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Quantitative Interferon Gamma Release Assay and Tuberculin Skin Test Results to Predict Incident Tuberculosis: A Prospective Cohort Study

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At a Glance Commentary

Scientific Knowledge on the Subject

Few studies have previously assessed the association between quantitative interferon gamma release assay (IGRA) results and tuberculosis (TB) incidence rates; all were restricted to only one test, the QuantiFERON Gold-In-Tube (QFT-GIT). While two studies have suggested that a QFT-GIT threshold of ≥4 IU/mL may improve prediction of incident TB, none were able to fully assess the potential impact of implementing higher thresholds on predictive values, or the proportion of incident cases missed by latent tuberculosis infection (LTBI) screening programmes.

What This Study Adds to the Field

This is the first study to comprehensively assess the potential impact of implementing higher diagnostic thresholds for all three available LTBI tests (tuberculin skin test (TST), QFT-GIT and T-SPOT.TB). We demonstrate that TB incidence rates increase incrementally with the magnitude of the T cell recall response for all three tests. However, while implementing higher thresholds leads to modest improvement in positive predictive value of these tests for incident TB, this benefit is offset by a marked loss in sensitivity, with the majority of incident TB cases being missed. Implementing higher diagnostic thresholds for the TST and commercial IGRAs is therefore unlikely to be of value for LTBI screening programmes in settings aiming towards TB elimination.

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Abstract

Rationale: Development of diagnostic tools with improved predictive value for tuberculosis (TB) is a global research priority.

Objectives: We evaluated whether implementing higher diagnostic thresholds than currently recommended for QuantiFERON Gold-in-Tube (QFT-GIT), T-SPOT.TB and the tuberculin skin test (TST) might improve prediction of incident TB.

Methods: Follow-up of a UK cohort of 9,610 adult TB contacts and recent migrants was extended by re-linkage to national TB surveillance records (median follow-up 4.7 years). Incidence rates and rate ratios, sensitivities, specificities and predictive values for incident TB were calculated according to ordinal strata for quantitative results of QFT-GIT, T-SPOT.TB and TST (with adjustment for prior BCG).

Measurements and Main Results: For all tests, incidence rates and rate ratios increased with the magnitude of the test result ($p<0.0001$). Over three years' follow-up, there was a modest increase in positive predictive value (PPV) with the higher thresholds (3.0% for QFT-GIT ≥0.35 IU/mL *vs.* 3.6% for ≥4.00 IU/mL; 3.4% for T-SPOT.TB ≥5 spots *vs.* 5.0% for ≥50 spots; and 3.1% for BCG-adjusted TST ≥5mm *vs.* 4.3% for ≥15mm). As thresholds increased, sensitivity to detect incident TB waned for all tests (61.0% for QFT-GIT ≥0.35 IU/mL *vs.* 23.2% for ≥4.00 IU/mL; 65.4% for T-SPOT.TB ≥5 spots *vs.* 27.2% for ≥50 spots; 69.7% for BCG-adjusted TST ≥5mm *vs.* 28.1% for ≥15mm).

Conclusions: Implementation of higher thresholds for QFT-GIT, T-SPOT.TB and TST modestly increases PPV for incident TB, but markedly reduces sensitivity. Novel biomarkers or validated multivariable risk algorithms are required to improve prediction of incident TB.

Words: 250

Keywords: latent tuberculosis; epidemiology; screening; quantiferon; t-spot.tb

Introduction

Treatment for latent tuberculosis infection (LTBI) reduces the risk of progression to tuberculosis (TB) disease, and thus offers an opportunity to prevent TB-related morbidity, while also interrupting onward transmission(1). Scaling up testing and treatment for LTBI among TB risk groups is therefore an integral component of the World Health Organization (WHO) End TB Strategy(2, 3). However, the effectiveness of LTBI screening programmes is undermined by the poor positive predictive value of currently available LTBI diagnostic tests for incident TB disease, which is <5% for both the tuberculin skin test (TST) and commercial interferon gamma release assays (IGRAs) over a two year period(4–6). As a result, the majority of individuals with a positive TST or IGRA will never develop TB disease. This leads to a large burden of unnecessary LTBI treatment, with associated risks of drug toxicity to patients, and economic costs to health services. Furthermore, poor predictive value may also undermine the uptake of LTBI treatment among target groups, due to the low perceived risk of TB(7). The WHO have therefore highlighted the development of novel biomarkers with better predictive value as a key research and development priority in a target product profile (TPP) consensus document, stating optimal performance criteria of sensitivity and specificity ≥90%(8).

Recent emerging data from studies in both adults and infants in low and high TB incidence settings have demonstrated that higher quantitative IGRA results are associated with increased risk of incident TB, thus raising hope that IGRAs themselves may go some way to fulfilling the WHO TPP(9–11). Moreover, since current diagnostic thresholds for scoring a positive test are based on detecting sensitisation to *M. tuberculosis* rather than development of incident TB disease, optimising these thresholds might lead to improved implementation of existing LTBI diagnostics, while novel biomarkers with improved predictive value are awaited. However, previous evaluations of quantitative IGRA results have been limited to the QuantiFERON Gold-In-Tube (QFT-GIT) assay only(9–13), and it remains unclear whether

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implementation of a higher threshold for positivity may actually be of use in clinical practice to improve the risk-stratification of patients with LTBI.

We sought to address these key knowledge gaps by extending follow-up of participants in the UK Prognostic Evaluation of Diagnostic IGRAs Consortium (UK PREDICT) TB study(6). Firstly, we aimed to test the hypothesis that higher quantitative QFT-GIT, T-SPOT.TB and TST results were associated with increased risk of incident TB. Secondly, we sought to evaluate the test sensitivities, specificities and predictive values when higher thresholds for a positive test than currently recommended are used over a fixed three-year follow-up period. Finally, we plotted receiver operating characteristic (ROC) curves for all three tests, to compare performance across the full range of test cut-offs. Some of the results of this study have been previously reported in the form of an abstract(14).

Methods

Population

The UK PREDICT study cohort has been described in detail previously(6). Briefly, individuals aged ≥16 years were recruited (01/05/2010-30/06/2015) from London, Birmingham and Leicester. Inclusion criteria were: recent contacts of patients with active TB; or recent migrants from, or prolonged travellers to, high TB burden countries. Participants treated for LTBI were excluded, as were participants diagnosed with suspected baseline prevalent TB (evidence of TB within 21 days of enrolment).

Study procedures

Participants were tested with QFT-GIT (Qiagen, Venlo, The Netherlands), T-SPOT.TB (Oxford Immunotec, UK) and then Mantoux TST (Statens Serum Institut) using standardised protocols on the same day, at least 6 weeks from last TB exposure or migration. Indeterminate results were classified as recommended by the manufacturers (Online Data Supplement). Incident TB cases were identified via telephone interview at 12 and 24 months, and by linkage to the

national TB surveillance system held at Public Health England, which includes all statutory TB notifications and all results of positive *M. tuberculosis* cultures. For this analysis, all participants were re-linked to national TB surveillance records to identify individuals notified with TB until 31/12/2017. Follow-up was censored on the earliest of date of TB diagnosis, death or 31/12/2017. The study procedures and protocol were approved by the Brent NHS Research Ethics Committee (10/H0717/14).

Statistical Analysis

Incidence rates and ratios relative to the negative test category (with 95% confidence intervals (CIs)) for incident TB were calculated using Poisson models, according to ordinal strata for quantitative results of each LTBI test during the full duration of follow-up. For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was subtracted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST'). The rationale for this was that, in the main UK PREDICT analysis, a BCG-stratified TST cut-off of 5mm in BCG-naïve or 15mm in vaccinated participants performed similarly to IGRA(6). For QFT-GIT and BCG-adjusted TST, test strata were based on previous data(9, 10, 15–17). For QFT-GIT, these were TB antigen interferon-γ minus unstimulated control interferon-γ levels of <0.35 IU/mL, 0.35–0.69 IU/mL, 0.7-3.99 IU/mL and ≥4.00 IU/mL. For BCG-adjusted TST, the strata used were <5mm, 5-9mm, 10-14mm and ≥15mm induration.

For T-SPOT.TB, no previous data were available to inform the test strata examined. We chose initial strata of spot counts in the maximal TB antigen panel minus the negative control of ≤4 spots and 5-7 spots, based on manufacturer test thresholds for borderline and positive results, and used restricted cubic spline models to investigate the non-linear association between quantitative T-SPOT.TB results and incident TB risk (Online Data Supplement). Informed by visualisation of these models, we defined further strata of spot counts in the maximal TB

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antigen panel minus the negative control of 8-49 spots and ≥50 spots (corresponding approximately to the top 5% of quantitative T-SPOT.TB results in the cohort).

Sensitivity, specificity, positive and negative predictive values and receiver operating characteristic (ROC) curves for incident TB over a fixed three-year follow-up period were calculated at the corresponding thresholds for each stratum.

Seven sensitivity analyses were performed, as detailed in the Online Data Supplement. All analyses were performed using Stata version 15.

