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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▶ Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2011-201542).

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Independence The authors' work was independent of the funders, who had only a minimal role in the study design but no role in the analysis of data, writing of the manuscript or decision to submit for publication.

Received 3 January 2012
Accepted 16 May 2012
Published Online First
12 June 2012

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.

Linked

▶ http://dx.doi.org/10.1136/thoraxjnl-2011-200956
▶ http://dx.doi.org/10.1136/thoraxjnl-2012-202184

To cite: Pareek M, Bond M, Shorey J, *et al*. *Thorax* 2013;**68**:230–239.

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.

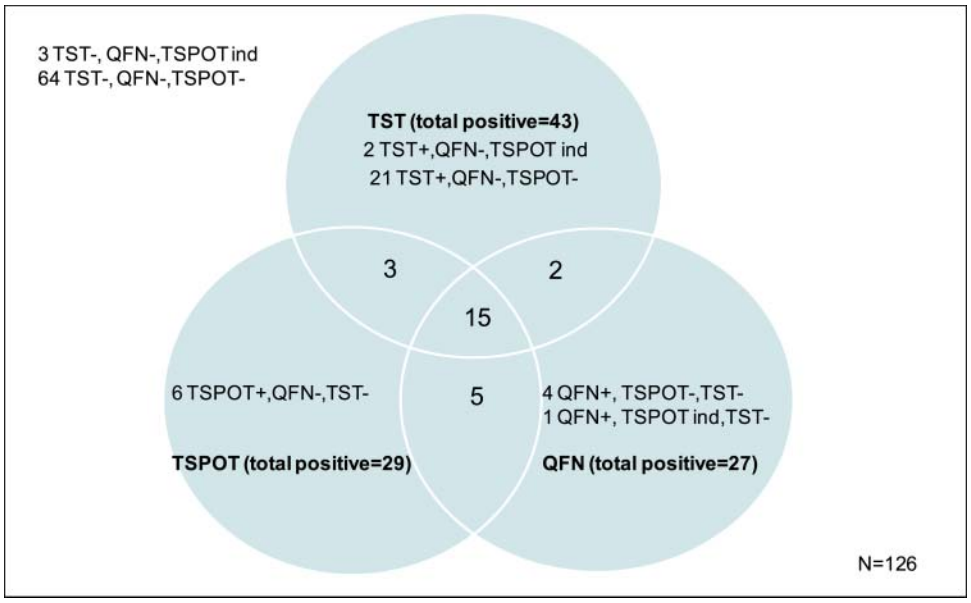

Figure 1 Venn diagram showing test results where all three screening tests were undertaken. Ind, indeterminate; QFN, QuantiFERON; TST, tuberculin skin test.

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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Acknowledgements The authors wish to acknowledge the contribution of the local primary care centres that ran the new entrant screening programmes: Lisson Grove Health Centre, Soho Square General Practice, Newton Medical Centre and the 574 Harrow Road Practice.

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.

Funding This study was undertaken at St Mary's Hospital, Imperial College Healthcare NHS Trust which is supported by the NIHR Biomedical Research Centre funding scheme. Westminster Primary Care Trust provided funding for the project. MP is funded by a Medical Research Council Capacity Building Studentship. PJW thanks the Medical Research Council for Centre funding. AL is a Wellcome Senior Research Fellow in Clinical Science and NIHR Senior Investigator.

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.

Ethics approval No patient-specific data or personal identifiers were used in the preparation of this report which was an analysis of routine data collected as part of service evaluation and therefore ethical approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Full numerical results of the scenarios described here are available from the corresponding author on request.

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