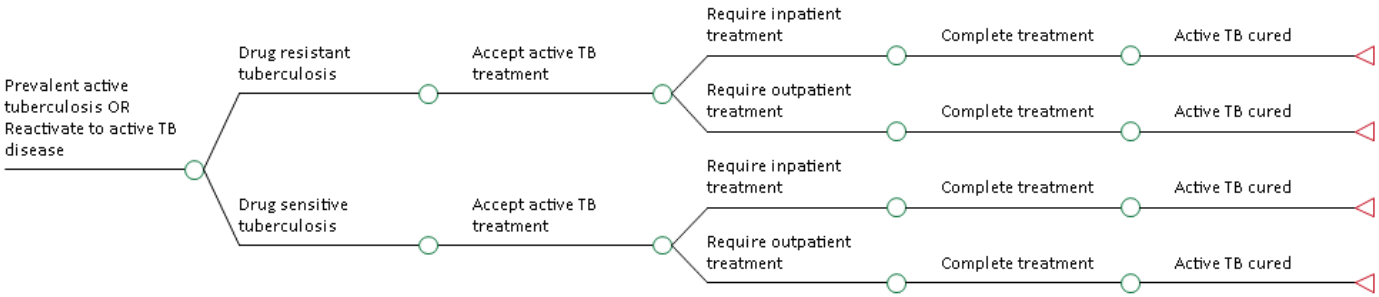
Supplementary figure 4. Decision tree used for the health economic analysis of immigrant screening with a dual tuberculin skin test plus confirmatory interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) approach for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity/space restrictions HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram.
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node).
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future.
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB.
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes.

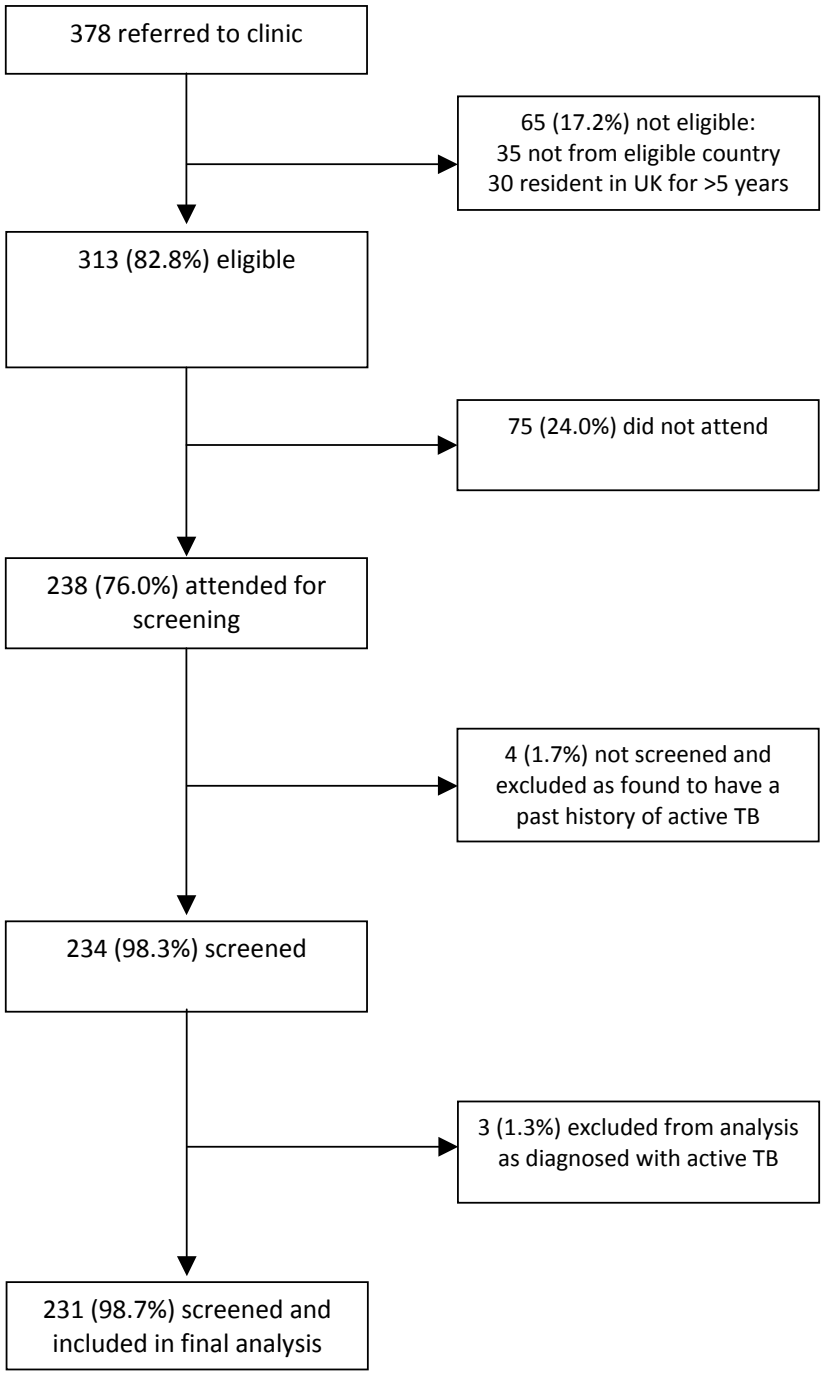
Supplementary figure 5. Decision subtree used to describe the events that occur if an individual is diagnosed with prevalent active TB at port-of-entry screening or reactivates to active TB from LTBI



