Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study

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Summary

Background Tackling tuberculosis requires testing and treatment of latent tuberculosis in high-risk groups. The aim of this study was to estimate the predictive values of the tuberculin skin test (TST) and two interferon-γ release assays (IGRAs) for the development of active tuberculosis in high-risk groups—ie, people in recent contact with active tuberculosis cases and from high-burden countries.

Method In this prospective cohort study, we recruited participants from 54 centres (eg, clinics, community settings) in London, Birmingham, and Leicester in the UK. Participants were eligible if they were aged 16 years or older and at high risk for latent tuberculosis infection (ie, recent contact with someone with active tuberculosis [contacts] or a migrant who had arrived in the UK in the past 5 years from—or who frequently travelled to—a country with a high burden of tuberculosis [migrants]). Exclusion criteria included prevalent cases of tuberculosis, and participants who were treated for latent tuberculosis after a positive test result in this study. Each participant received three tests (QuantiFERON-TB Gold-In Tube, T-SPOT.*TB*, and a Mantoux TST). A positive TST result was reported using three thresholds: 5 mm (TST-5), 10 mm (TST-10), and greater than 5 mm in BCG-naive or 15 mm in BCG-vaccinated (TST-15) participants. Participants were followed up from recruitment to development of tuberculosis or censoring. Incident tuberculosis cases were identified by national tuberculosis databases, telephone interview, and review of medical notes. Our primary objective was to estimate the prognostic value of IGRAs compared with TST, assessed by the ratio of incidence rate ratios and predictive values for tuberculosis development. The study was registered with ClinicalTrials.gov, NCT01162265, and is now complete.

Findings Between May 4, 2010, and June 1, 2015, 10 045 people were recruited, of whom 9610 were eligible for inclusion. Of this cohort, 4861 (50·6%) were contacts and 4749 (49·4%) were migrants. Participants were followed up for a median of 2·9 years (range 21 days to 5·9 years). 97 (1·0%) of 9610 participants developed active tuberculosis (77 [1·2%] of 6380 with results for all three tests). In all tests, annual incidence of tuberculosis was very low in those who tested negatively (ranging from 1·2 per 1000 person-years, 95% CI 0·6–2·0 for TST-5 to 1·9 per 1000 person-years, 95% CI 1·3–2·7, for QuantiFERON-TB Gold In-Tube). Annual incidence in participants who tested positively were highest for T-SPOT.*TB* (13·2 per 1000 person-years, 95% CI 9·9–17·4), TST-15 (11·1 per 1000 person-years, 8·3–14·6), and QuantiFERON-TB Gold In-Tube (10·1 per 1000 person-years, 7·4–13·4). Positive results for these tests were significantly better predictors of progression than TST-10 and TST-5 (eg, ratio of test positivity rates in those progressing to tuberculosis compared with those not progressing T-SPOT.*TB* *vs* TST-5: 1·99, 95% CI 1·68–2·34; p<0·0001). However, TST-5 identified a higher proportion of participants who progressed to active tuberculosis (64 [83%] of 77 tested) than all other tests and TST thresholds (≤75%).

Interpretation IGRA-based or BCG-stratified TST strategies appear most suited to screening for potential disease progression among high-risk groups. Further work will be needed to assess country-specific cost-effectiveness of each screening test, and in the absence of highly specific diagnostic tests, cheap non-toxic treatments need to be developed that could be given to larger groups of people at potential risk.

Funding National Institute for Health Research Health Technology Assessment Programme 08-68-01.

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Introduction

Between a quarter and a third of the world's population is estimated to be latently infected with *Mycobacterium tuberculosis*,[1,2] a state in which viable bacteria persist under immune control without clinically active tuberculosis.[3] Latent tuberculosis infection forms a reservoir from which active tuberculosis will continue to emerge, therefore presenting a major challenge to the global

Lancet Infect Dis 2018; 18: 1077–87

Published **Online** August 30, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30355-4

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Research in context

Evidence before this study

Multiple systematic reviews of the predictive value of interferon-γ release assays (IGRAs) have been done, with the most recent review for the WHO guidelines on latent tuberculosis. We did an up-to-date review, by searching PubMed, with no language restrictions, for publications between Jan 1, 2013, and June 1, 2017, using the search terms "interferon-γ release assay", "T-cell-based assay", "antigen-specific T cell", "T cell response", "interferon", "interferon-γ", "γ-interferon", "IFN", "elispot", "ESAT-6", "CFP-10", "culture filtrate protein", "Enzyme Linked Immunosorbent Spot", "Quantiferon", "Quantiferon-TB" AND "tuberculosis", "mycobacterium tuberculosis". We found only eight head-to-head studies that used commercial IGRAs and tuberculin skin tests (TSTs) and in which participants were not given preventive therapy to allow the calculation of prognostic predictive values, and of these studies only three had incidence rate ratio analyses. The WHO systematic review and our updated search found that the positive predictive value of IGRAs is low and similar to that of TSTs in high-burden settings, and the negative predictive value is high in all settings. Furthermore, the systematic review and subsequent published studies concluded that the quality of evidence was low because of risk of bias, inconsistency, imprecision, and indirectness. Notably, few studies were available that determined the predictive utility of the tests in subgroups (including people with and without previous BCG vaccination).

Added value of this study

To our knowledge, this is the largest and first adequately powered study in a country with a low incidence of tuberculosis where the risk of reinfection is low to provide evidence that the predictive value of IGRAs is less than estimated previously. Although we found no significant differences in negative predictive values between the two IGRAs and TST in head-to-head comparisons, we found differences in the proportion of participants who were classified as negative by these tests, and in the positive prediction of progression to active tuberculosis. A positive T-SPOT.*TB* result was a significantly better predictor of disease progression than all other tests, TST that accounted for BCG-vaccination status (TST-15) and QuantiFERON-TB Gold In-Tube were significantly better predictors of progression than TST-10 (with a 10 mm positive threshold), while a positive TST-5 result (5 mm positive threshold) was a significantly worse predictor of progression than all other tests. Additionally, we did subgroup analysis for migrants and contacts.

Implications of all the available evidence

Compared with the evidence in the WHO guidelines, among participants with positive IGRA results we found a decreased progression to active tuberculosis. This finding has implications for national and WHO policy and future recommendations. We provide evidence on which tests should be selected for the implementation of migrant testing for latent tuberculosis infection in countries with a low incidence of tuberculosis and for contact investigation. We found substantial differences in TST performance when stratified by BCG-vaccination status, which is relevant to cost-effectiveness analysis and future guidelines.

effort to end the tuberculosis epidemic. Current tests (ie, tuberculin skin test [TST] and interferon-γ release assays [IGRAs]) for latent tuberculosis infection detect memory T-cell responses to *M tuberculosis*.[4] The aim of these tests is to identify individuals who might benefit from treatment for latent tuberculosis infection, so reducing tuberculosis incidence and transmission.

