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Abstract

Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation

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Background: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB) [(Zopf 1883) Lehmann and Neumann 1896], is a major cause of morbidity and mortality. Nearly one-third of the world's population is infected with MTB; TB has an annual incidence of 9 million new cases and each year causes 2 million deaths worldwide.

Objectives: To investigate the clinical effectiveness and cost-effectiveness of screening tests [interferon-gamma release assays (IGRAs) and tuberculin skin tests (TSTs)] in latent tuberculosis infection (LTBI) diagnosis to support National Institute for Health and Care Excellence (NICE) guideline development for three population groups: children, immunocompromised people and those who have recently arrived in the UK from high-incidence countries. All of these groups are at higher risk of progression from LTBI to active TB.

Data sources: Electronic databases including MEDLINE, EMBASE, The Cochrane Library and Current Controlled Trials were searched from December 2009 up to December 2014.

Review methods: English-language studies evaluating the comparative effectiveness of commercially available tests used for identifying LTBI in children, immunocompromised people and recent arrivals to the UK were eligible. Interventions were IGRAs [QuantiFERON®-TB Gold (QFT-G), QuantiFERON®-TB Gold-In-Tube (QFT-GIT) (Cellestis/Qiagen, Carnegie, VA, Australia) and T-SPOT.*TB* (Oxford Immunotec, Abingdon, UK)]. The comparator was TST 5 mm or 10 mm alone or with an IGRA. Two independent reviewers screened all identified records and undertook a quality assessment and data synthesis. A de novo model, structured in two stages, was developed to compare the cost-effectiveness of diagnostic strategies.

Results: In total, 6687 records were screened, of which 53 unique studies were included (a further 37 studies were identified from a previous NICE guideline). The majority of the included studies compared the strength of association for the QFT-GIT/G IGRA with the TST (5 mm or 10 mm) in relation to the incidence of active TB or previous TB exposure. Ten studies reported evidence on decision-analytic models to determine the cost-effectiveness of IGRAs compared with the TST for LTBI diagnosis. In children, TST (≥ 5 mm) negative followed by QFT-GIT was the most cost-effective strategy, with an incremental cost-effectiveness ratio (ICER) of £18,900 per quality-adjusted life-year (QALY) gained. In immunocompromised people, QFT-GIT negative followed by the TST (≥ 5 mm) was the most cost-effective strategy, with an ICER of approximately £18,700 per QALY gained. In those recently arrived from high TB incidence countries, the TST (≥ 5 mm) alone was less costly and more effective than TST (≥ 5 mm) positive followed by QFT-GIT or T-SPOT.*TB* or QFT-GIT alone.

Limitations: The limitations and scarcity of the evidence, variation in the exposure-based definitions of LTBI and heterogeneity in IGRA performance relative to TST limit the applicability of the review findings.

Conclusions: Given the current evidence, TST (≥ 5 mm) negative followed by QFT-GIT for children, QFT-GIT negative followed by TST (≥ 5 mm) for the immunocompromised population and TST (≥ 5 mm) for recent arrivals were the most cost-effective strategies for diagnosing LTBI that progresses to active TB. These results should be interpreted with caution given the limitations identified. The evidence available is limited and more high-quality research in this area is needed including studies on the inconsistent performance of tests in high-compared with low-incidence TB settings; the prospective assessment of progression to active TB for those at high risk; the relative benefits of two-compared with one-step testing with different tests; and improved classification of people at high and low risk for LTBI.

Study registration: This study is registered as PROSPERO CRD42014009033.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of tables

List of figures

List of boxes

Glossary

Acid-fast bacilli Bacteria that, having been stained with a dye, retain their colour in acid alcohol. Used as a technique for the microscopic detection of mycobacteria.

Active tuberculosis Infection with mycobacteria of the *Mycobacterium tuberculosis* (MTB) [(Zopf 1883) Lehmann and Neumann 1896] complex in which mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent tuberculosis, in which mycobacteria are present, and may be dormant, but are not causing disease. The symptoms of disease include weakness, weight loss, fever, no appetite, chills and sweating at night. Other symptoms of tuberculosis disease depend on where in the body the bacteria are growing. If tuberculosis is in the lungs (pulmonary tuberculosis), the symptoms may include a cough, pain in the chest and coughing up blood [source: www.hpa.org.uk (accessed 12 December 2015)].

Adherence Refers to the patient's ability or choice to adhere to a treatment regimen. Also see *Concordance*.

Algorithm (in guidelines) A flow chart of the clinical decision pathway described in the guideline in which decision points are represented with boxes, linked by arrows.

Atypical mycobacteria Mycobacteria other than those of the *Mycobacterium tuberculosis* complex.

Bacillus Calmette–Guérin vaccine A vaccine for tuberculosis named after the French scientists Calmette and Guerin [source: www.hpa.org.uk (accessed 12 December 2015)].

Bias Deviation of results from the truth because of systematic error(s) in the methods used.

Cochrane review A systematic review of the evidence from randomised controlled trials relating to a particular health problem or health-care intervention, produced by the Cochrane Collaboration. Available electronically as part of The Cochrane Library.

Cohort study A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of the presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Compliance The extent to which a patient complies with a recommended treatment regimen. In recent years, use of the term 'compliance' has been discouraged because of its connotations of patient subservience (see *Concordance* and *Adherence*).

Concordance The percentage of agreement between two tests.

Confidence interval A range of values that contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data and generally straddles the sample estimate. The 95% confidence value means that, if the study, and the method used to calculate the interval, is repeated many times, 95% of the calculated intervals will actually contain the true value.

Contact (domestic, close, casual and workplace) A person who has spent time with a person with infectious tuberculosis [source: www.hpa.org.uk (accessed 12 December 2015)].

Cost-effectiveness analysis An economic study design in which the consequences of different interventions are measured using a single outcome, usually in natural units (e.g. life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost–utility analysis A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years.

Culture The process of growing tuberculosis bacteria from sputum or other samples for identification and diagnosis.

Discordance The percentage of disagreement between two tests.

Heterogeneity Variability or differences between studies in the estimates of effects (when the results or estimates from individual studies appear to have a different magnitude, if not a different sign or direction).

High-incidence country Following the widely used threshold, any country with an incidence of tuberculosis that is ≥ 40 cases per 100,000 population per year. A similar definition is made for areas within countries and may be used to decide on the local need for vaccination, for instance for neonatal bacillus Calmette–Guérin vaccination.

Immunocompromised Refers to an individual who has a significantly impaired immune system. This may be caused by prolonged steroid use, tumour necrosis factor alpha antagonists, antirejection therapy, immunosuppression-causing medication or comorbid states that affect the immune system, for example human immunodeficiency virus infection, chronic renal disease, many haematological and solid cancers, and diabetes.

Infectious tuberculosis Active sputum smear-positive pulmonary tuberculosis, that is, with acid-fast bacilli visible on microscopy. Active tuberculosis affecting other parts of the respiratory tract or oral cavity, although rare, is also considered infectious.

Interferon gamma test A blood test used to diagnose latent tuberculosis (which may be used as an alternative, or an addition, to tuberculin skin tests) based on detecting the response of white blood cells to tuberculosis antigens.

Latent tuberculosis Infection with mycobacteria of the *Mycobacterium tuberculosis* complex in which the bacteria are alive but are not currently causing active disease. Also known as latent tuberculosis infection.

Mantoux test A type of tuberculin skin test in which tuberculin is injected intracutaneously. The injection site is examined for signs of an immune response after 2–3 days.

Multidrug-resistant tuberculosis Tuberculosis resistant to isoniazid and rifampicin, with or without any other resistance.

***Mycobacterium tuberculosis* complex** The related mycobacterial species *Mycobacterium tuberculosis*, *Mycobacterium bovis* [(Hale et al. 1962) Askaa and Erno 1976] and *Mycobacterium africanum* [Castets *et al.* 1969], which can cause tuberculosis in humans.

Skin test See *Tuberculin skin test*.

Smear positive See *Sputum smear positive*.

Specificity (of a test) The proportion of individuals classified as negative by the gold (or reference) standard who are correctly identified by the study test.

Sputum Mucus expelled from the bronchi and lungs by coughing (or retrieved from gastric washings). Sputum is examined for tuberculosis bacteria by microscopic examination of a stained smear; part of the sputum can also be used for culture.