Results

A total of 10,045 participants were recruited to the study. Of these, 175 had possible prevalent TB at baseline and a further 260 were treated for LTBI. The remaining 9,610 were therefore included in the final study cohort, with median follow-up 4.7 years (interquartile range (IQR) 3.8-5.5). Baseline characteristics of the cohort are summarised in Table 1. A total of 5,526/9,610 (57.5%) participants were aged <35 years. The cohort included 4,781 (49.8%) recent TB contacts and 4,729 (49.2%) migrants from high-incidence countries, while 6,618/9,610 (68.9%) reported previous BCG vaccination. A total of 8,562 (89.1%), 8,079 (84.1%) and 7,833 (81.5%) of participants had available quantitative QFT-GIT, T-SPOT.TB and TST results, respectively. A total of 107 participants progressed to incident TB during follow-up, of which 47 (43.9%) had pulmonary involvement, and 59 (55.1%) were microbiologically confirmed by either culture or PCR. Median time to TB disease among the progressors was 188 days (IQR 76 – 488 days). A total of 71 (66.4%), 19 (17.8%) and 5 (4.7%) participants progressed during the first, second and third years of follow-up, respectively. The distributions of quantitative QFT-GIT, T-SPOT.TB and BCG-adjusted TST results, stratified by the development of incident TB, are shown in Figure 1.

Indeterminate results contributed 122/8,562 (1.4%) QFT-GIT results, and 121/8,079 (1.5%) T-SPOT.TB results. Of those with available results, 6,637 (77.5%), 405 (4.7%), 820 (9.6%) and

578 (6.8%) had QFT-GIT results in the <0.35 IU/mL, 0.35–0.69 IU/mL, 0.7-3.99 IU/mL and ≥4.00 IU/mL strata, respectively. For T-SPOT.TB, 6,290 (77.9%), 319 (3.9%), 906 (11.4%) and 443 (5.6%) of participants had results in the ≤4 spots, 5-7 spots, 8-49 spots and ≥50 spots strata, respectively. For BCG-adjusted TST, 5,769 (73.7%), 827 (10.6%), 630 (8.0%), and 607 (7.75%) had induration in the <5mm, 5-9mm, 10-14mm and ≥15mm strata, respectively. Duration of follow-up was similar between participants in different test strata (Figure 2).

For all tests, TB incidence rates and ratios increased with the magnitude of the test response (Figure 2). For QFT-GIT, TB incidence rates (per 1,000 person-years) increased from 1.10 (95% CI 0.78 - 1.53) in the <0.35 IU/mL stratum, to 10.02 (6.82 - 14.72) in the ≥4.00 IU/mL stratum (likelihood ratio test for trend p<0.0001). For T-SPOT.TB, TB incidence rates increased from 1.10 (0.78 - 1.54) in the ≤4 spots stratum to 12.73 (8.73 - 18.57) in the ≥50 spots stratum (p<0.0001). For the BCG-adjusted TST, TB incidence rates increased from 1.07 (0.75 - 1.54) in the <5mm stratum to 10.95 (7.70 - 15.57) in the ≥15mm stratum (p<0.0001).

Considering diagnostic test performance for the prediction of incident TB in the first three years of follow-up, positive predictive values (PPV) were uniformly low but increased modestly with the higher thresholds for all three tests (Table 2). PPVs were 3.0% (2.2 - 3.9) for QFT-GIT ≥0.35 IU/mL *vs.* 3.6% (2.2 - 5.5) for ≥4.00 IU/mL; 3.4% (2.6 - 4.4) for T-SPOT.TB ≥5 spots *vs.* 5.0% (3.2 - 7.5) for ≥50 spots; and 3.1% (2.4 - 4.0) for BCG-adjusted TST ≥5mm *vs.* 4.3% (2.8 - 6.2) for ≥15mm. However, as thresholds for test positivity increased, sensitivity declined for all tests (Table 2). For the QFT-GIT, sensitivity decreased from 61.0% (95% CI 49.6 - 71.6) with a threshold ≥0.35 to 23.2% (14.6 - 33.8) with a threshold ≥4.00 IU/mL. For T-SPOT.TB, sensitivity decreased from 65.4% (54.0 - 75.7) with a threshold ≥5 spots to 27.2% (17.9 - 38.2) with a threshold ≥50 spots. For BCG-adjusted TST, sensitivity was 69.7% (59.0 - 79.0) with a threshold ≥5mm, but only 28.1% (19.1 - 38.6) with a threshold ≥15mm.

ROC curve analysis revealed similar AUROCs of 0.77 (95% CI 0.72 - 0.82), 0.78 (0.72 - 0.83) and 0.74 (0.69 - 0.79) for QFT-GIT, T-SPOT.TB and BCG-adjusted TST for predicting incident

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TB over three years' follow-up, respectively (Figure 3). Paired DeLong tests(18) revealed no difference in AUROCs for QFT-GIT (p=0.21) or BCG-adjusted TST (p=0.14), when compared to T-SPOT.TB.

In the sensitivity analyses (Online Data Supplement), exclusion of incident TB cases <42 days from enrolment resulted in slightly lower TB incidence rates across all strata, but had little impact on IRRs between strata. Similarly, the sub-analyses restricted to TB contacts and migrants revealed lower TB incidence rates overall among migrants compared to TB contacts, but little difference in IRRs between strata for each test. Analysis of participants with indeterminate results revealed that only a small number of incident cases for both the QFT-GIT (n=3) and T-SPOT.TB (n=2), precluding further analysis. Inclusion of a fifth stratum for QFT-GIT (≥8 IU/mL) had no effect in increasing incidence rates further. Including fifth strata for T-SPOT.TB and BCG-adjusted TST (≥100 spots for T-SPOT.TB; ≥20mm for BCG-adjusted TST) led to further increases in the incidence rates in these strata. However, as for the main analysis, there was a further loss of sensitivity when implementing corresponding diagnostic thresholds. Analysis of quantitative TST results without subtracting the 10mm deduction for participants who reported BCG vaccination resulted in lower incidence rates in all strata, compared with the primary analysis, without changing the overall pattern observed. Limiting follow-up to six months produced similar sensitivity, specificity and predictive value results to the main analysis. Finally, associations between quantitative test results and incident TB in multivariable Poisson models adjusted for age, gender, ethnicity, country of birth and indication for screening (recent contact *vs.* migration) were similar to the primary univariable analyses.

Discussion

We have demonstrated that higher quantitative results for the QFT-GIT, T-SPOT.TB and TST were strongly associated with higher TB incidence rates, supporting existing data derived among adult and paediatric populations, from low and high TB incidence settings respectively

(9–11). This is the first study, however, to comprehensively assess the potential impact of implementing higher diagnostic thresholds for all three tests, using a uniquely powerful and well-characterised cohort. We found that implementing higher thresholds would lead to a marked loss of sensitivity for all three tests, whereby the majority of incident TB cases would test negative. A modest loss of test sensitivity may be acceptable in some circumstances, where the programmatic goal is to identify the subgroup with the highest risk of progression, if it is accompanied by a substantial improvement in PPV. However, PPV for all three tests remained ≤5%, even in the highest strata. While this is likely partly a reflection of the low pre-test probability of incident TB in low TB incidence settings (such as the UK), even among risk groups such as TB contacts and recent migrants, it also highlights the limitations of our existing diagnostic tests for predicting incident TB. Our previous analysis showed that TST stratified by BCG status yielded comparable performance to both commercial IGRAs(6). Our ROC curve data in the current analysis reinforces this conclusion, as AUROCs were very similar for all three tests, with overlapping 95% confidence intervals.

These data demonstrate that implementing higher diagnostic thresholds for QFT-GIT, T-SPOT.TB and TST is unlikely to be of use in settings aiming towards TB elimination, and fails to bridge the gap to the WHO TPP for biomarkers with greater predictive value for incident TB. One approach may be to offer preventative therapy to all patients with positive LTBI tests, using current thresholds, with the offer of additional support to complete treatment to those with higher quantitative results, who are at highest risk of disease. However, such an approach should ensure that current resources are not diverted away from supporting those with lower quantitative positive test results to commence and complete preventative therapy, since doing so would risk missing the majority of progressors.

Although our findings support the hypothesis that quantitative measures of T cell recall (as measured by IGRAs and the TST) are correlates of risk of disease, which may reflect underlying mycobacterial burden, test sensitivity for incident TB cases was only 61.0 - 69.7% when using conventional thresholds over three years' follow-up. This finding is consistent with

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recent data demonstrating IGRA sensitivity of 67-81%, even among prevalent TB cases(19). A negative IGRA in these examples may be a consequence of susceptibility to TB disease among a subgroup of exposed individuals who either fail to mount any adaptive immune response to *M. tuberculosis*, develop an immune response that is independent of interferon-gamma(20), or have a localised response in tissue compartments that is not reflected in blood. Furthermore, in contrast to the hypothesis that a positive IGRA or TST are correlates of risk, cases of Mendelian susceptibility to mycobacterial disease show that Th1 responses which underpin IGRAs and the TST are necessary for protection against TB(21). This contradiction reflects the fact that interferon-gamma polarised T cell responses do not discriminate between immunological protection and immunopathogenesis. Thus, these measures should be considered as imperfect correlates of risk when used for TB diagnosis, prognostication, or as outcome measures in vaccine efficacy studies(22).