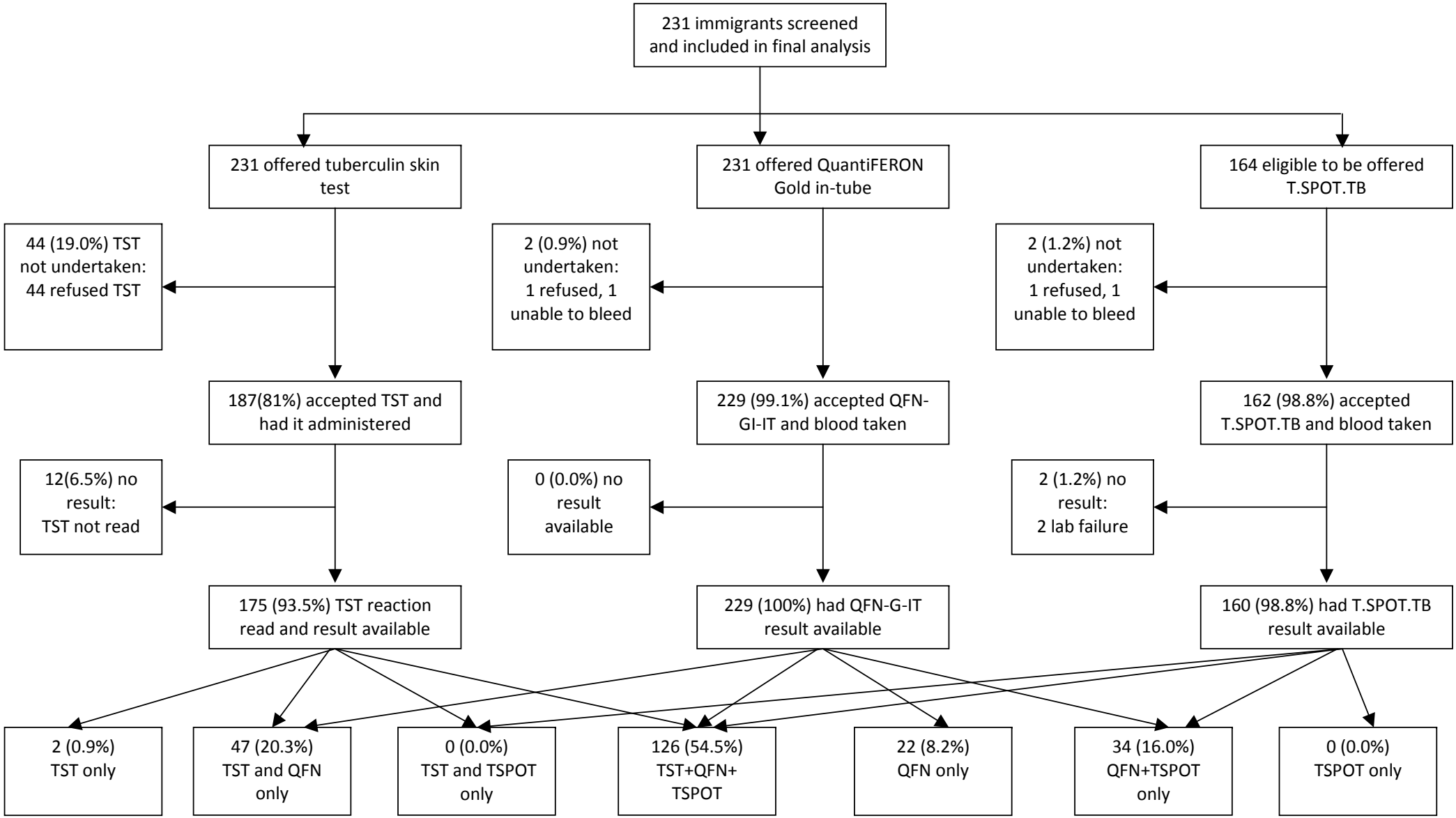
Footnotes

1. Individuals who are diagnosed with active tuberculosis through active screening with chest radiography (at port-of-entry) or passively after reactivating from latent tuberculosis infection to active tuberculosis are managed in the same way.