Sputum smear positive ('smear positive') Respiratory tuberculosis in which mycobacteria ('acid-fast bacilli') have been seen in a stained smear of sputum examined under a microscope [source: www.hpa.org.uk (accessed 12 December 2015)].

Weighted contact score The weighted contact score represents a weight based on the relationship (e.g. primary caregiver, secondary caregiver, relative or non-household contact) between the tuberculosis index case and an individual, the type (e.g. sleeps in the same house or lives in the same house) and duration (e.g. 0–3 hours or 4–7 hours of contact per day) of exposure to the index case and the infectivity (sputum acid-fast bacilli positivity) of the index case (Tieu HV, Suntarattiwong P, Puthanakit T, Chotpitayasunondh T, Chokephaibulkit K, Sirivichayakul S, *et al.* Comparing interferon-gamma release assays to tuberculin skin test in Thai children with tuberculosis exposure. *PLOS ONE* 2014;**9**:e105003).

List of abbreviations

AIDS	acquired immunodeficiency syndrome
BCG	bacillus Calmette–Guérin
CD4	cluster of differentiation 4
CEAC	cost-effectiveness acceptability curve
CFP-10	culture filtrate protein 10
CG	clinical guideline
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CIR	cumulative incidence ratio
DOR	diagnostic odds ratio
ELISPOT	enzyme-linked immunospot
ESAT-6	early secretion antigen target 6
ESRD	end-stage renal disease
GP	general practitioner
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IDRR	incidence density rate ratio
IFN-γ	interferon gamma
IGRA	interferon gamma release assay
JSNA	Joint Strategic Needs Assessment
LTBI	latent tuberculosis infection
MCMC	Markov chain Monte Carlo
MTB	*Mycobacterium tuberculosis*
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
NTM	non-tuberculous mycobacteria
OR	odds ratio
PHE	Public Health England
PPD	purified protein derivative
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QFT	QuantiFERON-TB
QFT-G	QuantiFERON®-TB Gold
QFT-GIT	QuantiFERON®-Gold-in-Tube
QUIPS	Quality in Prognosis Studies
R-CIR	ratio of cumulative incidence ratios
R-DOR	ratio of diagnostic odds ratios
R-IDRR	ratio of incidence density rate ratios
ROB	risk of bias
TB	tuberculosis
TNF-α	tumour necrosis factor alpha
TST	tuberculin skin test
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

Plain English summary

Tuberculosis (TB) is one of the biggest causes of illness and death worldwide. People with TB who are not infectious and have no symptoms (the majority) have latent tuberculosis infection (LTBI). Some people with LTBI may develop active TB during their lifetime.

There are two types of tests used to identify LTBI in the UK: (1) the tuberculin skin test (TST) and (2) interferon gamma release assays (IGRAs). This review compares whether the TST or IGRAs offer better value for money in detecting LTBI in children, in people who have low immunity and in recent arrivals from countries with high levels of TB.

We searched the evidence available and built a model to determine which test offers the best value for money in detecting LTBI.

We identified 90 studies. In children we found no difference between IGRAs and TST 5 mm but IGRAs performed better than TST 10 mm in identifying LTBI. In people with low immunity, IGRAs and TST performed better at ruling out LTBI than identifying people who did have LTBI. There was considerable variability in the results between different studies. For people recently arrived in the UK from high-incidence countries, TST performed better than IGRAs at identifying LTBI.

The economic model showed that the best-available options were:

- in children: TST followed by IGRAs if negative
- in people with low immunity: IGRAs followed by TST if negative
- in the recently arrived population: TST alone.

The evidence was limited and future research is needed.

Scientific summary

Background

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The timely identification and prophylactic treatment of people with latent tuberculosis infection (LTBI) is of public health and clinical importance. Unfortunately, there is no diagnostic gold standard for identification of LTBI. Instead, the available screening tests provide indirect and imperfect information. There are two types of tests in use in the UK: (1) the tuberculin skin test (TST), read at two levels (5 mm and 10 mm) and (2) the interferon gamma release assays (IGRAs).

In this review we updated a previous clinical guideline (CG) [National Collaborating Centre for Chronic Conditions, Centre for Clinical Practice at the National Institute for Health and Care Excellence. *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and Control*. *CG117*. London: NICE; 2011. URL: www.ncbi.nlm.nih.gov/books/NBK97852/ (accessed 27 February 2014)] and investigated the clinical effectiveness and cost-effectiveness of screening tests (IGRAs and TST) in LTBI diagnosis in three population groups: children, immunocompromised people and those who have recently arrived in the UK from high-incidence countries. All of these groups are at higher risk of progression from LTBI to active TB.

This review addressed the following questions:

1. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in children?
2. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in people who are immunocompromised?
3. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in people who are recent arrivals from countries with a high incidence of TB?

Methods

Clinical effectiveness

Search strategy

Search strategies included the following main elements: (1) search of electronic bibliographic databases (including MEDLINE, EMBASE, The Cochrane Library, the Science Citation Index and Conference Proceedings Citation Index, Health Economic Evaluations Database) (updated on 2 December 2014); (2) contact with experts in the field; (3) scrutiny of references of included studies and systematic reviews; and (4) screening of manufacturers' and other relevant websites.

Study eligibility criteria

English-language studies evaluating and comparing the effectiveness of commercially available tests used for identifying people with LTBI were eligible for inclusion in the review.

Populations

- Children (both sexes, aged < 18 years, immunocompetent).
- Those who are immunocompromised or at risk of immunosuppression [both sexes, any age, transplant recipients, human immunodeficiency virus (HIV) infection, renal disease, haematological disease, autoimmune disease, recipients of antitumour necrosis factor alpha treatment, steroids or ciclosporins].
- People recently arrived from regions with a high incidence/prevalence of TB (both sexes, any age, immunocompetent, areas with an estimated incidence of ≥ 40 per 100,000).

Interventions

Two IGRAs:

- QuantiFERON®-TB Gold-in-Tube (QFT-GIT) [old version QuantiFERON®-TB Gold (QFT-G)] (Cellestis/Qiagen, Carnegie, VA, Australia)
- T-SPOT.*TB* (Oxford Immunotec, Abingdon, UK).

Comparator

- TST 5 mm or 10 mm (Mantoux test) alone or plus IGRA (one- or two-step testing).

Outcomes

Associations between test results and validity constructs for LTBI:

- progression to active TB
- previous exposure to *Mycobacterium tuberculosis* [(Zopf 1883) Lehmann and Neumann 1896] (MTB; defined by proximity, duration, geographical location or dose–response gradient)
- people at low risk of MTB infection or healthy populations.

Studies

- Randomised controlled trials and retrospective or prospective cohort studies.
- Cross-sectional or case–control studies.

Economics

- Decision-analytic models investigating cost-effectiveness.
- Cost studies.

Exclusions

- Studies using test results as proxies for LTBI.
- Non-commercial/in-house IGRAs, first-generation QFT or tests unavailable in the UK.
- Studies reporting only between-test agreement.

Study selection, data extraction and quality assessment

Two independent reviewers screened all identified records. Disagreements were resolved by discussion and recourse to a third reviewer.

Similarly, relevant data were extracted independently and disagreements were resolved by recourse to a third reviewer. For each test, summary parameters (e.g. sensitivity, specificity, diagnostic odds ratios, cumulative incidence ratios, per cent concordance, kappa statistic) with corresponding measures of variability [95% confidence intervals (CIs), *p*-value] were extracted or calculated (e.g. using construct validity categories of exposure levels or progression to active TB, when data permitted).

Risk of bias and methodological quality were also assessed independently using the Quality in Prognosis Studies tool and a modified tool by Dinnes *et al.* [Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al.* A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess* 2007;**11**(3)] for incidence and exposure studies and the Consolidated Health Economic Evaluation Reporting Standards and Philips *et al.*'s checklists for economics studies [Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36)].

Data synthesis and analysis

Predictive values for IGRAs and TST for progression to active TB (incidence studies), the degree of association of IGRA and TST results with previous exposure to MTB (defined by proximity, duration or dose–response gradient) and the specificity of IGRAs and TST in healthy populations were assessed. We measured concordance/discordance between IGRAs and TST.

Summary effectiveness measures were pooled using a random-effects model. Heterogeneity was determined visually and by the I^2 statistic and chi-squared test (two tailed, $p \leq 0.10$). Subgroup analyses (by TST threshold, IGRA type, setting, TB burden and clinical condition) were undertaken to explore heterogeneity. Calculations were performed with Meta-DiSc version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) and Stata version 14 (StataCorp LP, College Station, TX, USA).