Evaluating these tests requires cohort studies that assess individuals' IGRA and TST status at baseline with prospective follow-up to determine the predictive values of each test for the development of active tuberculosis. Systematic reviews[5,6] have highlighted heterogeneity and a paucity of relevant studies, particularly of head-to-head comparisons of different testing strategies in countries with a low incidence of tuberculosis where the risk of reinfection is low. Previous head-to-head comparisons have been relatively small scale (ie, 135–1335 participants)[7–10] and most[7–9] have assessed only two testing strategies. To assess the prognostic value of tuberculosis testing kits, we did a head-to-head comparison of the incidence rate ratio (IRR) of tuberculosis as assessed by three different tests applied to the same individuals in a large prospective cohort of people who did not take preventive treatment.

For the **study protocol** see https://njl-admin.nihr.ac.uk/document/download/2006769

Methods

Study design and participants

The UK Prognostic Evaluation of Diagnostic IGRAs Consortium (UK PREDICT) tuberculosis study was a prospective cohort study in which participants were recruited from 54 UK National Health Service (NHS) centres and community settings (eg, places of worship, schools and colleges, and workplaces) in London, Birmingham, and Leicester. The study procedures and protocol were approved by the Brent NHS Research Ethics Committee (10/H0717/14). The full protocol is available online.

Individuals were eligible if they were aged 16 years and older and at high risk of latent tuberculosis infection. Individuals at high risk were classified into two groups, those who had recent contact with someone with active tuberculosis (ie, contacts, full definition in appendix), and migrants who arrived in the UK in the past 5 years from countries with a high burden of tuberculosis (ie, sub-Saharan African or Asian regions) or who frequently travelled to countries with a high burden of tuberculosis (ie, migrants). Participants who could classify as both contact and migrant were classified as

contacts if they were recruited from a contact clinic, otherwise they were classified as migrants. Recruitment of individuals older than 35 years was prioritised, since at the time of recruitment they would not be eligible for treatment with chemoprophylaxis for latent tuberculosis infection and would better show the natural progression to active disease. Participants who were diagnosed with active tuberculosis at baseline or within 21 days of study enrolment were considered prevalent cases and excluded from analysis. Participants were excluded if they were treated for latent tuberculosis infection after a positive test result from this study; however, we did not exclude those who had been treated for tuberculosis or latent tuberculosis infection before recruitment and had subsequent exposure. Further details of eligibility criteria and recruitment are in the appendix (pp 2–3). All participants provided written informed consent.

Data collection

Baseline demographic and clinical data were collected by trained research nurses using paper questionnaires including questions on age, sex, country of birth, date of entry to the UK, ethnicity, nature and duration of tuberculosis contact (eg, household or non-household, when applicable), BCG-vaccination status, self-reported HIV status, history of tuberculosis, other medical diagnoses, and use of immunosuppressive drugs (see protocol for complete data collected). For patients classified as contacts, the index cases were identified through records by centre staff and via a contact investigation (also known as contact tracing—ie, the process of assessing all contacts of tuberculosis patients to determine whether they are infected or have tuberculosis disease; the investigation is usually led by clinic staff).

Testing procedures and follow-up

The protocol required tests for latent tuberculosis infection to be done among participants with recent contact about 6 weeks after last known exposure (based on UK guidelines[11]) and among those who were new entrants to the UK at least 6 weeks after arrival in the country, to ensure sufficient time for development of a cell-mediated immune response that would be detectable by the tests. However, these intervals were longer than 10 weeks before testing for all participants.

Participants were tested with two IGRAs: QuantiFERON-TB Gold In-Tube (Cellestis, Chadstone, VIC, Australia), an ELISA-based test; T-SPOT.*TB* (Oxford Immunotec, Oxford, UK), an ELISpot-based test; and then with a Mantoux TST (Statens Serum Institut, Copenhagen, Denmark) in the same clinic visit by use of standardised protocols. Indeterminate results were classified as recommended by the manufacturer. IGRA results were provided to participants' clinicians only for samples that were to be processed in the Public Health England laboratory of participants aged 35 years or younger; at the time of the study, UK National Institute for Health and Care Excellence (NICE) guidelines did not recommend the testing of individuals older than 35 years for latent tuberculosis infection. Laboratory staff were not informed of TST results and each IGRA was done independently of the result of the other IGRA.

We assessed three different thresholds for a positive TST result. On the basis of 2016 NICE guidelines,[12] a skin induration measuring 5 mm or larger is considered a positive result irrespective of BCG vaccination status, and we refer to this threshold as TST-5. We used additional thresholds of TST-10 for skin indurations measuring 10 mm or more and also a BCG-dependent definition of TST-15, which for BCG-vaccinated participants was positive at 15 mm or larger, and for unvaccinated participants was positive at greater than 5 mm (previous NICE definition).[11] For the primary analysis, if BCG status was unknown participants were assumed to have been vaccinated if they were not UK born (consistent with international recommendations).

See Online for appendix

Participants were followed up from recruitment to the development of tuberculosis or censoring at data cutoff. Participants were contacted via telephone and interviewed at 12 and 24 months. At data cutoff, active tuberculosis was identified by use of the national tuberculosis database, which includes all statutorily notified tuberculosis patients and all results of positive *M tuberculosis* cultures. Clinical and laboratory information on all cases of active tuberculosis was obtained from patient notes. Of the participants who had recent contact with a case of tuberculosis, those who progressed to active tuberculosis had their strain compared with the index case by use of 24-locus mycobacterial interspersed repetitive unit-variable number tandem repeats (MIRU-VNTR) data.

Outcomes and identification of active tuberculosis

Our primary objective was to assess the prognostic value of the two IGRAs with the standard Mantoux TST in predicting active tuberculosis among untreated individuals who are at an increased risk. Active tuberculosis was defined as a culture-confirmed case of tuberculosis, or a clinical diagnosis of tuberculosis with radiological or histological evidence and treatment by a clinician with a full course of antituberculosis disease treatment (appendix p 4). Primary analysis was done by use of data from the participants who completed all tests and had full follow-up data (ie, per-protocol population).

Secondary objectives that are discussed in this Article were to independently quantify and compare the predictive value of the whole-blood ELISA-based test (QuantiFERON-TB Gold-In Tube) and the ELISpot-based test (T-Spot.*TB*).