This study reinforces an ongoing need for novel biomarkers that predict progression to incident TB more accurately, in order to facilitate precision delivery of therapy for LTBI to those who need it most, and thereby reduce the number needed to treat. While IGRAs and the TST aim to detect immune sensitisation to TB, it is increasingly recognised that tests that better delineate the spectrum of LTBI will be required to improve predictive value(23). One such example is whole-blood host transcriptional signatures, which have demonstrated promise for the detection of 'incipient', or subclinical, TB (24–27). However, a validated biomarker that achieves the WHO TPP for the prediction of incident TB has not yet been identified. In the interim, ensuring optimal implementation of existing LTBI tests is of paramount importance. While higher diagnostic thresholds for QFT-GIT, T-SPOT.TB and TST may not address this in isolation, inclusion of these quantitative results in a multivariable clinical risk model may improve prediction of incident TB, though existing tools remain unvalidated(4, 28).

This study has a number of strengths. Firstly, it is a very large scale (n=9,610), prospective study with lengthy median follow-up of almost five years, and robust identification of incident TB cases, including by linkage to national TB surveillance records. The study population,

consisting of UK recent TB contacts and migrants from high TB incidence settings, is well characterised and highly representative of target groups for LTBI screening programmes in low TB incidence settings(3). Our findings are therefore likely to be generalizable to other low TB incidence countries. Furthermore, availability of diagnostic test results was very high, with QFT-GIT, T-SPOT.TB and TST results available for 8,562 (89.1%), 8,079 (84.1%) and 7,833 (81.5%) of participants, respectively, while the inclusion of a large number of both TB contacts and recent migrants facilitated robust sensitivity analyses restricted to each sub-population.

A limitation was that an updated version of the QFT-GIT (QuantiFERON-TB Gold Plus; Qiagen, Venlo, The Netherlands), which became available late in the follow-up period, was not assessed in this study(29). Prospective evaluations of the predictive value of this assay for incident TB are required. Secondly, a positive LTBI test, done as part of the study, could potentially have led to differential reporting bias, as a positive result may have increased clinical suspicion of TB and therefore led to more TB diagnoses among participants with a positive test. However, test results were available to participants' clinicians only for TB contacts aged ≤35 years since, during the study period, these were the only participants who met NICE criteria for LTBI testing(15). The magnitude of this bias is therefore likely to be small. Thirdly, only baseline testing was performed. We are therefore unable to assess conversions or reversions during serial testing, which may be frequent(30). Since the reality of both contact and migrant LTBI screening programmes is that serial testing (beyond 6 weeks post-contact) is highly unlikely to be cost-effective, this limitation reflects the constraints of routine programmatic conditions; the ability of the tests to identify progressors at the point of initial screening is therefore a key attribute. Finally, we are also unable to account for any further TB exposure events between recruitment and diagnosis, which may have led us to underestimate test sensitivity. However, 66.4% of progression events occurred in the first year (median time to disease 188 days), and there is a generally low risk of TB transmission in the UK. Moreover, test sensitivity when using conventional thresholds remained 57.8-79.6% when follow-up was limited to six months; the impact of this bias is therefore likely small.

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In conclusion, optimal implementation of existing LTBI diagnostic tests is critical while we continue to develop novel commercial assays with improved predictive value. While higher quantitative QFT-GIT, T-SPOT.TB and TST results were associated with higher TB incidence rates in this study, the implementation of higher diagnostic thresholds for these tests comes at the cost of a marked loss of sensitivity, such that only a minority of incident TB cases are detected. Moreover, the improvement in PPV with higher test thresholds was modest. Incorporation of quantitative results into validated multivariable risk prediction models may be of use to further improve prediction of incident TB in the short-to-medium term. However, a better biomarker is ultimately required to transform risk stratification of patients with LTBI.

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Declaration of interests

This paper presents independent research supported by the NIHR. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

AL has issued several patents in relation to immunodiagnostics for tuberculosis and has entitlement to royalties from patents licensed to Oxford Immunotec plc, Abingdon, UK from the University of Oxford.

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Figure Legends

Figure 1: Cumulative distribution plots showing distribution of quantitative test results for the QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted tuberculin skin test (TST), stratified by whether participants progressed to incident TB during follow-up. Dashed lines indicate thresholds used in this analysis.

Figure 2: Tuberculosis (TB) incidence rates and ratios in ordinal strata for quantitative results of QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted TST. P values indicate likelihood ratio tests for trend**.** CI = confidence interval; IRR = incidence rate ratio; IQR = interquartile range. Data also presented as a table in Online Data Supplement.

Figure 3: Receiver operating characteristic curves for prediction of incident tuberculosis (TB) during three years' follow-up by quantitative QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted tuberculin skin test results. AUC = area under the curve. 95% confidence intervals indicated in brackets.

Table 1: Baseline characteristics of UK PREDICT TB cohort, stratified by whether or not participants progressed to incident TB during follow-up. TB = tuberculosis; IQR = interquartile range; CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test. Data are presented as n (%) or median (IQR).

	TB-free	**TB progressors**	**Total**
Sex			
Male	4673 (49.2)	56 (52.3)	4729 (49.2)
Female	4758 (50.1)	51 (47.7)	4809 (50)
Missing	72 (0.8)	0 (0)	72 (0.7)
Age			
≤35	5455 (57.4)	71 (66.4)	5526 (57.5)
>35	4026 (42.4)	36 (33.6)	4062 (42.3)
Missing	22 (0.2)	0 (0)	22 (0.2)
Median (IQR)	33 (26-47)	30 (26-39)	33 (26-47)
Ethnicity			
Indian	3939 (41.5)	42 (39.3)	3981 (41.4)
White	1161 (12.2)	12 (11.2)	1173 (12.2)
Black African	1126 (11.8)	12 (11.2)	1138 (11.8)
Mixed	881 (9.3)	11 (10.3)	892 (9.3)
Pakistani	891 (9.4)	15 (14)	906 (9.4)
Bangladeshi	712 (7.5)	4 (3.7)	716 (7.5)
Black Caribbean	237 (2.5)	5 (4.7)	242 (2.5)
Other	315 (3.3)	5 (4.7)	320 (3.3)
Missing	241 (2.5)	1 (0.9)	242 (2.5)
UK Born			
No	7917 (83.3)	91 (85)	8008 (83.3)
Yes	1536 (16.2)	16 (15)	1552 (16.1)
Missing	50 (0.5)	0 (0)	50 (0.5)
Contact or migrant			
Contact	4711 (49.6)	70 (65.4)	4781 (49.8)
Migrant	4692 (49.4)	37 (34.6)	4729 (49.2)
Missing	100 (1.1)	0 (0)	100 (1)
BCG vaccinated			
No	1457 (15.3)	13 (12.1)	1470 (15.3)
Yes	6538 (68.8)	80 (74.8)	6618 (68.9)
Missing	1508 (15.9)	14 (13.1)	1522 (15.8)
QFT-GIT			
<0.35	6603 (69.5)	34 (31.8)	6637 (69.1)
0.35-0.69	398 (4.2)	7 (6.5)	405 (4.2)
0.7-3.99	793 (8.3)	27 (25.2)	820 (8.5)
≥4	552 (5.8)	26 (24.3)	578 (6)
Indeterminate	119 (1.3)	3 (2.8)	122 (1.3)
Missing	1038 (10.9)	10 (9.3)	1048 (10.9)
T-SPOT.TB			
<5	6257 (65.8)	33 (30.8)	6290 (65.5)

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5 to 7	316 (3.3)	3 (2.8)	319 (3.3)
8 to 49	876 (9.2)	30 (28)	906 (9.4)
≥50	416 (4.4)	27 (25.2)	443 (4.6)
Indeterminate	119 (1.3)	2 (1.9)	121 (1.3)
Missing	1519 (16)	12 (11.2)	1531 (15.9)
BCG-adjusted TST* (mm)			
<5	5739 (60.4)	30 (28)	5769 (60)
5 to 9	805 (8.5)	22 (20.6)	827 (8.6)
10 to 14	612 (6.4)	18 (16.8)	630 (6.6)
≥15	576 (6.1)	31 (29)	607 (6.3)
Missing	1771 (18.6)	6 (5.6)	1777 (18.5)
Follow-up (years)			
Median (IQR)	4.69 (3.82-5.52)	0.51 (0.21-1.34)	4.68 (3.78-5.51)
Total	**9503**	**107**	**9610**

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

Table 2: Sensitivity, specificity, positive predictive values and negative predictive values during three years' follow-up with pre-specified test thresholds. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test; n = numerator; N = denominator.