Cost-effectiveness

A de novo model structured in two stages (decision tree for LTBI diagnosis and infectious disease model) was developed in R (version 3.1.1; The R Foundation for Statistical Computing, Vienna, Austria) to compare the cost-effectiveness of diagnostic strategies. The first stage included pathways following testing for 1 year before entering the second stage – an infectious disease model. Four diagnostic strategies were examined for each population:

- TST alone
- IGRA alone
- combinations of sequential TST and IGRA
- simultaneous testing.

For the infectious disease stage the following states were modelled:

- active TB
- LTBI – treated for LTBI
- LTBI – untreated
- no TB/LTBI – treated for LTBI
- no TB/LTBI – untreated.

Information required to parameterise the model included prevalence, sensitivity and specificity, adverse events, resource use, and costs and utilities. We used clinical information from the review. We used Bayesian Markov chain Monte Carlo methods to estimate study prevalence and test performance, accounting for the underlying prevalence in each of the studies in the evidence base. We then made a further assumption about the relationship between prevalence in the studies and that in the decision population. In the models, we used QFT-GIT results as the base-case values for the analysis.

Resource use and costs were obtained from the cost-effectiveness review, NHS reference costs 2012/13, the NHS drug tariffs and clinical experts. Costs were adjusted to 2012/13 prices. The simulation was run for 100 years with a 3.5% discount rate and from a NHS and Personal Social Services perspective. A utility decrement of 0.15 was applied to Health Survey for England values for people who received treatment for active TB.

Outcomes were expressed as incremental cost-effectiveness ratios (ICERs) for cost per quality-adjusted life-year (QALY) and cost per diagnostic error avoided. Univariate and probabilistic sensitivity analyses were undertaken.

Results

Clinical effectiveness

We identified 6687 records. After removing duplicates, 3757 records were screened, of which 54 (53 unique studies) were included. We included 37 additional studies from CG117.

The majority of included studies compared the strength of association between QFT-GIT/G IGRA and TST (5 mm or 10 mm) in relation to the incidence of active TB or previous TB exposure (e.g. proximity to, relationship with an active case or weighted contact score). Seven of the 15 incidence group studies had a high risk of bias, six had a moderate risk of bias and two had a low risk of bias. Twenty-nine of the 38 exposure studies were of lower quality.

Children

The results of the 27 studies were:

- Incidence studies:
  - TST 5 mm: there was no difference between TST 5 mm and QFT-GIT [two studies; pooled ratio of cumulative incidence ratios (R-CIR) 1.12, 95% CI 0.72 to 1.75].
  - TST 10 mm: QFT-GIT was better than TST 10 mm (three studies; pooled R-CIR 4.33, 95% CI 1.32 to 14.23).
- Sensitivity and specificity:
  - TST 5 mm: IGRA (QFT-GIT/G) had similar sensitivity (48–100% vs. 57–100%) to and slightly better specificity (49–90% vs. 45–65%) than TST 5 mm.
  - TST 10 mm: IGRA had a higher sensitivity (48–100% vs. 30–56%) and a slightly lower specificity (49–90% vs. 63–93%) than TST 10 mm.
- Exposure studies: IGRA performed better than TST 5 mm/10 mm in 14 studies [pooled ratio of diagnostic odds ratios (R-DOR) 1.98, 95% CI 1.19 to 3.28; $I^2 = 89\%$].
- Subgroup analyses (stratified by TB burden setting):
  - In low TB burden settings IGRAs were superior to TST 5 mm/10 mm (six studies; pooled R-DOR 4.74, 95% CI 2.15 to 10.44).
  - In high TB burden settings there was no difference between the tests (eight studies; pooled R-DOR 1.13, 95% CI 0.78 to 1.65).

Immunocompromised people

The 48 studies were stratified into those including participants with HIV infection, solid organ transplantation, post-kidney transplantation, haemodialysis (end-stage renal disease), immune-mediated inflammatory diseases before antitumour necrosis factor alpha (TNF-α) therapy, hepatitis C and lupus erythematosus. The results of the studies were as follows:

- Incidence studies: in the two studies reporting data, R-CIR estimates were non-significant with wide 95% CIs.
- Exposure studies:
  - IGRAs performed better than TST 5 mm/10 mm in people with:
    - haemodialysis (four studies; pooled R-DOR 2.53, 95% CI 1.48 to 4.34)
    - hepatitis C (one study; R-DOR 8.45, 95% CI 3.71 to 19.24).
  - TST 10 mm performed significantly better than QFT-GIT for people with HIV/acquired immunodeficiency syndrome (AIDS) (two studies; pooled R-DOR 0.35, 95% CI 0.15 to 0.83).
- Subgroup analysis (stratified by condition): R-DOR estimates were non-significant/inconclusive with wide 95% CIs in:
  - people with lupus erythematosus
  - people with immune-mediated inflammatory diseases before antiTNF-α therapy
  - solid organ transplantation candidates
  - kidney transplant recipients.

Recent arrivals from countries with a high incidence of tuberculosis

The results of the 15 studies were:

- Incidence studies:
  - There was no significant difference between TST 5 mm/10 mm and QFT-GIT (two studies; pooled R-CIR 1.57, 95% CI 0.52 to 4.76).
  - There was no significant difference between TST 10 mm and T.SPOT.*TB* (one study; R-CIR 0.37, 95% CI 0.10 to 1.41).
- Exposure studies: there was no significant difference between TST 10 mm and QFT-GIT (three studies; pooled R-DOR 0.96, 95% CI 0.69 to 1.33).

Cost-effectiveness

Ten relevant studies were identified and all performed well against frameworks for best practice for reporting economic evaluations.

Bayesian meta-analysis of relevant studies gave the following values with 95% credible intervals for use in the models:

- in children:
  - TST (≥ 5 mm): sensitivity 72.80% (60.59% to 72.94%); specificity 49.03% (47.96% to 50.08%)
  - TST (≥ 10 mm): sensitivity 53.51% (38.21% to 67.69%); specificity 74.81% (34.34% to 76.18%)
  - QFT-GIT: sensitivity 68.84% (58.56% to 78.20%); specificity 61.03% (60.30% to 61.76%)
  - T-SPOT.*TB*: sensitivity 50.00% (2.45% to 97.64%); specificity 77.58% (67.38% to 86.40%).

- In immunocompromised people:
  - TST (≥ 5 mm): sensitivity 32.42% (11.19% to 58.48%); specificity 74.22% (72.88% to 75.57%)
  - TST (≥ 10 mm): sensitivity 16.82% (2.52% to 38.99%); specificity 83.97% (78.99% to 88.31%)
  - QFT-GIT: sensitivity 55.48% (24.73% to 83.73%); specificity 82.27% (80.52% to 83.96%)
  - T-SPOT.*TB*: sensitivity 66.65% (35.17% to 91.44%); specificity 68.46% (63.46% to 73.37%).
- In recently arrived populations:
  - TST (≥ 5 mm): sensitivity 93.56% (77.86% to 99.77%); specificity 50.11% (47.90% to 52.29%)
  - QFT-GIT: sensitivity 59.15% (35.84% to 81.42%); specificity 79.29% (77.80% to 80.73%)
  - T-SPOT.*TB*: sensitivity 70.01% (39.78% to 92.42%); specificity 39.92% (34.39% to 45.54%).

Model outputs: incremental cost-effectiveness ratios – cost per quality-adjusted life-year and cost per diagnostic error avoided

- In children:
  - TST (≥ 5 mm) negative followed by QFT-GIT was the most cost-effective strategy with an ICER of £18,900 per QALY gained.
  - T-SPOT.*TB* was the most cost-effective strategy with an ICER of approximately £2700 per diagnostic error avoided compared with TST (≥ 10 mm).
- In immunocompromised people:
  - QFT-GIT negative followed by TST (≥ 5 mm) was the most cost-effective strategy with an ICER of approximately £18,700 per QALY gained.
  - QFT-GIT positive followed by TST (≥ 5 mm) was the most cost-effective strategy with an ICER of approximately £300 per diagnostic error avoided compared with TST (≥ 10 mm).
- In the recently arrived population:
  - TST (≥ 5 mm) alone was the most cost-effective strategy with an ICER of approximately £1500 per QALY gained compared with QFT-GIT.
  - TST (≥ 5 mm) positive followed by QFT-GIT was the most cost-effective strategy with an ICER of approximately £700 per diagnostic error avoided compared with QFT-GIT alone.