Statistical analysis

We summarised the predictive performance of each test by grouping the participants into those who tested

positively and those who tested negatively and calculating the incidence of active tuberculosis in each group, and we calculated the 95% CI of this estimate using a Poisson exact method. We calculated the incidences using all available follow-up data. The discriminatory predictive value of each test or strategy was estimated as the IRR comparing the incidence of tuberculosis among those who had a positive test result versus those who had a negative test result. In the primary analyses we only used data from participants with results for all three tests.

We made pairwise comparisons of the ability of tests and strategies (ie, use of TST thresholds) to identify participants who progressed to active tuberculosis and those who did not using generalised estimating equation marginal regression models (appendix p 5).[13] We used these models to estimate ratios of positive results and of negative results among those who progressed to active tuberculosis compared with those who did not (similar to positive and negative likelihood ratios for diagnostic studies). We calculated ratios of these ratios to make pairwise comparisons between tests, accounting for the paired data.

We calculated positive and negative predictive values of each test, with the positive predictive value being the proportion of participants with a positive result who developed tuberculosis by data cutoff, and the negative predictive value being the proportion of participants with a negative result who did not develop tuberculosis.

We did four sensitivity analyses. First, the main analysis was repeated excluding participants with an unknown BCG-vaccination status. Second, we did the analysis including all available test results, not just those from participants who had results from all three tests. Third, we repeated the analysis with stratification of participants by whether they were classified as a contact or a migrant. Finally, the analysis was restricted to data up to 1 year of follow-up.

We approached all tuberculosis clinics in London, Birmingham, and Leicester to participate, and we recruited from sites in the community with a large number of immigrants, including Hindu and Sikh temples, mosques, churches, doctor's surgeries, and work places.

We assumed that 50% of contacts and new entrants would be aged 35 years or older, so a cohort of 10 000 people would

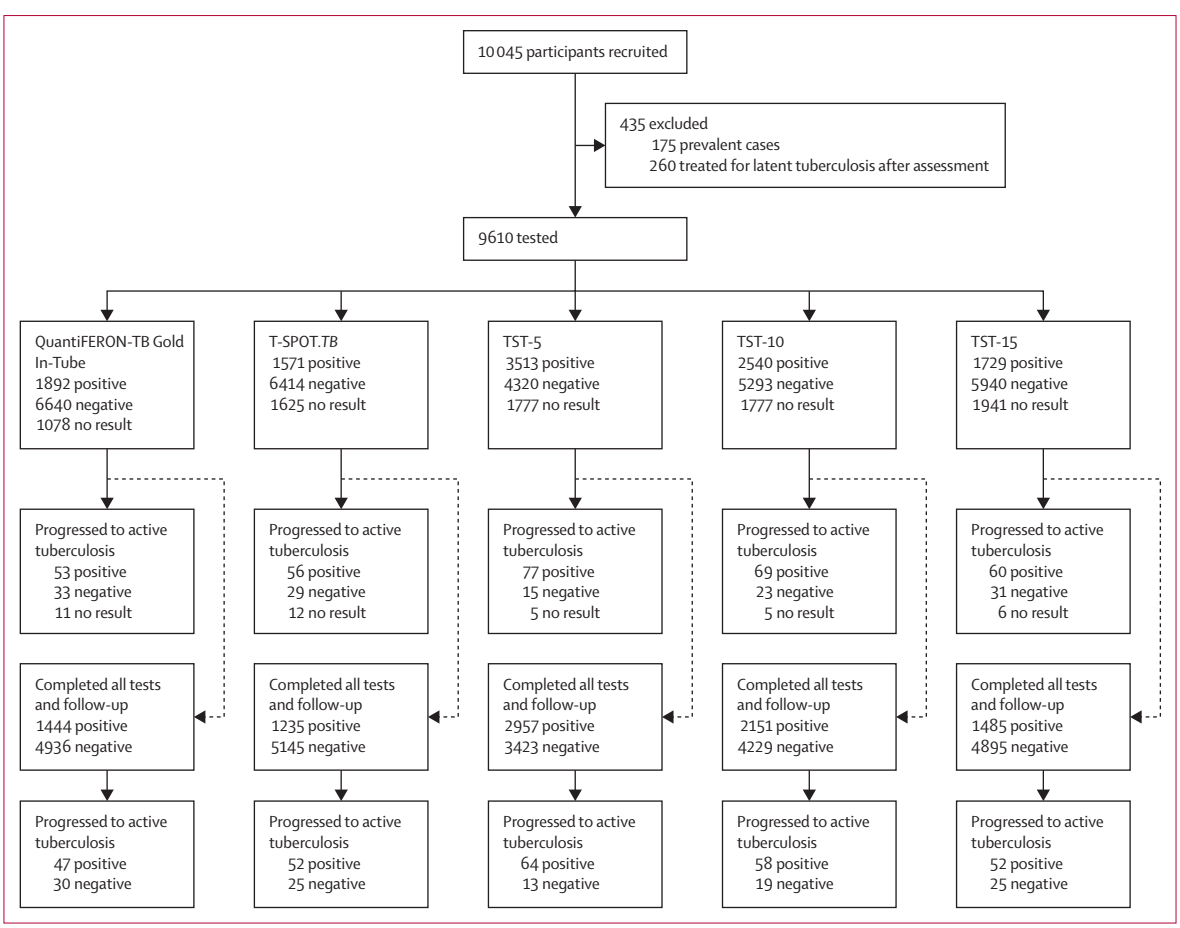


Figure 1: **Study profile of tests and results**
Of 9610 tested participants, 97 (1·0%) progressed to active tuberculosis, and 6380 (66·4%) completed all tests and follow-up (data allowing follow-up to be calculated were missing for six participants). Of the 6380 who completed all tests and follow-up (for whom we had data), 77 (1·2%) progressed to active tuberculosis.

initially yield at least 5000 participants for the primary analysis of progression without treatment, of whom 90 evaluable events would occur. Given probable loss to follow-up (which, based on clinic data, was likely to be around 20%) and the possibility that progression to disease could be less than 5%, we calculated that the power of the study would be maintained by including in the cohort all participants aged 16–35 years who did not take ciprofloxacin (estimated to be an additional 2500 participants). Overall, we calculated that 90 incident events would still be observed should 7500 participants be recruited, 20% lost to follow-up, and the rate of progression to disease only 4·2%. Our sample size calculations (appendix pp 5–6) indicated that a cohort of 5000 participants with 90 cases of active tuberculosis would have approximately 85% power to detect significant (p<0·05) differences in predictive performance arising from differences in sensitivity and specificity of 10% between tests.