		QFT-GIT (IU/mL)			T-SPOT.TB (spots)			BCG-adjusted TST* (mm)		
		≥0.35	*≥0.7*	*≥4*	*≥5*	*≥8*	*≥50*	*≥5*	*≥10*	*≥15*
Sensitivity	*n*	*50*	*44*	19	*53*	*50*	22	*62*	*42*	25
	N	82	82	82	81	81	81	89	89	89
	Estimate	61.0%	53.7%	23.2%	65.4%	61.7%	27.2%	69.7%	47.2%	28.1%
	95% CI	(49.6-71.6)	(42.3-64.7)	(14.6-33.8)	(54-75.7)	(50.3-72.3)	(17.9-38.2)	(59-79)	(36.5-58.1)	(19.1-38.6)
Specificity	*n*	6134	6511	7242	5856	6155	6948	5520	6295	6882
	N	7755	7755	7755	7363	7363	7363	7445	7445	7445
	Estimate	79.1%	84.0%	93.4%	79.5%	83.6%	94.4%	74.1%	84.6%	92.4%
	95% CI	(78.2-80)	(83.1-84.8)	(92.8-93.9)	(78.6-80.4)	(82.7-84.4)	(93.8-94.9)	(73.1-75.1)	(83.7-85.4)	(91.8-93)
Positive predictive value	*n*	50	44	19	53	50	22	62	42	25
	N	1671	1288	532	1560	1258	437	1987	1192	588
	Estimate	3.0%	3.4%	3.6%	3.4%	4.0%	5.0%	3.1%	3.5%	4.3%
	95% CI	(2.2-3.9)	(2.5-4.6)	(2.2-5.5)	(2.6-4.4)	(3-5.2)	(3.2-7.5)	(2.4-4)	(2.6-4.7)	(2.8-6.2)
Negative predictive value	*n*	6134	6511	7242	5856	6155	6948	5520	6295	6882
	N	6166	6549	7305	5884	6186	7007	5547	6342	6946
	Estimate	99.5%	99.4%	99.1%	99.5%	99.5%	99.2%	99.5%	99.3%	99.1%
	95% CI	(99.3-99.6)	(99.2-99.6)	(98.9-99.3)	(99.3-99.7)	(99.3-99.7)	(98.9-99.4)	(99.3-99.7)	(99-99.5)	(98.8-99.3)