Discussion

Summary of results

In children the limited evidence suggested that TST 5 mm was the best test for predicting LTBI. TST (≥ 5 mm) negative followed by QFT-GIT was the most cost-effective strategy.

Interferon gamma release assays appeared to outperform TST in low TB burden settings but not high TB burden settings, a finding that is consistent with a growing body of evidence showing reduced sensitivity and specificity of IGRAs in high TB burden settings. This type of effect modification could be explained by higher frequency of exposure to MTB, different transmission dynamics, malnutrition, comorbidity, coinfection with HIV or helminthic infection.

For immunocompromised people most of the evidence was insufficient and inconsistent. There was large variation in the performance of IGRAs compared with TST across different clinical subgroups. QFT-GIT and T-SPOT.*TB* performed better than TST 5 mm/10 mm in those undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT performed significantly worse than TST 10 mm in people with HIV/AIDS. This observation could potentially be explained by T-lymphocyte depletion. For other clinical subgroups of immunocompromised people the evidence was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates. The QFT-GIT negative followed by TST (≥ 5 mm) strategy was the most cost-effective in this group with an ICER of approximately £18,700 per QALY.

Among recently arrived people from countries with a high TB burden, there was no significant difference between the performance of IGRAs and the performance of TST in identifying LTBI. The TST (≥ 5 mm) alone strategy was the most cost-effective with an ICER of approximately £1500 per QALY.

Strengths and limitations

The findings of this review warrant a cautious interpretation. The evidence was inconclusive, in large part because of unexplained heterogeneity, poor reporting, missing data and great uncertainty around the effect estimates for the association between test results and the constructs of validity for LTBI. With no 'gold standard' and an inadequate definition of construct validity for LTBI (e.g. definitions of previous exposure may not represent the true presence of LTBI), exposure misclassification was probably an important issue.

Other factors that may have contributed to this variability are study setting, type of population, type of test, previous bacillus Calmette–Guérin (BCG) vaccination and the limitations of screening tests (inter-/intrarater variability in the interpretation of test results, boosting, conversion, reversion, different cut-offs for test positivity, assay manufacturing, pre-analytical processing and/or incubation delay). Apart from these issues, various sources of methodological bias may have independently distorted the review findings. For example, the study findings may have been biased because of a lack of blinding, selection bias, partial verification bias because of incomplete outcome data assessment and incorporation bias.

The strengths of the cost-effectiveness assessment include the building of a de novo two-stage model and the use of the review findings (coupled with Bayesian meta-analysis) to derive summary estimates of diagnostic accuracy, although we did not adjust for BCG status because of a lack of data. A number of assumptions were made, including that the TST was costed similarly for those that were read and those that were not read. Resource use was estimated with input from our clinical advisors.

Implications

The findings should be viewed by clinicians and policy makers cautiously because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made. Clinicians should be mindful of the variation in performance of the different testing strategies among different populations.

Research priorities

- The inconsistent performance of IGRAs in high- and low-TB settings should be investigated to see whether or not it is replicable.
- Prospective studies are needed for people at high risk of TB to assess progression to active TB.
- The relative benefits of two-step testing with different combinations of IGRAs and TST compared with single-step testing should be investigated.
- For retrospective or cross-sectional studies a standard set of component exposures to aid classification into high and low risk for LTBI is needed, alongside identification of more accurate markers of LTBI.

Study registration

This study is registered as PROSPERO CRD42014009033.

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Chapter 1 Background

Overview

Tuberculosis (TB) is a major cause of morbidity and mortality globally. Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB) [(Zopf 1883) Lehmann and Neumann 1896]; TB has an annual incidence of 9 million new cases and each year causes 2 million deaths annually worldwide. TB ranks as the second leading cause of death from an infectious disease.[1–3]

In the UK, the prevalence of TB steadily decreased until the mid-1980s but has started to rise over the last 20 years, especially in ethnic minorities born in places with a high TB prevalence.[4,5] Between 1998 and 2009, annual TB notifications in the UK rose by 44%, from 6167 to 8900 cases.[4,6] Since 2005, this rate has remained high, leading to projections that in 2 years there will be more TB cases in the UK than in the USA,[7] thereby posing a major public health challenge. The re-emergence has been largely driven by recently arriving immigrants in whom latent infection has been reactivated or who have acquired new infection as a result of their maintaining links with high-prevalence countries.

Aetiology and pathology of tuberculosis

Tuberculosis infection is transmitted to a healthy person through the air by inhaling respiratory fluids/sputum droplets containing MTB discharged by a person with active TB. The infected sputum droplets can dry and form into droplet nuclei, which can float in the air for a long period of time and penetrate the host.[8] TB can be transmitted through other routes including ingestion (e.g. from drinking unpasteurised cow's milk)[9] and inoculation (e.g. Prosector's wart), although such cases are rare in the UK.

Once the bacteria are inhaled, the droplet nuclei travel through the mouth or nasal passages to the upper respiratory tract, bronchi and finally the alveoli of the lungs. The bacteria grow slowly and multiply in the alveoli over several weeks. Sometimes a small number of tubercle bacilli enter the bloodstream and spread throughout the body such as to the bones, lymph nodes or brain.[8] In > 80% of cases the immune system kills and removes the bacteria from the body.[10] If the immune system does not kill the bacteria, macrophages within the immune system ingest and surround the tubercle bacilli within 2–8 weeks. The cells form a barrier shell that keeps the bacteria suppressed and under control, resulting in latent tuberculosis infection (LTBI). Individuals with LTBI do not exhibit any clinical, radiological or bacteriological evidence of the pathogen. They are not infectious and may remain asymptomatic.[11] However, the latent infection may reactivate later in life, causing the individual to develop symptoms and become infectious. It has been estimated that people with LTBI are at 5–10% risk for developing active TB during their lifetime.[12,13] Therefore, this large pool of LTBI is an important reservoir of infection.[8,12]

If the immune system cannot keep the bacteria suppressed or the barrier fails later, the bacilli begin to multiply and the individual develops active TB disease. Individuals who have active TB are infectious and each can spread MTB to up to 10–15 close contacts within a year.[14] The pathogen affects primarily the lungs (pulmonary TB) but can also involve other organs of the body (extrapulmonary TB). In the UK in 2012, pulmonary TB accounted for about 53% of all TB cases.[5]

The period between infection and first signs of illness (incubation period) varies between 8 weeks and decades. The greatest chance of progressing to disease is within the first 2 years after infection, when approximately 50% of the 5–10% lifetime risk occurs.[15] The risk of infection and progression to active TB disease depends mostly on the host's immune function as well as on the duration and proximity of exposure to a source afflicted with active MTB.[16] Therefore, certain population groups have a higher

lifetime risk of developing TB. These vulnerable groups with low immunity and/or high exposure include long-term care facility workers, people born in or coming from countries with a high prevalence of TB, infants, children, those infected with human immunodeficiency virus (HIV), people with close contacts suspected of having active TB or those living in confined facilities (e.g. prison, homeless shelters).[5] These groups are particularly important as a reservoir of latent infection that could reactivate, and explain the trends observed for TB in the UK.[17]

Active tuberculosis

When infection with MTB becomes active TB disease, the symptoms that occur are non-specific and depend on the site of TB infection.[18,19] Common signs and symptoms of active pulmonary TB may include a chronic cough for weeks or months accompanied by the coughing up of blood or blood-stricken mucus, pain in the chest, weight loss, intermittent fever and/or night sweats, poor appetite, chills, weakness or fatigue, and listlessness.[1,18,20] The clinical diagnosis of TB is based on TB-characteristic clinical signs and symptoms, chest radiography and microscopy of tissue biopsy or sputum samples. A definitive diagnosis of TB, however, is made through the identification of MTB in clinical samples (e.g. pus, tissue biopsy, sputum) using culture.[21,22] TB is difficult to culture and it takes several weeks to obtain a definitive result.