The study was registered with ClinicalTrials.gov, NCT01162265, and is now complete.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 4, 2010, and June 1, 2015, 10 045 people were recruited from 54 centres in London, Birmingham, and Leicester, of whom 435 (4·3%) were excluded because of possible active tuberculosis at baseline (175 [1·7%]) and treatment for latent tuberculosis infection subsequent to initial testing (260 [2·6%]; figure 1). The 9610 remaining participants were classified into two groups, 4861 (50·6%) as contacts (of whom 3075 [63·3%] were household contacts), and 4749 (49·4%) as migrants from a country with a high incidence of tuberculosis. Full baseline demographic and clinical data are in table 1.

Index cases were identified for 2211 (45·5%) of 4861 contacts. 693 (54·9%) of 1263 index cases (some index cases were shared between contacts, and some were not found for the purposes of this study) had pulmonary tuberculosis, with (138 [20%] of 693) or without (555 [80%] of 693) tuberculosis disease at extra-pulmonary sites. 578 (46%) of 1263 index cases had pulmonary tuberculosis and known sputum smear status, 461 (80%) of whom were sputum smear positive. All other contacts were identified during contact investigations but no information on the index cases for these contacts was available.

By data cutoff (May 30, 2016), 97 (1·0%) of 9610 participants had developed tuberculosis (table 2, figure 1). The median duration of follow-up for all participants was 2·9 years (range 21 days to 5·9 years).

	Contacts (n=4861)	Migrants (n=4749)	All participants (n=9610)
Sex			
Female	2400 (49·4%)	2329 (49·0%)	4729 (49·2%)
Male	2433 (50·1%)	2376 (50·0%)	4809 (50·0%)
Data missing	28 (0·6%)	44 (0·9%)	72 (0·8%)
Ethnicity			
Bangladeshi	201 (4·1%)	515 (10·8%)	716 (7·5%)
Black African	770 (15·8%)	368 (7·8%)	1138 (11·8%)
Black Caribbean	235 (4·8%)	7 (0·2%)	242 (2·5%)
Indian	1352 (27·8%)	2629 (55·4%)	3981 (41·4%)
Mixed	654 (13·5%)	238 (5·0%)	892 (9·3%)
Other	194 (4·0%)	126 (2·7%)	320 (3·3%)
Pakistani	398 (8·2%)	508 (10·7%)	906 (9·4%)
White	942 (19·4%)	231 (4·9%)	1173 (12·2%)
Data missing	115 (2·4%)	127 (2·7%)	242 (2·5%)
Age (years)			
Median (IQR)	32 (25–44)	33 (26–51)	33 (26–47)
≤35 years	2849 (58·6%)	2677 (56·4%)	5526 (57·5%)
>35 years	2005 (41·3%)	2057 (43·3%)	4062 (42·3%)
Data missing	7 (0·1%)	15 (0·3%)	22 (0·2%)
UK born			
No	3414 (70·2%)	4594 (96·7%)	8008 (83·3%)
Yes	1423 (29·3%)	129 (2·7%)	1552 (16·2%)
Data missing	24 (0·5%)	26 (0·6%)	50 (0·5%)
Previous tuberculosis contact before recent exposure			
Yes	670 (13·8%)	537 (11·3%)	1207 (12·6%)
No	4035 (83·0%)	3988 (84·0%)	8023 (83·5%)
Data missing	156 (3·2%)	224 (4·7%)	380 (4·0%)
Previous tuberculosis diagnosis			
Yes	140 (2·9%)	213 (4·5%)	353 (3·7%)
No	4642 (95·5%)	4428 (93·2%)	9070 (94·4%)
Data missing	79 (1·6%)	108 (2·3%)	187 (2·0%)
BCG-vaccination status*			
Vaccinated	3685 (75·8%)	2933 (61·8%)	6618 (68·9%)
Not vaccinated	536 (11·0%)	934 (19·7%)	1470 (15·3%)
Data missing	640 (13·2%)	882 (18·6%)	1522 (15·8%)
BCG vaccination (all)†			
Vaccinated	4155 (85·5%)	3791 (79·8%)	7946 (82·7%)
Not vaccinated	536 (11·0%)	934 (19·7%)	1470 (15·3%)
Data missing	170 (3·5%)	24 (0·5%)	194 (2·0%)
Diabetes			
Yes	325 (6·7%)	481 (10·1%)	806 (8·4%)
No	4519 (93·0%)	4245 (89·4%)	8764 (91·2%)
Data missing	17 (0·3%)	23 (0·5%)	40 (0·4%)
Haematological malignancy			
Yes	10 (0·2%)	6 (0·1%)	16 (0·2%)
No	4815 (99·1%)	4689 (98·7%)	95.4 (98·9%)
Data missing	36 (0·7%)	54 (1·1%)	90 (0·9%)
HIV status (self-reported)			
Positive	43 (0·9%)	12 (0·3%)	55 (0·6%)
Negative	4636 (95·4%)	4239 (89·3%)	8875 (92·4%)
Data missing	182 (3·7%)	498 (10·5%)	680 (7·1%)

(Table 1 continues on next page)