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

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Figure 1

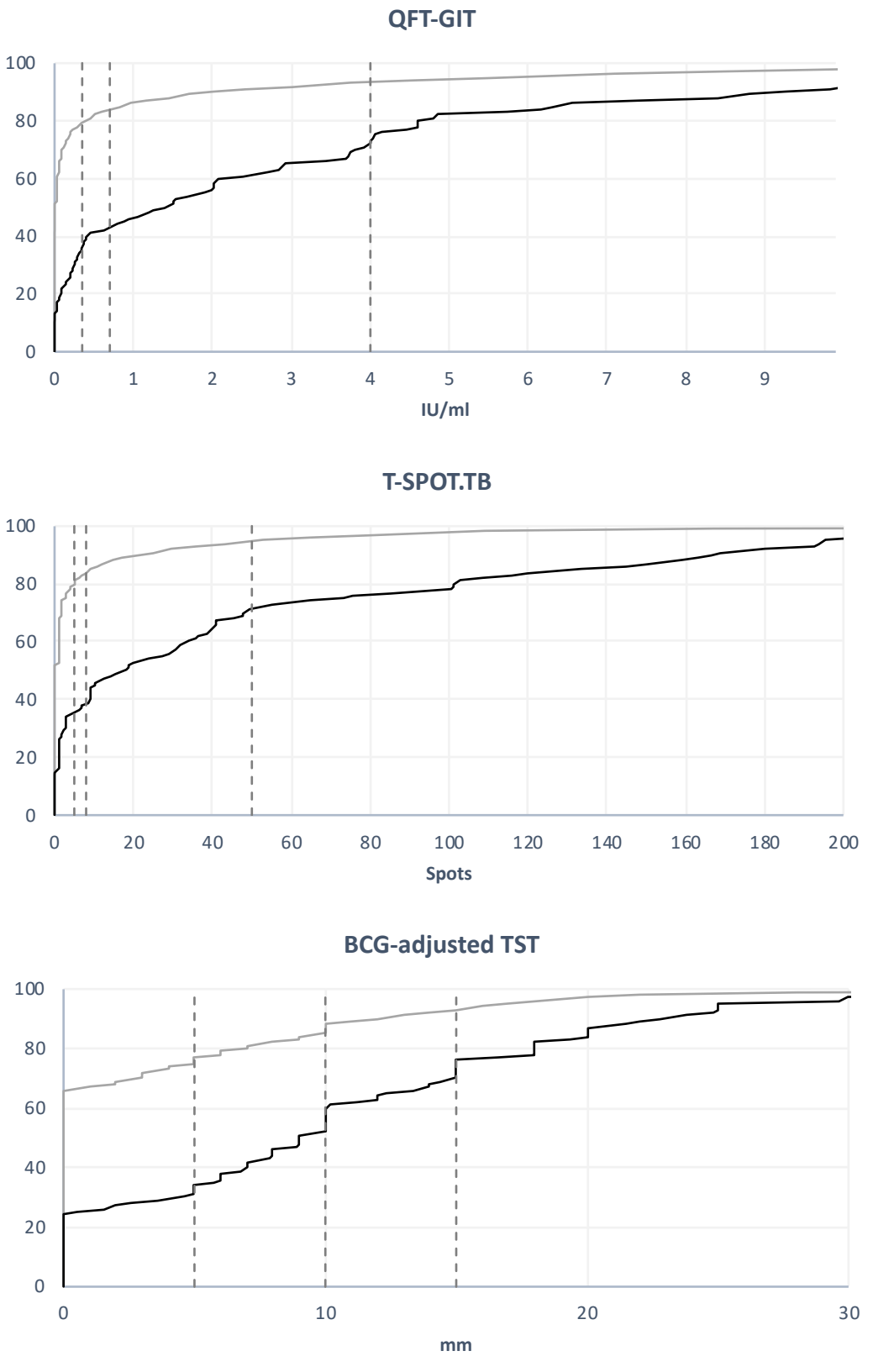

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Figure 2

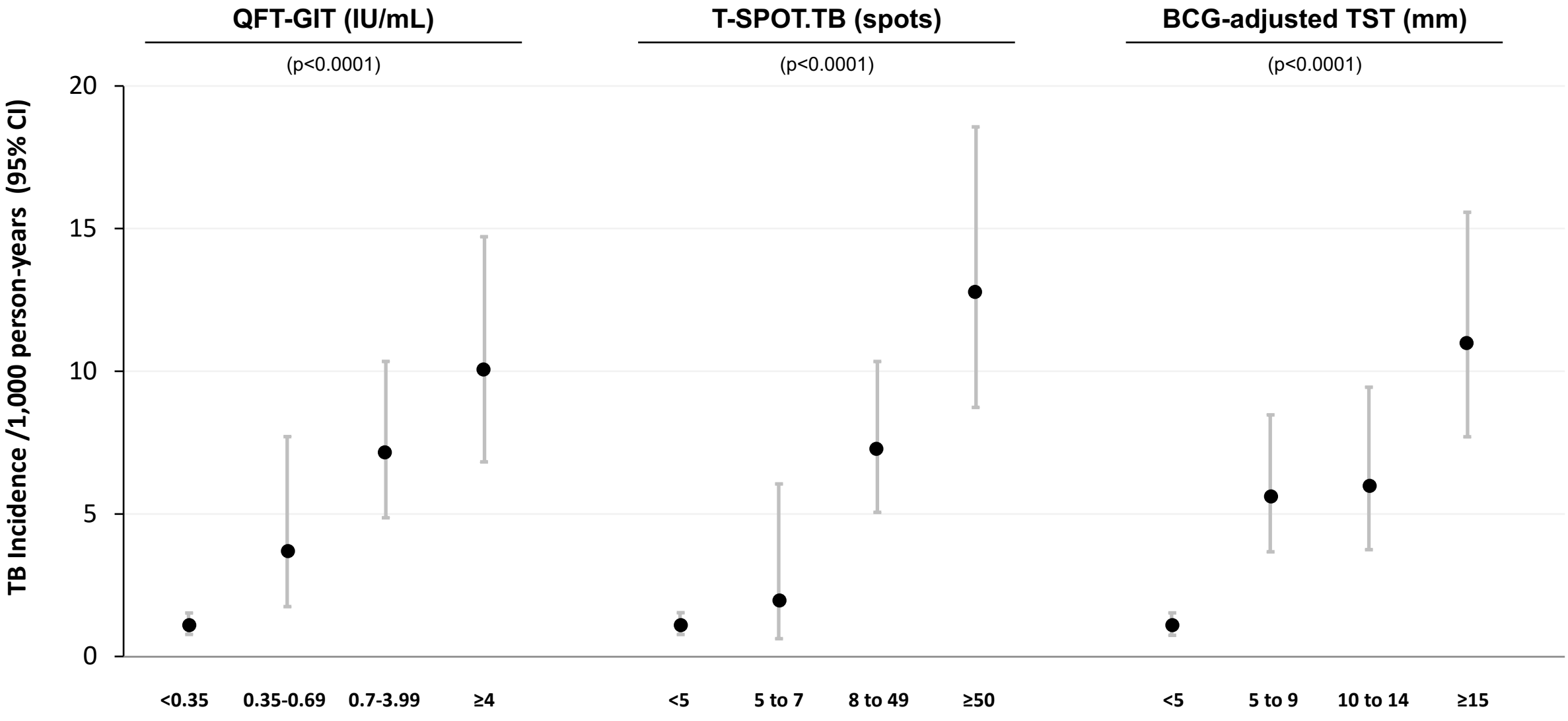

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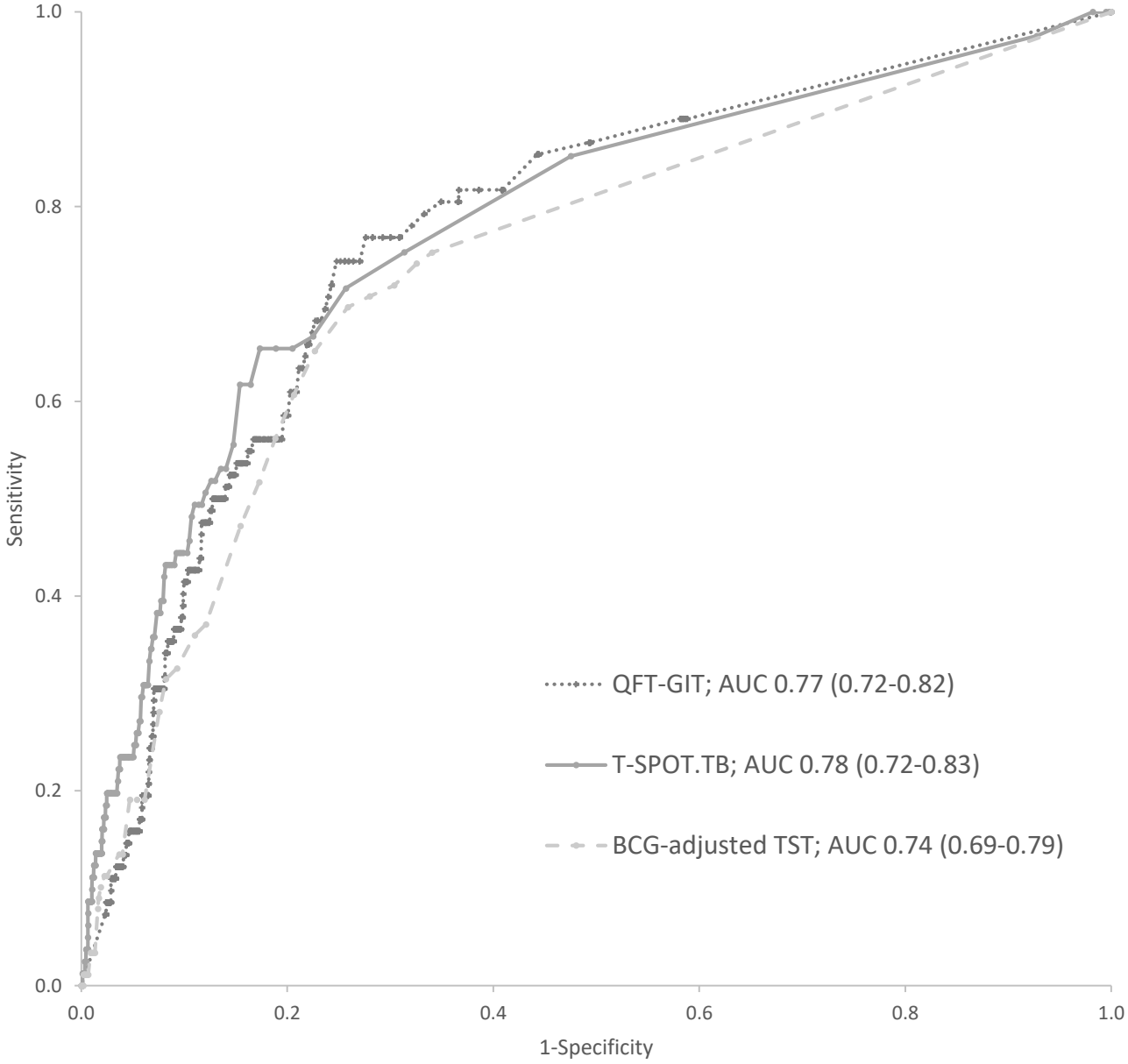
Figure 3



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Quantitative Interferon Gamma Release Assay and Tuberculin Skin Test Results to Predict Incident Tuberculosis: A Prospective Cohort Study

Online Data Supplement

Rishi K. Gupta, Marc Lipman, Charlotte Jackson, Alice Sitch, Jo Southern, Francis Drobniewski, Jonathan J. Deeks, Chuen-Yan Tsou, Chris Griffiths, Jennifer Davidson, Colin Campbell, Oliver Stirrup, Mahdad Noursadeghi, Heinke Kunst, Pranab Haldar, Ajit Lalvani, Ibrahim Abubakar

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Contents

S1: Definitions of indeterminate test results

QFT-GIT and T-SPOT.TB were classified as per the manufacturers' guidance, following the algorithms below.

Indeterminate QFT-GIT:

- TB antigen minus negative control <0.35 IU/mL with positive control minus negative control <0.5 IU/mL; OR
- TB antigen minus negative control ≥0.35 IU/mL & <25% of negative control with positive control minus negative control <0.5 IU/mL; OR
- negative control >8.0 IU/mL.

Indeterminate T-SPOT.TB:

- >10 spots in the negative control panel; OR
- <20 spots in the positive control panel.

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S2: Further details of restricted cubic splines models, modelling approach and sensitivity analyses

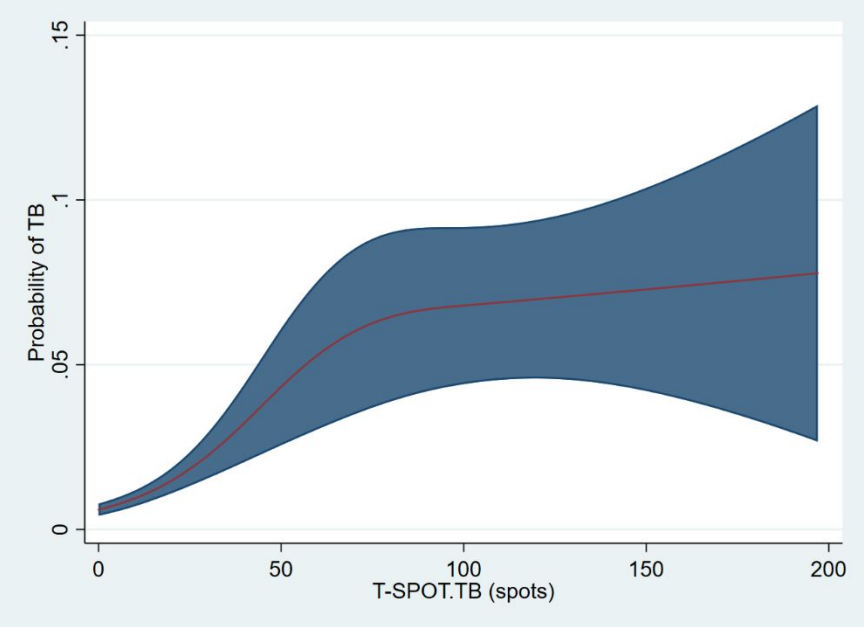
Since no previous data were available to inform the definition of test strata for T-SPOT.TB, we modelled the non-linear relationship between the maximal T-SPOT.TB antigen minus negative control result and probability of incident TB within three years using restricted cubic splines logistic regression models. This analysis was performed in Stata version 15, using the 'postrcspline' package. We developed two models: (A) knots at 8 (based on the manufacturer threshold for positivity), 50 and 100 (based approximately on the 95th and 97.5th centiles, respectively); and (B) knots at 6, 20 and 110, based approximately on the 10th, 50th and 90th centiles for participants with T-SPOT.TB results ≥5 (the threshold for a 'borderline' result). Both models produced similar results (Supplementary Figure 1), and showed reasonable fit when compared visually with the raw data (Supplementary Table 1). These models therefore informed our selection of ≥50 spots as the highest stratum in the primary analysis, and ≥100 spots as the highest stratum in the sensitivity analysis.

Seven sensitivity analyses were performed:

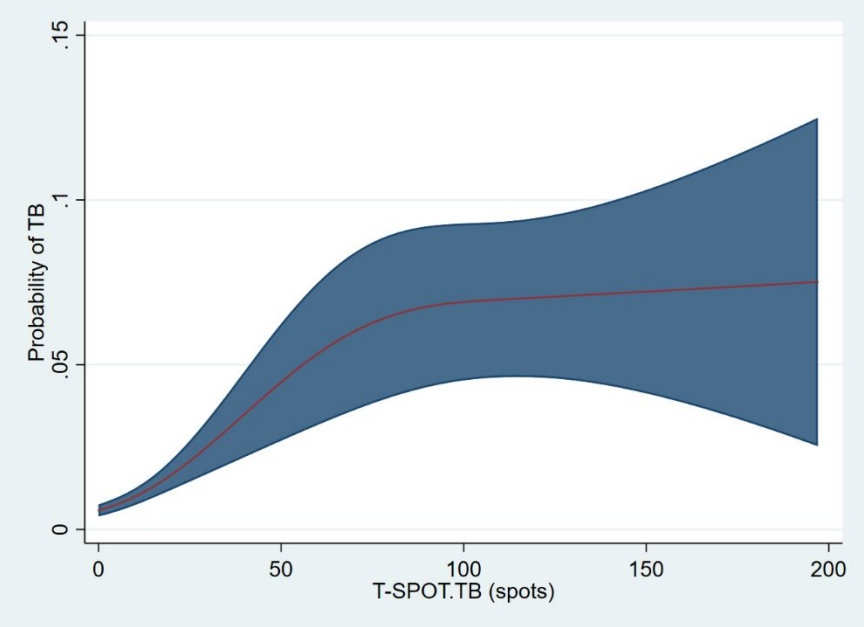
a) A prevalent TB case (excluded from the analysis) was defined as a TB case diagnosed <42 days from enrolment (versus <21 days in the primary analysis).
b) Sub-analyses were performed restricted to only contacts and migrants, respectively.
c) A fifth stratum was also included for each diagnostic test (≥8·00 IU/mL for QFT-GIT; ≥100 spots for T-SPOT.TB (based on restricted cubic splines model); ≥20mm for BCG-adjusted TST), due to the arbitrary nature of the defined thresholds.
d) TB incidence rates among subjects with indeterminate results were also examined.
e) Quantitative TST results were analysed without subtracting the 10mm deduction for participants who reported BCG vaccination.
f) We recalculated sensitivity, specificity and predictive values for a fixed follow-up period of six months to assess test performance for predicting short-term risk of progression.
g) In the primary analysis, we intentionally did not perform a multivariable analysis to assess whether higher quantitative test results remained independently associated with risk of incident TB following adjustment for other co-variates. The rationale for this is that our aim was to assess the potential programmatic impact of implementing higher diagnostic thresholds alone among target groups for LTBI screening programmes, rather than developing a multivariable risk prediction model. However, we examined associations between quantitative test results and incident TB in multivariable Poisson models adjusted for age, gender, ethnicity, country of birth and indication for screening (recent contact *vs.* migration) as a sensitivity analysis.