Tuberculosis is a curable disease; however, treatment is long and requires adherence, even through the side effects of treatment.[23] In the UK, most MTB infections are sensitive to the antibiotics used.[10] The routine management of active pulmonary TB includes a combination of antibiotics (e.g. isoniazid, rifampicin, pyrazinamide and ethambutol) given over 6 months.[18] Although patients start to feel better after 2 months of treatment and are not infectious any longer, it is vital that they complete their treatment.[24,25] This ensures that the TB bacteria are completely killed off, preventing the return of symptoms and the risk of bacteria becoming drug resistant. Treatment of drug-resistant forms of TB is less effective, requires longer than 6 months and causes greater side effects.[10,26]

Measurement of latent tuberculosis infection

Unfortunately, there is no diagnostic gold standard for the identification of individuals with LTBI. Instead, the available screening tests for LTBI provide an indirect assessment of the presence of LTBI by relying on a host's immunological response to TB antigens.[27] In addition, none of the available LTBI tests can accurately differentiate between people with LTBI and people with active TB.[11]

There are two types of commercially available tests used to identify LTBI in the UK: (1) the tuberculin skin test (TST) and (2) the interferon gamma (IFN-γ) release assays (IGRAs).[5] Until recently, the TST (introduced by Mantoux in 1907) has been the only standard test used for the identification of LTBI.[13] The administration of the TST involves an intradermal injection of purified protein derivative (PPD) in the forearm. The immune response (i.e. delayed hypersensitivity caused by T cells) to the TST is determined 48–72 hours after the injection by measuring the transverse diameter (in mm) of skin induration.[13,16] There is no international agreement on cut-off values for the definition of a positive tuberculin reaction.[12] The choice among commonly used cut-off values (e.g. a diameter of induration of ≥ 5 mm, ≥ 10 mm or ≥ 15 mm) depends on an individual's risk factor profile for TB. Usually, a lower cut-off value of ≥ 5 mm is used for individuals at higher risk of TB (e.g. patients with organ transplants, immunocompromised patients, patients with HIV infection and those who have had recent contacts with an active TB patient) and a higher cut-off value of ≥ 10 mm is applied for individuals at lower risk of TB (e.g. high-risk racial minorities, children, recently arrived immigrants from high-prevalence countries and patients with diabetes, malignancies or renal failure).[16] The administration of the TST is relatively cheap and does not require a laboratory, but it does require a skilled operator.

Interferon gamma release assays have been recently developed as alternative screening tests for LTBI. There are two types of IGRA: QuantiFERON®-TB Gold-in-Tube (QFT-GIT) [old version: QuantiFERON®-TB Gold (QFT-G)] (Cellestis/Qiagen, Carnegie, Australia) and T-SPOT.*TB* (Oxford Immunotec, Abingdon, UK). Both tests are commercially available in the UK. The QFT test is a whole-blood test based on an enzyme-linked immunosorbent assay whereas the T-SPOT.*TB* test uses peripheral blood mononuclear cells and is based on an enzyme-linked immunospot (ELISPOT) assay.[11] Both tests measure the cluster of differentiation 4 (CD4) cell-released IFN-γ response to MTB-specific antigens [early secretion antigen target 6 (ESAT-6), culture filtrate protein 10 (CFP-10) and tb7.7] in in vitro blood samples.[12,13,16]

Treatment of latent tuberculosis infection

The aim of LTBI treatment is to prevent MTB bacteria from developing into active TB disease. Before treatment, all individuals found to have LTBI need to be tested for active TB. For individuals in whom active TB is ruled out, the prophylactic treatment of choice is isoniazid. For adults and children, the treatment should be given for between 3 and 6 months depending on the treatment regime. For individuals affected by HIV, treatment is given for 6 months. Rifampicin given for 4 months is the second-line treatment that can be used as an alternative in individuals who are resistant to isoniazid or at high risk of side effects from isoniazid.[16]

Incidence, prevalence and epidemiology

All forms of active TB are legally notifiable by the physician making or suspecting the diagnosis under the Public Health (Control of Disease) Act 1984[28] in England and Wales. It first became a statutory requirement to notify TB cases in 1913. Known as the Notifications of Infectious Diseases system, it continues to play a valuable role in the surveillance of TB; however, the information collected is limited and trends within subgroups of the population cannot be monitored.[29]

In 1999, the Enhanced Tuberculosis Surveillance system was established to collect more detailed information on annual TB cases, including patient age, sex, ethnic group, country of birth, site of disease, NHS region and treatment outcomes. It has been reported that the Enhanced Tuberculosis Surveillance system reflects the true incidence of TB better than the Notifications of Infectious Diseases system as many measures are used to ensure that quality standards are met annually, thereby providing a corrected analysis of TB cases.[30] In 2012, completeness of data was 100% for mandatory fields and approximately 91% across other key fields for England and 89% for Wales.[5] This system provides the most comprehensive, timely and accurate information on active TB incidence in the UK[29] and is therefore robust.

There is no national system that collects data for LTBI. For this reason there are no robust data for LTBI, although we can predict that for every person with active TB there are likely to be several with undiagnosed LTBI. Therefore, it seems reasonable to extrapolate from active TB and make the assumption that LTBI will follow a similar epidemiological pattern.

The rates of active TB peaked during the early 1900s with an annual incidence rate of approximately 320 per 100,000. The rate declined dramatically until at least 1987 to as low as 10.1 per 100,000 population per year. However, since the 1980s, the incidence rate began reversing and has reached highs of between 13.6 and 14.4 per 100,000 since 2005.[5] The most recent figures in 2012 report a total of 8751 active TB cases across the UK, giving an incidence rate of 13.9 per 100,000.[5] The burden of TB is highest in England, where in 2012 there were 8130 cases of active TB, a rate of 15.2 per 100,000; in Wales there were 136 active TB cases, a rate of 4.4 per 100,000.[5] Between 2010 and 2011, a total of 436 people died of TB in the UK.[5]

Place of birth and ethnic minorities

The re-emergence of TB has been attributed to international migration, as recently arriving migrants have accounted for the majority of TB cases since 2000. In 2011 and 2012, foreign-born individuals accounted for 73% of reported TB cases.[5] It has been reported that there has been a 98% increase in the number of TB cases in individuals born overseas.[4,6,31] The rate of TB among the non-UK-born population is 80 per

100,000, which is almost 20 times the rate in the UK-born population. Almost half of the patients born outside the UK were diagnosed within 5 years of coming to the UK, with another 30% diagnosed within 2 years.[5] In total, 60% of foreign-born patients originated from South Asia, followed by 22% from sub-Saharan Africa. With respect to country of origin of foreign-born patients, the highest proportions are from India (31%), Pakistan (18%) and Somalia (6%). Similarly, a higher proportion of non-UK-born patients (> 50%) than UK-born patients (31%) present with extrapulmonary TB.[32]

Among UK-born individuals, the highest rate of TB is found in ethnic minority groups. The largest proportions of cases are found in those of Indian (27%, 2296/8525), white (21%, 1814/8525) and Pakistani (17%, 1418/8525) ethnic origin. The highest rates of TB per 100,000 population are found in Indian, Pakistani and black ethnic groups (155, 132 and 97 per 100,000, respectively).[5] It has been indicated that recently arriving immigrants and ethnic minorities are vulnerable as a result of reactivation of latent infection once in the country or acquiring new infection as a result of their maintaining links with high-prevalence countries (e.g. they may visit rural Pakistan or they may have relatives from high-prevalence areas visit them).[33] In addition, having diabetes increases the likelihood of reactivation of TB, and diabetes is more common in individuals from South-East Asia, including the ethnic groups highlighted above.[34]

Geographical difference

Since the establishment of the enhanced TB surveillance system, it has become clear that there is a drastic regional variation in the burden of TB. Active TB is highly concentrated in large cities, with London consistently accounting for the highest rates and sharpest increases since the early 1990s. In 2012, London accounted for almost 40% of all TB cases, with an annual rate of 41.8 per 100,000. London has the highest TB rate among all high-income European countries.[35,36] London is followed by the West Midlands, which accounts for 12% of the burden and has an annual rate of 19.3 per 100,000.[5] Both London and the West Midlands have high rates of immigration.[37]

Within London there is great variation between boroughs. Twelve of the 33 local authorities have an annual incidence rate of 40 per 100,000. The boroughs with the highest annual incidence rates of TB are Newham (122 per 100,000) and Brent (100 per 100,000). However, other boroughs, such as Havering and Richmond-upon-Thames, have an annual incidence rate of < 10 per 100,000.[38] Similar to regional variation, borough variation within London may reflect demographic characteristics as Newham and Brent have some of the highest rates of immigrants and ethnic minorities.[39]

A similar picture is seen in Birmingham. Annual incidence rates for Birmingham as a whole fluctuated between 33.7 and 44.8 cases per 100,000 between 2009 and 2013. In the fourth quarter of 2013, Sandwell and West Birmingham Clinical Commissioning Group had an annual incidence rate of 49.6 per 100,000 [95% confidence interval (CI) 43.5 per 100,000 to 56.4 per 100,000] whereas in Solihull it was 1.9 per 100,000 (95% CI 0.5 per 100,000 to 4.9 per 100,000). Again, this reflects the ethnic make-up of the areas [Helen Bagnall, Public Health England (PHE), West Midlands, May 2014, personal communication].