	Contacts (n=4861)	Migrants (n=4749)	All participants (n=9610)
(Continued from previous page)			
Smoking status			
Smoker	1172 (24·1%)	635 (13·4%)	1807 (18·8%)
Non-smoker	3659 (75·3%)	4078 (85·9%)	7736 (80·5%)
Data missing	31 (0·6%)	36 (0·8%)	67 (0·7%)
Previous solid organ transplant			
Yes	15 (0·3%)	10 (0·2%)	25 (0·3%)
No	4813 (99·0%)	4697 (98·9%)	9510 (99·0%)
Data missing	33 (0·7%)	42 (0·9%)	75 (0·8%)
Anti-TNF α (self-report)			
Yes	17 (0·3%)	15 (0·3%)	32 (0·3%)
No	4664 (96·0%)	4114 (86·6%)	8778 (91·3%)
Data missing	180 (3·7%)	620 (13·1%)	800 (8·3%)
Immunosuppressive drug use			
Yes	43 (0·9%)	32 (0·7%)	75 (0·8%)
No	4639 (95·4%)	4086 (86·0%)	8725 (90·8%)
Data missing	179 (3·7%)	631 (13·3%)	810 (8·4%)
Drug or alcohol misuse			
Yes	166 (3·4%)	32 (0·7%)	198 (2·1%)
No	4672 (96·1%)	4677 (98·5%)	9349 (97·3%)
Data missing	23 (0·5%)	40 (0·8%)	63 (0·7%)
Homeless status			
Homeless	111 (2·3%)	73 (1·5%)	184 (1·9%)
Not homeless	4728 (97·3%)	4642 (97·8%)	9370 (97·5%)
Data missing	22 (0·5%)	34 (0·7%)	56 (0·6%)
BMI (kg/m²)			
Mean (SD)	25·3 (4·9)	25·0 (4·6)	25·1 (4·8)
Data missing	368 (7·6%)	307 (6·5%)	675 (7·0%)
Occupation			
Health-care sector	257 (5·3%)	95 (2·0%)	352 (3·7%)
Social or prison sector	33 (0·7%)	9 (0·2%)	42 (0·4%)
Laboratory or pathology worker	11 (0·2%)	4 (0·1%)	15 (0·2%)
Agricultural or animal care	0	0	0
Education	974 (20·0%)	708 (14·9%)	1682 (17·5%)
None	1119 (23·0%)	1881 (39·6%)	3000 (31·2%)
Other	2257 (46·4%)	1691 (35·6%)	3948 (41·1%)
Unknown	210 (4·3%)	361 (7·6%)	571 (5·9%)
Travel in previous 2 years‡			
Yes	1822 (37·5%)	1741 (36·7)	3563 (37·1%)
No	2880 (59·2%)	2071 (43·6%)	4951 (51·5%)
Data missing	159 (3·3%)	937 (19·7%)	1096 (11·4%)
Travel before previous 2 years‡			
Yes	1630 (33·5%)	1403 (29·5%)	3033 (31·6%)
No	2817 (58·0%)	2247 (47·3%)	5064 (52·7%)
Data missing	414 (8·5%)	1099 (23·1%)	1513 (15·7%)

Data are n (%), median (IQR), or mean (SD). BMI=body-mass index. TNF=tumour necrosis factor. *Ascertained by scar, medical record, or reliable recall. †Includes those assumed to have BCG (BCG data missing and participant non-UK born). ‡Travelled or lived outside of the UK (not including western Europe, the USA, Canada, and Australia).

Table 1: **Baseline demographic and clinical data**

6380 (66·4%) participants completed all tests and follow-up (the per-protocol population) and were included in the primary analysis, of whom 77 (1·2%) developed tuberculosis. Figures 2A–F show Kaplan-Meier graphs of time to progression to tuberculosis in the per-protocol population and each test by result. Of the 77 participants who developed active tuberculosis, the QuantiFERON-TB Gold-In Tube test identified 47 (61%) participants as positive, T-SPOT.*TB* identified 52 (68%) as positive, the TST-5 threshold identified 64 (83%) as positive, the TST-10 threshold identified 58 (75%) as positive, and the TST-15 threshold identified 52 (68%) as positive (figure 1). The 5 mm threshold TST (TST-5) positively identified more participants who progressed to tuberculosis than any of the other TST thresholds or tests (figure 1). The proportion of participants who classified as test negative varied considerably across the tests, largely driven by the TST threshold. Only 3423 (54%) participants tested negative by use of TST-5, which increased to 4229 (66%) with TST-10 and 4895 (77%) with TST-15. 5145 (81%) participants tested as negative with T-SPOT.*TB* and 4936 (77%) with QuantiFERON-TB Gold-In Tube test, similar to the results of TST-15.

Of 14 participants classified as contacts who developed tuberculosis and for whom MIRU-VNTR data were available for the contact and index case, strain comparison suggested that 13 cases were probably related to the index case.

Across the three index tests and TST thresholds, little variation was seen in tuberculosis incidence among

	All participants (n=97)	Per-protocol population (n=77)
Contact	63 (65%)	51 (66%)
Immigrant	34 (35%)	26 (34%)
Sex		
Female	47 (48%)	37 (48%)
Male	50 (52%)	40 (52%)
Age (years)		
Median (IQR)	30 (26–38)	30 (26–38)
≤35 years	66 (68%)	52 (68%)
>35 years	31 (32%)	25 (32%)
UK born		
No	81 (84%)	64 (83%)
Yes	16 (16%)	13 (17%)
BCG vaccination*		
Yes	72 (74%)	57 (74%)
No	11 (11%)	10 (13%)
Data missing	14 (14%)	10 (13%)
Ever smoked		
Yes	18 (19%)	15 (19%)
No	79 (81%)	62 (81%)
BMI (kg/m²)		
Mean (SD)	23·6 (4·5)	23·4 (4·5)
Data missing	8 (8%)	6 (8%)

Data are n (%), median (IQR), or mean (SD). BMI=body-mass index. *Ascertained by scar inspection, emdical record, or reliable recall.

Table 2: **Characteristics of participants who progressed to active tuberculosis**