2. Onward transmission to contacts, the subsequent secondary cases of active tuberculosis and latent infections and the contact tracing procedures are not represented due to clarity/lack of space.

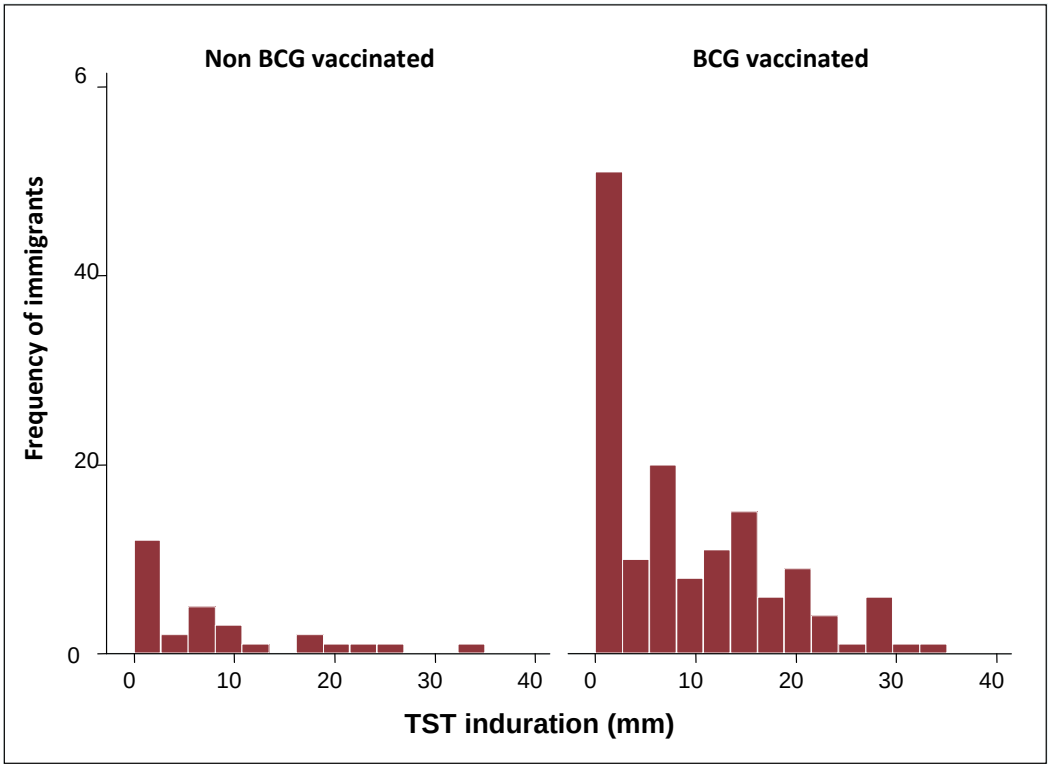
Supplementary figure 6. Study flow chart