Age differences

The majority of patients with TB (60%) are aged between 15 and 44 years, followed by patients aged 45–64 years (21%) and patients aged ≥ 65 years (14%). The groups with the lowest rates of TB are those aged 5–14 years (3%) and those aged < 5 years (2%). Although children have a low burden of overall TB cases, once TB is transmitted to them they are more likely than adult hosts to develop active TB. Most cases in those aged 0–14 years are in the UK-born population from black African, Pakistani and white ethnic groups.[5]

Immunosuppression and tuberculosis

In addition to young children, the risk of progression from LTBI to active TB is higher in people coinfected with HIV, patients immunocompromised because of comorbidity (e.g. diabetes, malignancy, renal disease) and/or people with long-term use of immunosuppressant medications [e.g. corticosteroids, tumour necrosis factor alpha (TNF-α) antagonists].[11,16,40] Coinfection with HIV and TB has been internationally well

documented.[41–43] In the UK there has been a decrease in the number of coinfected HIV–TB cases, from 9% of TB cases in 2003/4 to 3.6% of TB cases in 2013.[5] This has been in line with the general downward trends in HIV and TB in migrants from sub-Saharan Africa.[32]

Social risk factors

There are defined social factors that contribute to the burden of TB in the UK. These social risk factors include homelessness (2.4%), a history of imprisonment (2.8%), and drug (2.8%) and alcohol (3.2%) misuse.[5] It is indicated that approximately 7.7% of TB cases present with at least one of these risk factors. These social risk factors are more common in UK-born (13.4%) than foreign-born (5.4%) cases. Within UK-born cases, almost half with at least one risk factor (46%) are from the white ethnic group.[5]

Impact of the health problem

Significance for patients

For the 5–10% of patients who develop active TB, those with pulmonary TB can suffer extreme pain from the symptoms for weeks to months.[44] Similarly, extrapulmonary TB can result in serious complications for the bones, brain, liver, kidneys and heart.[44] Tissue damage can be permanent if TB is not treated early.[45] As a result of tissue damage, active TB can be fatal. In addition to the impact on physical functioning, active TB can also have psychosocial impacts, in particular from the isolation experienced during the treatment of TB. This can include anxiety, depression, disorientation, feelings of loss of control and mood swings.[46,47] A diagnosis of TB can also bring related stigma through which individuals face social and economic consequences.[48]

Treatment of active TB causes many side effects depending on the regimen prescribed. Some symptoms are mild but other side effects can be serious and potentially life-threatening. These can include loss of appetite, nausea, vomiting, jaundice, fever, abdominal pain, lower chest pain or heartburn, skin rash, bleeding gums and nose, blurred vision, ringing sounds, hearing loss, peripheral neuropathy and hepatotoxicity.[16] Individuals on antiretroviral treatment for HIV infection may suffer more side effects with certain TB drugs. These side effects cause poor adherence to treatment. If treatment is incomplete, active TB is more likely to be complex and drug-resistant and result in the need for treatments with greater side effects.[16,49] To avoid the consequences of the disease and the side effects of treatment, it would be easier for patients to undergo LTBI treatment and prevent active disease.

However, the treatment of LTBI uses the same medication, with the same side effects, albeit usually for a shorter period of time. Adherence to treatment is likely to be a factor as taking medicines when you feel well is much harder than taking them when you feel unwell.

Significance for the NHS

The impact of TB as a health problem is extensive. As TB possesses the capacity to spread through the air to practically anyone it is a serious public health threat, although, in practice, infection beyond family members or close contacts is unusual. TB is on the increase in the UK and is decreasing in the USA. It has been estimated that in 2–5 years the burden of TB in the UK will be higher than that in the whole of the USA.[7] Furthermore, drug-resistant TB is increasing in the UK, which means that transmission of drug-resistant strains of TB may continue to increase and complicate the fight against TB.

The health-care costs associated with active TB include the costs of diagnosing and treating pulmonary TB, extrapulmonary TB, multidrug-resistant TB and extensively drug-resistant TB. In the UK, the normal cost of treating a case of active TB is £5000 but the cost of treating multidrug-resistant TB is between £50,000 and £70,000 and the cost of treating extensively drug-resistant TB can be up to £100,000.[35,50] Using 2012 figures, we have estimated that annually TB treatment could cost approximately £50M. Given that LTBI represents a reservoir of potential TB disease, it is important to identify and, if appropriate, treat people with LTBI to reduce the spread and burden of TB disease.[13,18]

Current service provision

Management of latent tuberculosis infection

The goal of screening for LTBI is to identify individuals who are at high risk of developing active TB who would potentially benefit from prophylactic treatment. In the UK, LTBI screening is recommended for contacts of patients diagnosed with active TB and recently arrived migrants. Contacts include household contacts defined as those who share a bedroom, kitchen, bathroom or sitting room with the index active TB case, as well as boyfriends or girlfriends and frequent visitors to the home. Workplace associates in close proximity to a patient for extended periods may be judged to be household contacts; however, the majority of workplace contacts are not screened. Casual contacts should be assessed only if the index case is particularly infectious or the contact case is at increased risk from infection. Nevertheless, all contacts should be offered information and advice about TB. Similar risk assessments take place in schools, nurseries, institutions such as prisons and hospitals, and for aircraft passengers, leading to screening of those perceived to be at risk.[10,51]

Active case finding is recommended for migrants who have recently arrived in the UK from countries with a TB incidence of ≥ 40 per 100,000.[10] Identification of new migrants is recommended from port of arrival reports, new registrations with primary care, entry to education and links with statutory or voluntary groups working with new migrants. Health-care professionals responsible for new migrant screening are advised to co-ordinate a programme to detect and treat active and latent TB, provide the bacillus Calmette–Guérin (BCG) vaccination when appropriate and provide relevant referrals and information. Commissioners, NHS employees and providers of TB services, and other statutory and voluntary organisations, are particularly advised to identify and manage TB in hard-to-reach groups such as the homeless, substance misusers, prisoners and vulnerable migrants.[52]

A simplified care pathway for LTBI screening derived from the National Collaborating Centre for Chronic Conditions[10,51] is presented in *Figure 1* and further details about testing strategies for people being screened for LTBI are provided in *Box 1*.

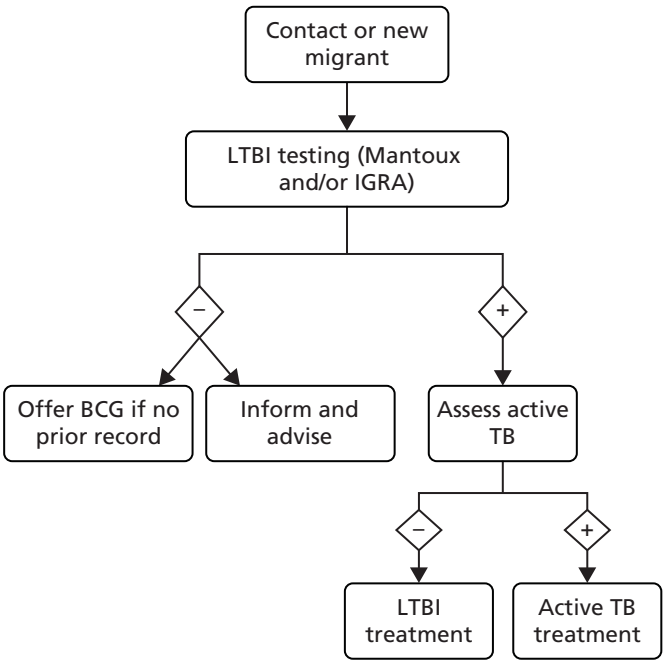


FIGURE 1 Care pathway of LTBI screening.[5,51]