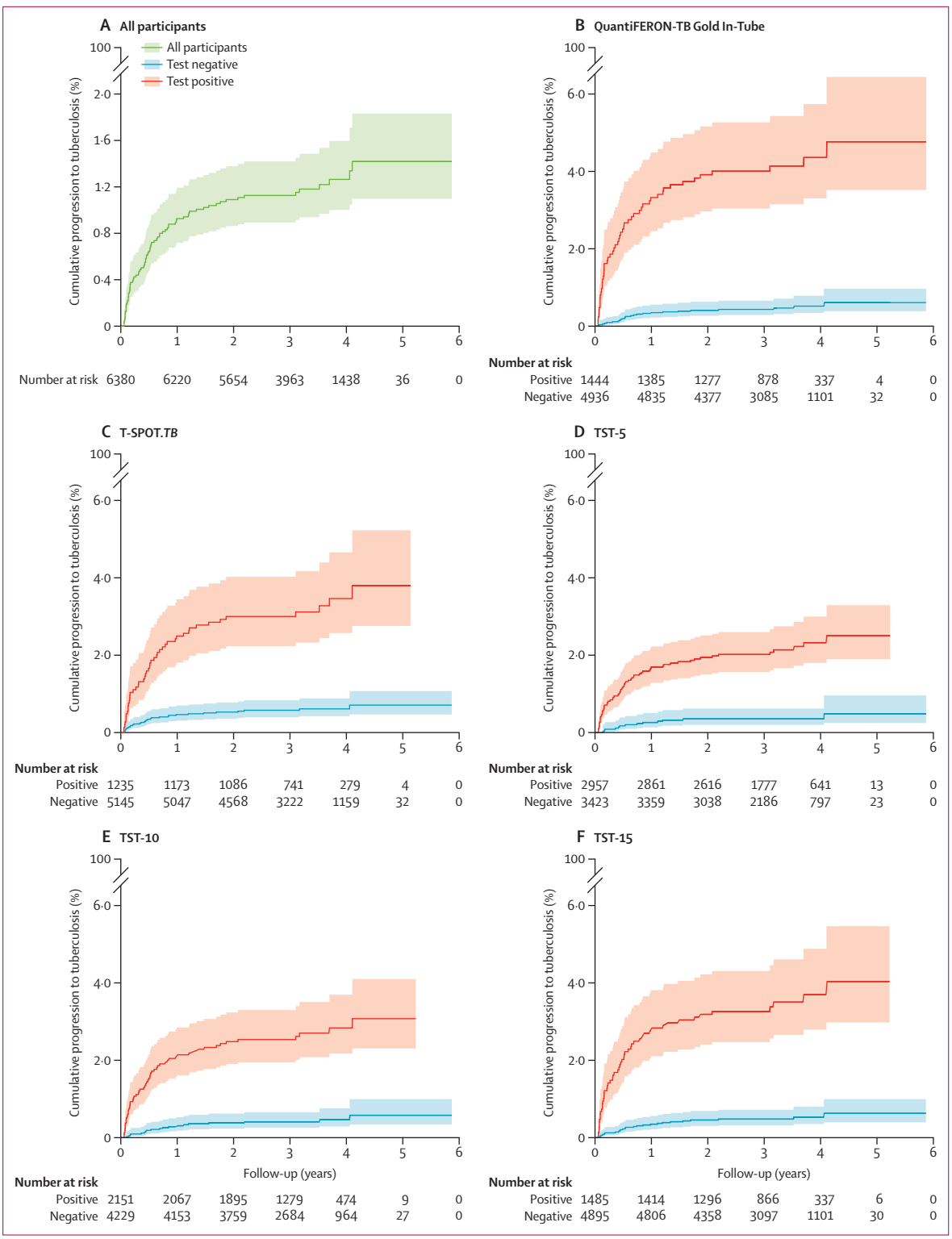


***Figure 2*: Time to progression to tuberculosis in all participants (A) and according to tuberculosis test result (B–F)**
Lines are estimates, with 95% CIs as the shaded area. Data are shown for per-protocol population. Scale for cumulative progression to tuberculosis in panel A is greater than in B–F.

	Progressed	Did not progress	Person-years at risk	Annual incidence per 1000 person-years (95% CI)	IRR (95% CI)
QuantiFERON-TB Gold In-Tube					
Test positive	47/1444 (3·3%)	1397/1444 (96·7%)	4649·9	10·1 (7·4–13·4)	..
Test negative	30/4936 (0·6%)	4906/4936 (99·4%)	15 921·6	1·9 (1·3–2·7)	..
Positive vs negative	..	..	..	..	5·4 (3·4–8·5)
T-SPOT.*TB*					
Test positive	52/1235 (4·2%)	1183/1235 (95·8%)	3926·2	13·2 (9·9–17·4)	..
Test negative	25/5145 (0·5%)	5120/5145 (99·5%)	16 645·3	1·5 (1·0–2·2)	..
Positive vs negative	..	..	..	..	8·8 (5·5–14·2)
TST-5					
Test positive	64/2957 (2·2%)	2893/2957 (97·8%)	9416·8	6·8 (5·2–8·7)	..
Test negative	13/3423 (0·4%)	3410/3423 (99·6%)	11 154·6	1·2 (0·6–2·0)	..
Positive vs negative	..	..	..	..	5·8 (3·2–10·6)
TST-10					
Test positive	58/2151 (2·7%)	2093/2151 (97·3%)	6822·3	8·5 (6·5–11·0)	..
Test negative	19/4229 (0·4%)	4210/4229 (99·6%)	13 749·2	1·4 (0·8–2·2)	..
Positive vs negative	..	..	..	..	6·2 (3·7–10·3)
TST-15					
Test positive	52/1485 (3·5%)	1433/1485 (96·5%)	4674·8	11·1 (8·3–14·6)	..
Test negative	25/4895 (0·5%)	4870/4895 (99·5%)	15 896·6	1·6 (1·0–2·3)	..
Positive vs negative	..	..	..	..	7·1 (4·4–11·4)

Data are n/N (%), when N is number of participants with that result, and n is number of participants who progressed or did not progress to tuberculosis. IRR=incidence rate ratio. TST=tuberculin skin test. TST-5=TST with threshold ≥5 mm. TST-10=TST with threshold ≥10 mm. TST-15=BCG-dependent definition of TST: ≥15 mm for BCG-vaccinated participant and >5 mm non-vaccinated participant.

Table 3: **Incidences and rate ratios for individual tests**

	TST-5	TST-10	TST-15	T-SPOT.*TB*	QuantiFERON-TB Gold In-Tube
TST-5	..	1·25 (1·15–1·36; <0·0001)	1·64 (1·44–1·87; <0·0001)	1·99 (1·68–2·34; <0·0001)	1·52 (1·26–1·83; <0·0001)
TST-10	..	..	1·31 (1·617–1·47; <0·0001)	1·59 (1·34–1·88; <0·0001)	1·21 (1·01–1·46; 0·041)
TST-15	..	..	..	1·21 (1·01–1·43; 0·037)	0·93 (0·76–1·13; 0·453)
T-SPOT.*TB*	..	..	..	..	0·77 (0·66–0·89; 0·0003)

Values indicate the ratio of test positivity rates (with 95% CI and p values) in participants who progressed to active tuberculosis compared with those who did not comparing test A (horizontally across table) with test B (vertically up table). A value above 1 indicates a positive result on test A is a stronger predictor of progression to tuberculosis than a positive result on test B. TST=tuberculin skin test. TST-5=TST with threshold ≥5 mm. TST-10=TST with threshold ≥10 mm. TST-15=BCG-dependent definition of TST: ≥15 mm for BCG-vaccinated participant and >5 mm non-vaccinated participant.

Table 4: **Predictive value of tests by pairwise comparisons for progression to tuberculosis**

participants with negative results, with annual incidences of 1·2 per 1000 person-years (95% CI 0·6–2·0) for TST-5 to 1·9 per 1000 person-years (1·3–2·7) for QuantiFERON-TB Gold-In Tube test (table 3). By contrast, the annual incidence among the participants who tested positive varied a lot more between tests, with T-SPOT.*TB* having the highest annual incidence (13·2 per 1000 person-years, 95% CI 9·9–17·4), but only slightly higher than was found for TST-15 (11·1 per 1000 person-years, 8·3–14·6) and QuantiFERON-TB Gold-In Tube (10·1 per 1000 person-years, 7·4–13·4). Both TST-5 and TST-10 were worse predictors than TST-15.