Supplementary Figure 1: Restricted cubic splines models to examine the non-linear association between quantitative T-SPOT.TB results and probability of incident TB within three years' follow-up, using logistic regression models. Blue shaded area indicates 95% confidence intervals.

Model 1 (knots at 8, 50 and 100 spots)



Model 2 (knots at 6, 20 and 110 spots)



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Supplementary Table 1: Raw data showing risk of incident TB within three years' follow-up in ordinal T-SPOT.TB strata based on deciles of quantitative results for participants with a result >0 spots. These raw data facilitate visual comparison with restricted cubic splines models shown in Supplementary Figure 1 above. TB risk shown as % (95% confidence interval).

T-SPOT.TB (Spots)	No TB	TB	TB risk (95% CI)	All
0	3863	12	0.3 (0.2-0.5)	3875
1	1192	8	0.7 (0.3-1.3)	1200
2	418	3	0.7 (0.1-2.1)	421
3 to 5	501	5	1 (0.3-2.3)	506
6 to 10	356	10	2.7 (1.3-5)	366
11 to 23	335	7	2 (0.8-4.2)	342
24 to 57	334	17	4.8 (2.8-7.6)	351
≥58	364	19	5.0 (3-7.6)	383

S3: Tuberculosis (TB) incidence rates and ratios in ordinal strata for quantitative results of QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted TST.

Supplementary Table 2: Table of tuberculosis (TB) incidence rates and ratios in ordinal strata for quantitative results of QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted TST. P values indicate likelihood ratio tests for trend. CI = confidence interval; IRR = incidence rate ratio; IQR = interquartile range. Data shown graphically in Figure 2 in main manuscript.

	QFT-GIT				**T-SPOT.TB**				**BCG-adjusted TST**			
	<0.35	*0.35-0.69*	*0.7-3.99*	*≥4*	*<5*	*5 to 7*	*8 to 49*	*≥50*	*<5*	*5 to 9*	*10 to 14*	*≥15*
TB cases	34	7	27	26	33	3	30	27	30	22	18	31
Person-years (1,000s)	31.05	1.90	3.80	2.59	30.07	1.54	4.15	2.12	27.91	3.94	3.03	2.83
IR (per 1,000)	1.10	3.68	7.10	10.02	1.10	1.95	7.23	12.73	1.07	5.58	5.95	10.95
95% CI	(0.78-1.53)	(1.75-7.71)	(4.87-10.35)	(6.82-14.72)	(0.78-1.54)	(0.63-6.06)	(5.06-10.35)	(8.73-18.57)	(0.75-1.54)	(3.67-8.47)	(3.75-9.44)	(7.7-15.57)
IRR	ref	3.36	6.48	9.15	ref	1.78	6.59	11.60	ref	5.19	5.54	10.19
95% CI		(1.49-7.57)	(3.91-10.74)	(5.49-15.25)		(0.55-5.80)	(4.02-10.81)	(6.98-19.3)		(3.00-9.00)	(3.09-9.93)	(6.17-16.84)
Follow-up (median years)	4.78	4.82	4.78	4.57	4.88	4.92	4.68	4.99	4.92	4.92	5.00	4.77
IQR	(3.93-5.53)	(4.01- 5.53)	(3.98- 5.57)	(3.69-5.45)	(4.05-5.59)	(4.16-5.59)	(3.87-5.55)	(4.36-5.68)	(4.14-5.62)	(4.10-5.63)	(4.12-5.63)	(4.11-5.56)

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S4: Sensitivity analysis (a): *Alternative definition of 'prevalent' tuberculosis (<42 days from enrolment)*

Supplementary Table 3: Estimates of incidence rates of TB according to test strata under sensitivity analysis in which cases of prevalent TB are defined as those <42 days from enrolment and excluded, in comparison to results of primary analysis (with prevalent TB defined as <21 days from enrolment). IR = incidence rate; CI = confidence intervals.

QFT-GIT (IU/mL)	TB cases	Person-years (1,000s)	IR (per 1,000)	95% CI
<0.35	28	31.05	0.90	0.62 - 1.31
0.35-0.69	6	1.90	3.15	1.42 - 7.02
0.7-3.99	25	3.80	6.57	4.44 - 9.72
≥4	23	2.59	8.87	5.89 - 13.34
T-SPOT.TB (spots)				
<5	31	30.07	1.03	0.72 - 1.47
5 to 7	2	1.54	1.30	0.33 - 5.21
8 to 49	26	4.15	6.27	4.27 - 9.21
≥50	22	2.12	10.38	6.83 - 15.76
BCG-adjusted TST* (mm)				
<5	28	27.91	1.00	0.69 - 1.45
5 to 9	19	3.94	4.82	3.07 - 7.56
10 to 14	13	3.02	4.30	2.50 - 7.40
≥15	26	2.83	9.19	6.26 - 13.49

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

S5: Sensitivity analysis (b): *Sub-analyses among contacts and migrants*

Supplementary Table 4: Estimates of incidence rates of TB by test strata according to risk group (contacts *vs.* migrants). IR = incidence rate; CI = confidence intervals.

CONTACTS				
QFT-GIT (IU/mL)	**TB cases**	**Person-years (1,000s)**	**IR (per 1,000)**	**95% CI**
<0.35	22	16.08	1.37	0.90 - 2.08
0.35-0.69	5	0.90	5.55	2.31 - 13.34
0.7-3.99	18	2.01	8.97	5.65 - 14.23
≥4	15	1.11	13.53	8.16 - 22.45
T-SPOT.TB (spots)				
<5	25	16.56	1.51	1.02 - 2.23
5 to 7	3	0.89	3.39	1.09 - 10.50
8 to 49	16	2.04	7.86	4.81 - 12.82
≥50	18	1.10	16.37	10.31 - 25.98
BCG-adjusted TST* (mm)				
<5	22	15.15	1.45	0.96 - 2.21
5 to 9	11	2.21	4.99	2.76 - 9.01
10 to 14	12	1.80	6.66	3.78 - 11.74
≥15	21	1.76	11.96	7.80 - 18.34
MIGRANTS				
QFT-GIT (IU/mL)	**TB cases**	**Person-years (1,000s)**	**IR (per 1,000)**	**95% CI**
<0.35	12	14.59	0.82	0.47 - 1.45
0.35-0.69	2	0.99	2.02	0.50 - 8.07
0.7-3.99	9	1.76	5.12	2.66 - 9.84
≥4	11	1.47	7.50	4.16 - 13.55
T-SPOT.TB (spots)				
<5	8	13.10	0.61	0.31 - 1.22
5 to 7	0	0.64	0.00	-
8 to 49	14	2.08	6.74	3.99 - 11.37
≥50	9	0.99	9.12	4.75 - 17.53
BCG-adjusted TST* (mm)				
<5	8	12.34	0.65	0.32 - 1.30
5 to 9	11	1.71	6.45	3.57 - 11.65
10 to 14	6	1.20	4.98	2.24 - 11.09
≥15	10	1.06	9.42	5.07 - 17.51

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

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Supplementary Table 5: Sensitivity, specificity, positive predictive values and negative predictive values among contacts in UK PREDICT TB cohort, during three years' follow-up with pre-specified test thresholds. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test; n = numerator; N = denominator.