BOX 1 Testing strategies for people being screened for LTBI

- Generally, individuals are tested for LTBI using TST (Mantoux), IGRA, both or a dual strategy of TST followed by IGRA. If the results are positive, individuals are assessed for active TB; if the results are positive they are treated for active TB and if they are negative they are then treated for LTBI. If the results for LTBI are negative the individual is offered a BCG vaccination if aged < 16 years or aged 16–35 years and from sub-Saharan Africa or from an area with an incidence of > 500 per 100,000. Individuals are given information and advice about TB. However, different testing and treatment pathways are recommended for different populations, including different age groups, new migrants and immunocompromised individuals.[10,51]
- TST is recommended for contacts aged > 5 years for the diagnosis of LTBI. IGRA is recommended for individuals whose TST shows positive results (≥ 5 mm diameter for those who have not been vaccinated with BCG and ≥ 15 mm diameter for those who have been vaccinated) or in people for whom TST would be less reliable, such as BCG-vaccinated people. Individuals with a positive IGRA or inconclusive TST are referred to specialist TB care. For contacts who are aged 2–5 years, a TST should be offered as the initial diagnostic test and, if the result if positive, taking BCG history into account, they should be referred to a TB specialist to exclude the possibility of active disease and to determine treatment, depending on the result. If the result of the TST is negative but the child is a contact of a person with sputum smear-positive disease, then an IGRA should be offered after 6 weeks alongside a repeat TST to increase sensitivity.[10,51]
- For child contacts of a person with sputum smear-positive disease aged 4 weeks to 2 years who have not been vaccinated, isoniazid should be started and a TST should be performed. If the TST is reported as positive, the child should be assessed for active TB and if active TB is excluded the child should then be offered full treatment for LTBI. If the TST is negative (< 5-mm induration), isoniazid should be continued for 6 weeks after which a repeat TST and IGRA should be performed. If repeat tests are negative, isoniazid should be stopped and BCG offered, whereas if either is positive active TB should be assessed and, if excluded, treatment for LTBI should be considered. For child contacts of a person with sputum smear-positive disease aged 4 weeks to 2 years who have been vaccinated, a TST should be performed and any positive results (≥ 15 mm) should be assessed for active TB. If active TB is excluded then a regimen of either 3 months of rifampicin and isoniazid or 6 months of isoniazid should be given. If the TST is negative (< 15 mm) it should be performed again with an IGRA after 6 weeks. If both tests are negative no further action is needed. If either is positive, active TB has to be excluded and treatment for LTBI followed.[10,51]
- To diagnose LTBI in recently arriving migrants from high-incidence countries, for children aged 5–15 years a TST should be offered and if positive an IGRA should be performed. For individuals aged 16–35 years, either an IGRA alone or in a dual strategy with a TST should be offered. For those aged > 35 years, the individual risks and benefits of treatment should be considered before testing. For children aged < 5 years, a TST should be offered and if the initial test is positive taking BCG history into account then active TB disease should be excluded and LTBI treatment considered.[10,51]
- Regarding those who are immunocompromised, children should be referred to a TB specialist. For people with HIV infection and a CD4 count of < 200 cells/mm^3 or between 200 and 500 cells/mm^3, an IGRA should be offered with a concurrent TST. If either is positive, active TB should be ruled out before LTBI treatment is given. For other people who are immunocompromised, an IGRA should be offered alone or with a TST.[10,51]
- Once active TB has been excluded by chest radiography and examination, individuals should be offered treatment. Individuals aged ≥ 35 years without HIV infection should be assessed further and counselled about treatment because of the increasing risk of hepatotoxicity from medication. For those aged 16–35 years and not known to have HIV infection, treatment should include either 6 months of isoniazid or 3 months of rifampicin and isoniazid.[10,51]

BOX 1 Testing strategies for people being screened for LTBI (*continued*)

- Neonates who have been in close contact with people who have sputum smear-positive TB and who have not received at least 2 weeks of antiTB drug treatment should be started on isoniazid for 3 months and then a TST performed after 3 months of treatment. If the TST is positive, active TB should be assessed and, if found negative for active TB, isoniazid should be continued for a total of 6 months. If the TST is negative it should be repeated with an IGRA and if both are negative isoniazid should be stopped and BCG vaccination performed. In children aged > 2 years, 3 months of rifampicin and isoniazid or 6 months of isoniazid should be given.

Current service cost

Estimates for the costs of diagnosing and treating LTBI have been provided by the National Institute for Health and Care Excellence (NICE) (*Table 1*). These costs are based on NICE guidelines from 2006[51] and the partial update from 2011.[10] The costs shown include the unit costs of the disposables, the time to administer and read tests and the costs of collecting a blood sample per patient for the tests, calculated in 2011. The cost of chemoprophylaxis includes the cost of drugs, active TB tests, consultations and nurse visits, which were calculated in 2006. BCG costs are also from 2006. Compared with the cost of treating active TB (≥ £5000), diagnosing and treating LTBI per patient is less costly.

TABLE 1 Unit costs for LTBI diagnosis and treatment[10,51]

Description	Test type	Unit cost (£)
Cost of TST	–	16.42
Cost of IGRA	–	30.34
Household and other close contacts aged ≥ 5 years	TST	16.42
New entrants from high-incidence countries		
Children aged < 5 years	TST	16.42
Children aged 5–15 years	TST	16.42
Adults aged 16–34 years	IGRA or dual	30.34 or 46.76
People aged > 35 years	Consider individual risk	
Household contacts aged 2–5 years	TST	16.42
	IGRA if contact with a sputum smear-positive person and TST is negative	30.34
Contacts aged ≥ 5 years – outbreak	IGRA	30.34
Immunocompromised HIV CD4 count < 200 cells/mm^3	IGRA with concurrent TST	46.76
Immunocompromised HIV CD4 count 200–500 cells/mm^3	IGRA test or	30.34
	IGRA with concurrent TST	46.76
Cost of complete chemoprophylaxis treatment	–	483.74
BCG vaccination	–	11.71

Variation in services and/or uncertainty about best practice

Limitations of latent tuberculosis infection screening tests

The main limitation of the TST is its inability to distinguish between reactions caused by MTB and those caused by BCG vaccination or non-tuberculous mycobacteria (NTM).[11] The BCG vaccination is routinely used in countries with a high TB prevalence to prevent the spread of TB infection in infants and young children. The use of the TST test in such areas results in high false-positive rates. The boosting phenomenon, which occurs after repeated TSTs, may also lead to false positives, thereby limiting the specificity of the test. The TST has limited sensitivity when used in certain subpopulations (e.g. people with active TB, immunocompromised patients, the elderly and people with HIV infection, malnutrition or renal failure). The above-mentioned limitations are compounded by issues related to the interpretation of test results, which may independently influence false-positive and false-negative rates of the TST (e.g. different cut-off values, PPD dose).[12,13,16] Two health visits are required for the completion of the TST, which results in missed diagnoses in 10% of cases.[53] Measurement of the TST is also dependent on interobserver variability, which therefore requires adequate training to reduce variability.[54,55]

Because the antigens in the IGRA tests are not present in the BCG vaccination and most NTM, the IGRAs are less influenced by previous BCG vaccinations and are less susceptible to false-positive NTM reactions, leading to higher specificity of these tests compared with the TST.[56] IGRAs also have the advantage of requiring a single patient visit rather than the sequential two-step testing required with the TST. Automated testing also means increasing the objectivity in the interpretation of test results. Finally, there is no influence from the boosting effect and so repeat screening is feasible.[57] The IGRAs, however, have their own limitations: specifically, they are more costly and labour intensive than the TST. Moreover, care in blood sampling is required and the time available for blood sample storage and analysis is restricted to 8–12 hours after collection.[12]