Formal statistical comparisons of the predictive value of positive and negative results of tests showed that a positive result for TST-5 was a significantly worse predictor of progression to active tuberculosis than positive results for any of the other tests (table 4). A positive T-SPOT.*TB* result was a significantly better predictor of progression to active tuberculosis than all other tests. A positive result from TST-15 or QuantiFERON-TB Gold-In Tube were also significantly better predictors of progression to active tuberculosis than a positive result for TST-10. The difference between a positive TST-15 result and a positive result for QuantiFERON-TB Gold In-Tube was not significant in predicting progression. We found no significant differences between negative results for single tests in predicting non-progression to active tuberculosis (table 5).

Sensitivity analyses, including analysis stratified by contacts and migrants, gave results consistent with the main study findings (appendix pp 7–11).

The positive predictive values for each test were calculated. QuantiFERON-TB Gold In-Tube had a positive predictive value of 3·3%, T-SPOT.*TB* had a value of 4·2%, TST-5 had a value of 2·2%, TST-10 had a value of 2·7%, and TST-15 had a value of 3·5% (table 3). The negative predictive values of each test were 99·4% for

QuantiFERON-TB Gold In-Tube, 99·5% for T-SPOT.*TB*, 99·6% for TST-5, 99·6% for TST-10, and 99·5% for TST-15 (table 3). In the sensitivity analyses, for contacts the positive predictive values of each test were slightly higher than for the whole per-protocol population, and the positive predictive values for migrants were lower than for the whole per-protocol population (appendix p 11).

Discussion

In this prospective cohort study, we used the annual incidences of tuberculosis to quantify the ability of TST and two IGRAs to predict progression to active tuberculosis among high-risk populations. We found that the IGRA T-SPOT.*TB* had a positive predictive value of 4·2%, and the BCG-stratified TST, TST-15, had a positive predictive value of 3·5%, with the highest IRRs (comparing the incidence of tuberculosis for those with positive and negative results; 8·8 [95% CI 5·5–14·2] for T-SPOT.*TB* and 7·1 [4·4–11·4] for TST-15).

To identify the most suitable screening test to assess the progression of disease, three criteria need to be met: a high proportion of tested individuals should be classified as test negative and therefore require no further monitoring; a low rate of progression to tuberculosis in those who tested as negative, indicating the test's ability to successfully categorise individuals who are at low progression risk; and increased likelihood of progression in those who test as positive, indicating the ability of the test to correctly predict disease.

Although little between-test variation was seen in tuberculosis incidence in participants who tested negative, the proportion of participants who were classified as test negative (and hence considered unlikely to progress) varied considerably, especially by TST threshold, for which TST-5 classified the lowest proportion of participants as negative, followed by TST-10 and TST-15. The proportion of participants who tested negative was similar for T-SPOT.*TB*, QuantiFERON-TB Gold-In Tube, and TST-15. The incidence among participants who tested positive varied, such that T-SPOT.*TB* was the best predictor of disease progression, although the incidence was only slightly different from that found among those who tested positive by use of TST-15 and QuantiFERON-TB Gold In-Tube. Both TST-5 and TST-10 were less predictive than TST-15.

While the low fixed thresholds for the TST-positive cutoff detected the highest proportion of individuals who progressed to tuberculosis (83% at 5 mm and 75% at 10 mm compared with 68% for TST-15), they also led to a substantially higher number of participants categorised as at risk of progression and lower progression among the participants who tested positively than was found with the high threshold TST. Compared with TST-15, TST-10 reclassified 666 (10·4%) of 6380 participants tested as high risk (of whom six progressed to tuberculosis) and TST-5 reclassified a further 806 (12·6%) participants as high risk (of whom a further six progressed to tuberculosis). The incidence in those reclassified from TST-15 to TST-10 was 2·8 per 1000 person-years, (95% CI 1·0–6·1) and from TST-10 to TST-5 was 2·3 per 1000 person-years (95% CI 0·8–5·0).

	TST-5	TST-10	TST-15	T-SPOT.*TB*	QuantiFERON-TB Gold In-Tube
TST-5	..	1·18 (0·86–1·63; 0·300)	1·35 (0·90–2·01; 0·147)	1·28 (0·77–2·12; 0·337)	1·60 (0·97–2·65; 0·065)
TST-10	..	..	1·14 (0·86–1·51; 0·368)	1·08 (0·72–1·62; 0·704)	1·35 (0·91–2·01; 0·130)
TST-15	..	..	..	0·95 (0·67–1·36; 0·784)	1·19 (0·84–1·68; 0·319)
T-SPOT.*TB*	..	..	..	..	1·25 (0·97–1·61; 0·081)

Values indicate the ratio of test negativity rates (with 95% CI and p values) in participants who progressed to active tuberculosis compared with those who did not comparing test A (horizontally across table) with test B (vertically up table). A value below 1 indicates a negative result on test A is a stronger predictor of no progression to tuberculosis than a negative result on test B. TST=tuberculin skin test. TST-5=TST with threshold ≥5 mm. TST-10=TST with threshold ≥10 mm. TST-15=BCG-dependent definition of TST: ≥15 mm for BCG-vaccinated participant and >5 mm non-vaccinated participant

Table 5: **Predictive value of tests by pairwise comparisons for no progression to tuberculosis**

When the intention is to identify the largest proportion of individuals with a positive test result who might progress to active tuberculosis, such as among household contacts of patients with smear-positive pulmonary tuberculosis, TST-5—as currently recommended in US Centers for Disease Control and Prevention guidelines[14]—might be the best approach. By contrast, screening programmes (eg, of migrants) should consider progression rates, the trade-off between the three criteria of selecting the most appropriate testing method outlined earlier, and the cost-effectiveness of the selected testing strategy.

We compared our results with the review that informed the WHO guidelines on managing latent tuberculosis[15,16] and summarised all existing pairwise comparisons of an IGRA versus TST. We identified several studies in our literature search and from the WHO review that evaluated TST versus a single IGRA in high incidence countries,[16] and four did head-to-head comparisons in low incidence countries.[7–10] However, only one of these studies compared TST with each of the commercially available IGRAs,[10] and the other three studies only compared TST with QuantiFERON-TB Gold In-Tube.[7–9] Although sample sizes ranged from 339 to 1335 participants, all four studies had 15 or fewer individuals who progressed to active tuberculosis. To our knowledge, our study is the largest head-to-head comparison of the three available diagnostic tests for latent tuberculosis infection, both in terms of the number of participants and progressions to active tuberculosis. Our estimates of positive predictive value are towards the low end of those previously reported[7–10,17–23] and are less than were found in two other small cohort studies.[8,24] Positive predictive values for the development of active tuberculosis depend in part on the incidence of tuberculosis in the study population—ie, the positive predictive value is higher when the incidence is greater.[8] Our analysis of TST stratified by BCG-vaccination status

showed similar IRRs to those for both IGRAs, which is in contrast with the WHO guidelines review[16] that concluded TSTs had a lower IRR than IGRAs for progression to active tuberculosis in low incidence countries. In our study, progression of disease was increased among the recently exposed participants compared with migrants whose infection had probably been acquired in another country.