		QFT-GIT (IU/mL)			T-SPOT.TB (spots)			BCG-adjusted TST* (mm)		
		≥0.35	*≥0.7*	*≥4*	*≥5*	*≥8*	*≥50*	*≥5*	*≥10*	*≥15*
Sensitivity	*n*	31	27	10	32	29	14	38	28	17
	N	51	51	51	53	53	53	57	57	57
	Estimate	60.8%	52.9%	19.6%	60.4%	54.7%	26.4%	66.7%	49.1%	29.8%
	95% CI	(46.1-74.2)	(38.5-67.1)	(9.8-33.1)	(46-73.5)	(40.4-68.4)	(15.3-40.3)	(52.9-78.6)	(35.6-62.7)	(18.4-43.4)
Specificity	*n*	2999	3169	3533	3074	3239	3610	2847	3270	3606
	N	3740	3740	3740	3822	3822	3822	3945	3945	3945
	Estimate	80.2%	84.7%	94.5%	80.4%	84.7%	94.5%	72.2%	82.9%	91.4%
	95% CI	(78.9-81.5)	(83.5-85.9)	(93.7-95.2)	(79.1-81.7)	(83.6-85.9)	(93.7-95.2)	(70.7-73.6)	(81.7-84.1)	(90.5-92.3)
Positive predictive value	*n*	31	27	10	32	29	14	38	28	17
	N	772	598	217	780	612	226	1136	703	356
	Estimate	4.0%	4.5%	4.6%	4.1%	4.7%	6.2%	3.3%	4.0%	4.8%
	95% CI	(2.7-5.7)	(3-6.5)	(2.2-8.3)	(2.8-5.7)	(3.2-6.7)	(3.4-10.2)	(2.4-4.6)	(2.7-5.7)	(2.8-7.5)
Negative predictive value	*n*	2999	3169	3533	3074	3239	3610	2847	3270	3606
	N	3019	3193	3574	3095	3263	3649	2866	3299	3646
	Estimate	99.3%	99.2%	98.9%	99.3%	99.3%	98.9%	99.3%	99.1%	98.9%
	95% CI	(99-99.6)	(98.9-99.5)	(98.4-99.2)	(99-99.6)	(98.9-99.5)	(98.5-99.2)	(99-99.6)	(98.7-99.4)	(98.5-99.2)

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

Supplementary Table 6: Sensitivity, specificity, positive predictive values and negative predictive values among migrants in UK PREDICT TB cohort, during three years' follow-up with pre-specified test thresholds. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test ; n = numerator; N = denominator.

		QFT-GIT (IU/mL)			T-SPOT.TB (spots)			BCG-adjusted TST* (mm)		
		≥0.35	*≥0.7*	*≥4*	*≥5*	*≥8*	*≥50*	*≥5*	*≥10*	*≥15*
Sensitivity	*n*	19	17	9	21	21	8	24	14	8
	N	31	31	31	28	28	28	32	32	32
	Estimate	61.3%	54.8%	29.0%	75.0%	75.0%	28.6%	75.0%	43.8%	25.0%
	95% CI	(42.2-78.2)	(36-72.7)	(14.2-48)	(55.1-89.3)	(55.1-89.3)	(13.2-48.7)	(56.6-88.5)	(26.4-62.3)	(11.5-43.4)
Specificity	*n*	3065	3270	3629	2706	2838	3254	2600	2946	3193
	N	3932	3932	3932	3451	3451	3451	3414	3414	3414
	Estimate	78.0%	83.2%	92.3%	78.4%	82.2%	94.3%	76.2%	86.3%	93.5%
	95% CI	(76.6-79.2)	(82-84.3)	(91.4-93.1)	(77-79.8)	(80.9-83.5)	(93.5-95)	(74.7-77.6)	(85.1-87.4)	(92.6-94.3)
Positive predictive value	*n*	19	17	9	21	21	8	24	14	8
	N	886	679	312	766	634	205	838	482	229
	Estimate	2.1%	2.5%	2.9%	2.7%	3.3%	3.9%	2.9%	2.9%	3.5%
	95% CI	(1.3-3.3)	(1.5-4)	(1.3-5.4)	(1.7-4.2)	(2.1-5)	(1.7-7.5)	(1.8-4.2)	(1.6-4.8)	(1.5-6.8)
Negative predictive value	*n*	3065	3270	3629	2706	2838	3254	2600	2946	3193
	N	3077	3284	3651	2713	2845	3274	2608	2964	3217
	Estimate	99.6%	99.6%	99.4%	99.7%	99.8%	99.4%	99.7%	99.4%	99.3%
	95% CI	(99.3-99.8)	(99.3-99.8)	(99.1-99.6)	(99.5-99.9)	(99.5-99.9)	(99.1-99.6)	(99.4-99.9)	(99-99.6)	(98.9-99.5)

* For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

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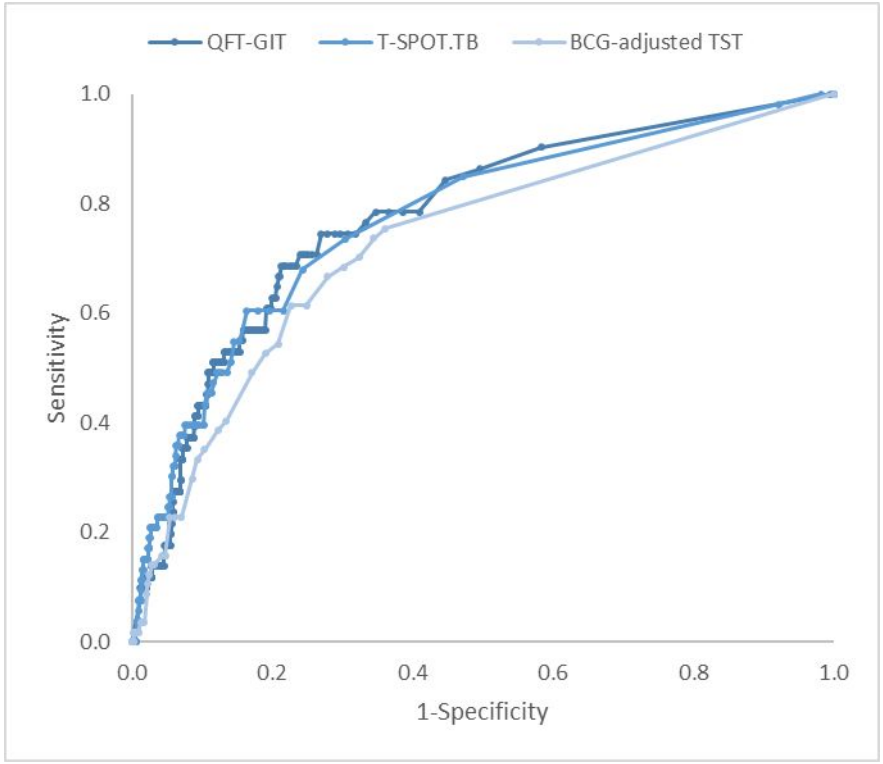
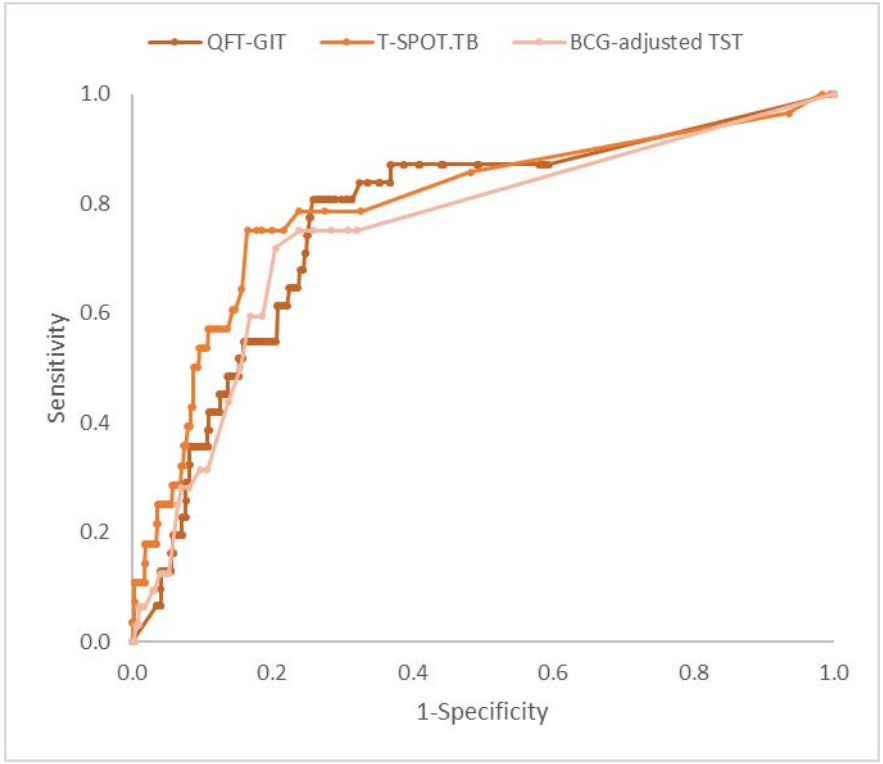
Supplementary Figure 2: Receiver operating characteristic curves for prediction of incident tuberculosis (TB) during three years' follow-up among (a) contacts; and (b) migrants in UK PREDICT TB cohort, by quantitative QuantiFERON Gold-In-Tube (QFT-GIT), T-SPOT.TB and BCG-adjusted tuberculin skin test results. AUC = area under the curve.

(a)



(b)



S6: Sensitivity analysis (c): *Additional (fifth) stratum included for each diagnostic test*

Supplementary Table 7: Tuberculosis (TB) incidence rates in ordinal strata including fifth stratum for quantitative results of each diagnostic test (≥8.00 IU/mL for QFT-GIT; ≥100 spots for T-SPOT.TB; ≥20mm for BCG-adjusted TST). CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test; IR = incidence rate.