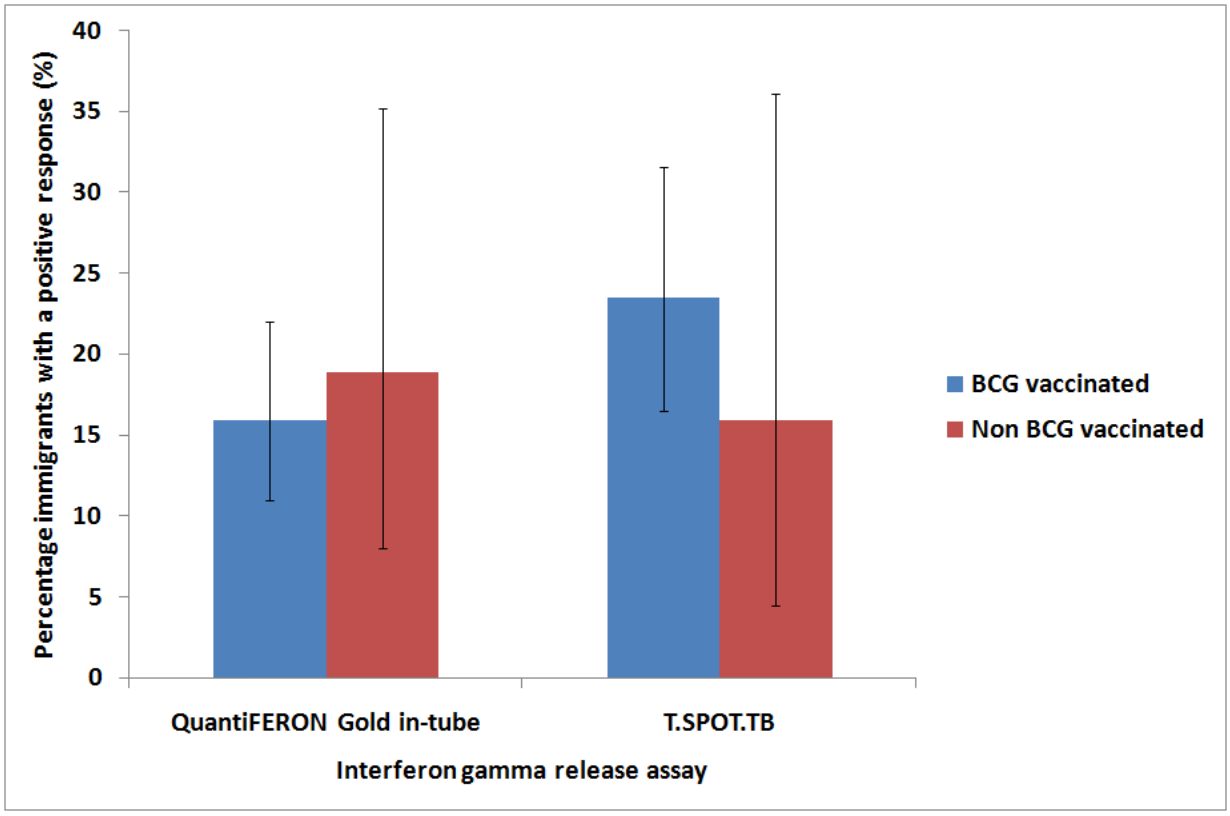
Supplementary figure 7. Study flow chart outlining uptake of screening tests (note: As testing with T-SPOT.TB started later than with TST and QuantiFERON Gold in-tube the numbers offered T-SPOT.TB were smaller)



Supplementary figure 8. Histogram showing TST induration (in millimetres) stratified by BCG vaccination status



Supplementary figure 9. Bar chart (with 95% confidence intervals) showing the proportion of immigrants who were IGRA positive stratified by BCG vaccinations status



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