In the primary analysis, we used data only from participants with all test results and follow-up data available. While this choice for analysis could potentially lead to selection bias, a sensitivity analysis that included data from participants with incomplete test results gave similar results. We assessed exposure, outcome, and covariates using the same standards for all participants, minimising the chance of information bias and enhancing data completeness. We used manufacturer-defined methods for both IGRAs, and the TSTs were administered by trained research nurses. We used multiple approaches to identify participants who progressed to active tuberculosis, maximising ascertainment of the outcome. Prevalent cases (active tuberculosis at baseline) were excluded to increase the probability that detected cases reflected progression from latent infection. When possible, we used MIRU-VNTR data to assess whether progression among contacts was most likely due to transmission from the index case; 13 (93%) of 14 identified case-contact pairs were consistent with transmission having occurred.

Our study has some limitations. Although follow-up within the UK was rigorous, cases of tuberculosis in participants who left the UK during the study period or follow-up might not have been identified. We were also unable to examine long-term progression risk. Incorporation bias can arise when the study of immune-based results influences the diagnosis of active tuberculosis (eg, if the IGRA result influences the clinician's investigation for tuberculosis, then those classified as having active tuberculosis would be more likely to have been from the IGRA-positive group, consequently favouring IGRAs for prediction of disease). However, most participants were recruited at sites that did not use IGRA results from the study in patient management (in the UK at the time of the study, latent tuberculosis infection screening was standard practice only for people who had been in contact with active tuberculosis and were younger than 35 years), which would minimise this effect. Notably, this incorporation bias similarly applies to TST, which is more difficult to mask. A further limitation of our study is the self-reported nature of data on comorbidities, particularly HIV. The small number of participants on treatment for latent tuberculosis infection and with self-reported HIV infection prevented us from doing our intended subgroup analysis.

Our results have implications for guidelines and future cost-effectiveness analyses, particularly in the screening of tuberculosis contacts for latent tuberculosis infection and also recent migrants (ie, in the past 5 years) from high-burden countries. Although negative predictive values were similar for all tests, we have found statistically significant differences for the positive prediction of progression to active tuberculosis between tests, with a positive TST-5 result being a significantly worse predictor than all other tests, and a positive T-SPOT.*TB* result being a significantly better predictor than all other tests, except for TST-15, and QuantiFERON-TB Gold In-Tube was significantly better than TST-10. Although the review of the WHO guidelines[15,16] did not examine TST stratified by BCG-vaccination status compared with IGRAs, we show for the first time, to our knowledge, that by use of this stratification method, TST is equivalent to IGRAs. The most recent WHO guidelines[16] recommend either a TST or IGRA as equivalent alternatives without taking into account previous BCG vaccination. Our results contradict this recommendation. The screening strategy by which participants are identified for treatment influences the cost-effectiveness of any test-and-treat programme; the more people who are identified as positive and eligible for treatment, the greater the cost.[25] The trade-offs of testing with TST-5 (which identified the most progressors but with potentially the highest number needed to treat) versus IGRAs and TST-15 (which are likely to have the lowest numbers needed to treat) has implications for WHO guidelines depending on the uptake of testing and adherence to management in different settings. In the absence of a highly specific diagnostic test for latent tuberculosis infection at risk of progression, a cheap and non-toxic treatment is needed that can be given to a larger proportion of screened people than is the case with current treatment options.

A new version of QuantiFERON-TB Gold In-Tube[26] has been developed subsequent to the end of the study period that could have greater sensitivity for detecting latent tuberculosis infection; assessment of its ability to predict progression to active tuberculosis will be important in future studies. Although other new assays, such as transcriptional profiling, could improve the detection of incipient tuberculosis,[27] the increase in positive predictive value of these tests compared with IGRAs appears small because of low specificity.[28] Better use of existing assays remains crucial until a more specific and highly predictive commercial test is developed.

In conclusion, our data provide evidence that TST stratified by BCG-vaccination status yields similar predictive values to the two commonly used IGRAs. IGRA or TST-15 strategies gave a high proportion of negative test results, with low progression among these individuals, and correctly identified a high risk of progression in participants who had positive test results, supporting their use in screening programmes. TST-5 will identify most individuals who will benefit from treatment in high-risk groups at the cost of increasing the number of patients classified as more likely to progress to tuberculosis. Country-specific cost-effectiveness analyses, stratification of progression risk in sub-populations, and

treatment uptake of preventive therapies should inform screening strategies.

Contributors

IA, FD, JJD, JMW, and AL designed the study. IA and JS led recruitment and follow-up of participants with all site principal investigators. AJS did the main statistical analyses with oversight from JJD, and CJ did descriptive analyses with input from IA, AL, and ML. Laboratory analyses were done by AL, FD, SS, C-YT, VN, MR-R, and HW. IA wrote the first draft of the manuscript with input from CJ, AJS, and JJD. All other authors contributed to the interpretation of data, revisions of the manuscript, recruitment of participants, and have seen and agreed on the final submitted version of the manuscript. IA is chief investigator and guarantor of the study. Study governance was overseen by a trial steering committee and data monitoring committee. The governance groups had oversight of the study protocol including definitions, governance, finance, participant recruitment, and advice to the study funders.

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Declaration of interests

IA was funded by the UK National Institute for Health Research (NIHR; SRF-2011–04–001; NF-SI-0616–10037), Medical Research Council, UK Department of Health, and the Wellcome Trust. AL was funded by a Wellcome Trust Senior Research Fellowship in Clinical Science and an NIHR Senior Investigator Award. AL has issued several patents associated with immunodiagnostics for tuberculosis and has entitlement to royalties from patents licensed to Oxford Immunotec, Abingdon, UK, from the University of Oxford, Oxford, UK. All other authors declare no competing interests.

Acknowledgments

We thank the study administrator, laboratory staff who did the tests, clinical and nursing colleagues who contributed to participant recruitment, and our study steering committee. We also thank all the temples, mosques, offices, and other community settings for their assistance. This study was funded by the UK National Institute for Health Research Health Technology Assessment Programme 08-68-01.

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