QFT-GIT (IU/mL)	TB cases	Person-years (1,000s)	IR (per 1,000)	95% CI
<0.35	34	31.05	1.10	0.78 - 1.53
0.35-0.69	7	1.90	3.68	1.75 - 7.71
0.7-3.99	27	3.80	7.10	4.87 - 10.35
4-7.99	15	1.30	11.55	6.96 - 19.16
≥8	11	1.30	8.49	4.70 - 15.33
T-SPOT.TB (spots)				
<5	33	30.07	1.10	0.78 - 1.54
5 to 7	3	1.54	1.95	0.63 - 6.06
8 to 49	30	4.15	7.23	5.06 - 10.35
50 to 99	6	1.18	5.07	2.28 - 11.28
≥100	21	0.94	22.42	14.62 - 34.38
BCG-adjusted TST* (mm)				
<5	30	27.91	1.07	0.75 - 1.54
5 to 9	22	3.94	5.58	3.67 - 8.47
10 to 14	18	3.03	5.95	3.75 - 9.44
15 to 19	14	1.47	9.55	5.66 - 16.13
≥20	17	1.36	12.46	7.75 - 20.04

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

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Supplementary Table 8: Sensitivity, specificity, positive predictive values and negative predictive values, during three years' follow-up with additional test thresholds. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test; n = numerator; N = denominator.

		QFT-GIT ≥ 8 IU/mL	T-SPOT.TB ≥ 100 spots	BCG-adjusted TST* ≥ 20mm
Sensitivity	*n*	9	16	12
	N	82	81	89
	Estimate	11.0%	19.8%	13.5%
		(5.1-19.8)	(11.7-30.1)	(7.2-22.4)
Specificity	*n*	7501	7181	7172
	N	7755	7363	7445
	Estimate	96.7%	97.5%	96.3%
		(96.3-97.1)	(97.1-97.9)	(95.9-96.7)
Positive predictive value	*n*	9	16	12
	N	263	198	285
	Estimate	3.4%	8.1%	4.2%
		(1.6-6.4)	(4.7-12.8)	(2.2-7.2)
Negative predictive value	*n*	7501	7181	7172
	N	7574	7246	7249
	Estimate	99.0%	99.1%	98.9%
		(98.8-99.2)	(98.9-99.3)	(98.7-99.2)

*For participants with previous BCG vaccination (defined by self-report and scar inspection), 10mm was deducted from the quantitative TST result to adjust for the associated sensitisation to BCG ('BCG-adjusted TST')

S7: Sensitivity analysis (d): *TB incidence rates among participant with indeterminate test results*

Supplementary Table 9: Tuberculosis (TB) incidence rates among subjects with indeterminate results. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test; IR = incidence rate.

	TB cases	Person-years (1,000s)	IR (per 1,000)	95% CI
Indeterminate QFT-GIT	3	0.58	5.21	1.69 - 16.17
Indeterminate T-SPOT.TB	2	0.60	3.32	0.84 - 13.29

S8: Sensitivity analysis (e): *Quantitative TST results analysed without subtracting the 10mm deduction for participants who reported BCG vaccination*

Supplementary Table 10: Tuberculosis (TB) incidence rates in ordinal TST strata without subtracting a 10mm deduction for participants who reported BCG vaccination. TST = tuberculin skin test; IR = incidence rate.

Unadjusted TST (mm)	TB cases	Person-years (1,000s)	IR (per 1,000)	95% CI
<5	16	20.89	0.77	0.47 - 1.25
5 to 9	10	4.69	2.13	1.15 - 3.97
10 to 14	10	4.81	2.08	1.12 - 3.86
≥15	65	7.33	8.87	6.96 - 11.31

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S9: Sensitivity analysis (f): *Sensitivity, specificity and predictive values recalculated for a fixed follow-up period of six months*

Supplementary Table 11: Sensitivity, specificity, positive predictive values and negative predictive values in UK PREDICT TB cohort, with follow-up limited to six months, using pre-specified test thresholds. CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test ; n = numerator; N = denominator.

		QFT-GIT (IU/mL)			T-SPOT.TB (spots)			BCG-adjusted TST* (mm)		
		≥0.35	*≥0.7*	*≥4*	*≥5*	*≥8*	*≥50*	*≥5*	*≥10*	*≥15*
Sensitivity	*n*	26	22	13	33	31	17	39	29	18
	N	45	45	45	44	44	44	49	49	49
	Estimate	57.8%	48.9%	28.9%	75.0%	70.5%	38.6%	79.6%	59.2%	36.7%
	95% CI	(42.2-72.3)	(33.7-64.2)	(16.4-44.3)	(59.7-86.8)	(54.8-83.2)	(24.4-54.5)	(65.7-89.8)	(44.2-73)	(23.4-51.7)
Specificity	*n*	6618	7019	7829	6278	6595	7487	5758	6575	7194
	N	8394	8394	8394	7913	7913	7913	7783	7783	7783
	Estimate	78.8%	83.6%	93.3%	79.3%	83.3%	94.6%	74.0%	84.5%	92.4%
	95% CI	(78-79.7)	(82.8-84.4)	(92.7-93.8)	(78.4-80.2)	(82.5-84.2)	(94.1-95.1)	(73-75)	(83.7-85.3)	(91.8-93)
Positive predictive value	*n*	26	22	13	33	31	17	39	29	18
	N	1802	1397	578	1668	1349	443	2064	1237	607
	Estimate	1.4%	1.6%	2.2%	2.0%	2.3%	3.8%	1.9%	2.3%	3.0%
	95% CI	(0.9-2.1)	(1-2.4)	(1.2-3.8)	(1.4-2.8)	(1.6-3.2)	(2.3-6.1)	(1.3-2.6)	(1.6-3.3)	(1.8-4.6)
Negative predictive value	*n*	6618	7019	7829	6278	6595	7487	5758	6575	7194
	N	6637	7042	7861	6289	6608	7514	5768	6595	7225
	Estimate	99.7%	99.7%	99.6%	99.8%	99.8%	99.6%	99.8%	99.7%	99.6%
	95% CI	(99.6-99.8)	(99.5-99.8)	(99.4-99.7)	(99.7-99.9)	(99.7-99.9)	(99.5-99.8)	(99.7-99.9)	(99.5-99.8)	(99.4-99.7)

S10: Sensitivity analysis (g): *Multivariable analysis of association between quantitative test results and incident TB*

Supplementary Table 12: Associations between quantitative test results and incident TB in multivariable Poisson models adjusted for age, gender, ethnicity, country of birth and indication for screening (recent contact *vs.* migration). CI = confidence interval; QFT-GIT = QuantiFERON Gold-In-Tube; TST = tuberculin skin test. P values for categorical variables with multiple levels indicate likelihood ratio tests.

	IRR	95% CI	p		IRR	95% CI	p		IRR	95% CI	p
QFT-GIT result (IU/mL)				**T-SPOT.TB result (spots)**				**BCG-adjusted TST (mm)**			
<0.35	1 (ref)			*<5*	1 (ref)			*<5*	1 (ref)		
0.35-0.69	3.61	1.59 - 8.16	<0.0001	*5 to 7*	1.85	0.57 - 6.05	<0.0001	*5 to 9*	5.12	2.95 - 8.9	<0.0001
0.7-3.99	6.93	4.15 - 11.58		*8 to 49*	7.51	4.51 - 12.5		*10 to 14*	5.66	3.13 - 10.22	
≥4	10.36	6.15 - 17.44		*≥50*	13.41	7.91 - 22.73		*≥15*	10.30	6.19 - 17.12	
Age				**Age**				**Age**			
≤35	1 (ref)			*≤35*	1 (ref)			*≤35*	1 (ref)		
>35	0.65	0.42 - 0.99	0.046	*>35*	0.58	0.38 - 0.91	0.017	*>35*	0.71	0.47 - 1.07	0.10
Gender				**Gender**				**Gender**			
Male	1 (ref)			*Male*	1 (ref)			*Male*	1 (ref)		
Female	1.10	0.73 - 1.65	0.66	*Female*	1.07	0.71 - 1.62	0.75	*Female*	1.03	0.7 - 1.53	0.88
Ethnicity				**Ethnicity**				**Ethnicity**			
White	1 (ref)			*White*	1 (ref)			*White*	1 (ref)		
South Asian	0.98	0.5 - 1.94	0.68	*South Asian*	0.88	0.44 - 1.74	0.69	*South Asian*	1.03	0.52 - 2.06	0.95
Black African or Caribbean	0.68	0.3 - 1.54		*Black African or Caribbean*	0.66	0.3 - 1.47		*Black African or Caribbean*	0.87	0.4 - 1.91	
Other	0.89	0.4 - 1.97		*Other*	0.75	0.33 - 1.69		*Other*	1.00	0.45 - 2.21	
UK born				**UK born**				**UK born**			
No	1 (ref)			*No*	1 (ref)			*No*	1 (ref)		
Yes	0.96	0.52 - 1.78	0.90	*Yes*	0.96	0.51 - 1.82	0.91	*Yes*	0.78	0.42 - 1.44	0.43
Contact or migrant				**Contact or migrant**				**Contact or migrant**			
Migrant	1 (ref)			*Migrant*	1 (ref)			*Migrant*	1 (ref)		
Contact	1.90	1.2 - 3.02	0.007	*Contact*	1.98	1.24 - 3.18	0.004	*Contact*	1.47	0.94 - 2.3	0.09