Diagnostic accuracy of latent tuberculosis infection tests

Since the introduction of IGRAs evidence on estimating and comparing the performance of the TST and IGRAs in people with LTBI has emerged; however, this assessment has been hampered by the absence of a gold standard for the diagnosis of LTBI, which would allow direct calculation of sensitivity and specificity for both types of tests.[11,12,18,40,57–59] Most studies have, instead, determined associations [e.g. diagnostic odds ratios (DORs) and other regression-based effect measures] between test results (i.e. TST or IGRAs) and surrogate measures of LTBI such as duration/proximity of exposure to a person with active TB or risk of development of active TB, or progression from LTBI to active TB [e.g. sensitivity, DORs, positive predictive values (PPVs) and negative predictive values (NPVs), incidence rate ratios, cumulative incidence ratios (CIRs)].[18,58,60] Some studies have assessed and compared the specificity of these tests in people at very low risk for MTB infection (e.g. healthy individuals, residents of low-incidence countries)[57] or compared sensitivity in culture-confirmed individuals with active TB (taken as a surrogate reference standard for LTBI).[40,57,59] Using suboptimal reference standards for diagnostic accuracy testing can lead to an overestimation or underestimation of the true accuracy of a test. The degree of concordance (inter-rater or intrarater agreement, kappa statistic) and discordance between the results of the two tests (IGRAs and TST) has also been used. In general, both pooled sensitivity and specificity values of the IGRAs and the TST were similarly high in people who were not vaccinated with BCG (> 90%); however, the pooled specificity of the TST in BCG-vaccinated populations was much lower than that of IGRAs (about 56% vs. 96%).[11,53,57] In contrast, prospective longitudinal studies showed that neither the IGRAs nor the TST had a high prognostic value in predicting the risk of progression to active TB.[11,18]

Treatment of latent tuberculosis infection

Once patients are diagnosed with LTBI using any of the available tests, there are claims of low adherence to chemotherapy treatment.[61] As a result of low adherence, an alternative therapy recommended in the USA[62] has been implemented in some hospitals in the UK. It includes a new combination of isoniazid and a long-acting rifampicin called rifapentine given weekly for 12 weeks. Each of the 12 doses is directly observed being taken by a treatment supervisor. After LTBI is confirmed and active TB excluded, individuals are assessed for suitability for the rifapentine/isoniazid regimen.[61] Suitability is based on certain criteria including normal renal and liver function, aged ≥ 16 years, not pregnant, HIV-infected patients not on

antiretroviral treatment, agreeable to direct observations and direct observations are feasible. If suitable, the regimen is prescribed and a TB specialist nurse sets up the direct observations. If it is not suitable other latent TB treatment is offered. This combination has been found to be as effective as the 9-month daily isoniazid regime used in the USA, with higher completion rates as only 12 doses are needed.[61]

Relevant national guidelines including National Service Frameworks

The latest guidelines on the diagnosis, management and prevention of TB are available from NICE. There is a 2006 clinical guideline[51] on the clinical diagnosis and management of TB and measures for its prevention and control, with a partial update in 2011,[10] as well as 2012 public health guidance[52] to identify and manage TB among hard-to-reach groups. The Department of Health has also published guidelines for the planning, commissioning and delivery of TB services,[63] guidelines for testing health-care workers,[64] a wider action plan for stopping TB in England[65] and guidance for the prevention and control of HIV-related and drug-resistant TB.[66] Finally, the British Thoracic Society has published guidelines on the prevention, risk assessment and management of TB in adult patients with chronic kidney disease[67] and in patients due to start antiTNF-α treatment,[68] management of air travel passengers[69] and management of opportunist mycobacterial infections.[70]

Description of the technology under assessment

Summary of the intervention

As noted earlier, screening for LTBI is crucial to curb the re-emergence of TB as the majority of TB cases consist of latent TB that has been reactivated.[71] Testing and treating high-risk individuals for LTBI would not only prevent active TB illness for the individual but also would reduce the transmission of TB, thus reducing the pool of infection.[72]

There is much interest in using IGRAs to identify individuals at high risk of LTBI because of the advantages that they have over the traditional TST, particularly that they require only one visit and that previous BCG status does not interfere with the results. For IGRAs to replace the TST in the current care pathway, they would have to show improved cost-effectiveness relative to the TST, although in the absence of a gold standard this is difficult.[73] Otherwise, IGRAs may have to be used as complementary tests to the TST, as is currently recommended in the national guidelines.[10]

The results of an IGRA test depend on local arrangements but can be available within 1 week.[74] The TST takes 2–3 days as individuals must return to have the test read.[13,16] In combination, therefore, both tests take several days to be completed. IGRA testing comes at a higher cost than the TST and shifts the costs and labour from the clinic to the laboratory.[75] Both the TST and IGRAs require specific equipment either for administering the injection or taking a blood sample. In addition, IGRA testing requires advanced laboratory facilities.[75] Skilled personnel are needed to administer both tests and, in the case of the TST, are needed to read the result, whereas for IGRA testing laboratory personnel are needed to process the result.[73] In both cases patients follow a common pathway, with nurses providing patients with the result, following up patients for testing of active TB and offering treatment and advice.[10] IGRAs can be used in similar settings to the TST as long as there is access to a laboratory and pathways are negotiated so that samples can be analysed within 12 hours.[46]

Screening tests for latent tuberculosis infection in special subgroups at risk

It has been suggested that screening tests applied to presumably healthy populations or those at low risk for progression to active TB may not be justified given the potential harms from unnecessary treatment.[16,76] It is also not feasible or cost-effective to universally screen the population as the administrative and clinical costs outweigh the benefits of identifying TB cases.[46] The benefits of screening for LTBI using these tests

are likely to be maximal in individuals at high risk of contracting MTB (e.g. those recently arrived from countries with a high TB incidence, close contacts of those with active TB) and those with suspected LTBI who are at high risk of progression to active TB and complications associated with the infection (e.g. immunocompromised patients, young children). As these subgroups are at higher risk of developing active TB, it is of public health importance to identify LTBI in them.

Studies comparing the TST and IGRAs for detecting LTBI in children have mostly demonstrated better specificity for IGRAs than the TST.[59] Sensitivity has been shown to be comparable between the TST and the IGRAs but to vary considerably between studies. Both specificity and sensitivity depend on an implied association between LTBI and exposure to TB (as a proxy for true-positive LTBI). The comparative evidence in immunocompromised people has been too scarce to draw definitive conclusions. One systematic review showed suboptimal but comparable performance between the TST and the IGRAs for identifying LTBI in HIV-infected patients.[40] In general, based on limited data, the accuracy indices for the TST and IGRAs in the subgroups of children and immunocompromised people have been shown to be suboptimal. However, the absence of a gold standard, small samples, indeterminate test results and heterogeneity between the studies make adequate comparisons between tests difficult.[11,16]

One study has compared the TST and the two IGRAs (QFT-GIT and T-SPOT.*TB*) for detecting LTBI in migrants to the UK.[77] However, comparison of the tests was carried out only by evaluating the positive results of each, concordance between the tests and the factors associated with positivity. Yields of the test were computed at different incidence thresholds and the cost-effectiveness of the tests was estimated. The authors found that the TST was positive in 30.3% (53/175) of individuals who completed screening, QFT-GIT was positive in 16.6% (38/229) of individuals and T-SPOT.*TB* was positive in 22.5% (36/160) of individuals. The higher rate for the TST could be a result of the effect of BCG vaccination. Although NICE recommends that recently arriving migrants from countries with a TB incidence of ≥ 40 per 100,000 should be screened, the study found that this would require 97–99% of the cohort to be screened and would identify 98–100% of cases of LTBI whereas screening migrants from countries with an incidence of 150 per 100,000 would identify 49–71% of cases of LTBI but would require screening of only half of the cohort. The most cost-effective option was to screen recently arriving migrants from countries with a TB incidence of > 250 per 100,000 with one QFT-GIT test (£21,565.3 per case prevented) but, as this would miss many cases, screening recently arriving migrants from countries with a TB incidence of 150 per 100,000 was recommended as it was only slightly less cost-effective (£31,867 per case prevented) and would prevent an additional 7.8 cases of TB. This was confirmed in a previous study assessing groups of new migrants in the UK who should be screened for LTBI.[6] Despite these findings it is difficult to draw firm conclusions about the accuracy of identifying LTBI in immigrants as no reference test was used for LTBI when comparing the tests.

New evidence is needed to determine the best approaches for identifying LTBI in all three groups of people (children, immunocompromised individuals and recently arrived immigrants from high-incidence countries). This will help in deciding whether IGRAs should replace or complement the TST and, if so, in which circumstances. There is an ongoing large multicentre cohort study assessing the efficacy and cost-effectiveness of IGRAs compared with the TST for predicting active TB in recently arrived migrants in the UK from high-incidence countries (> 40 per 100,000) and people who have been in contact with TB cases. In total, 10,000 participants (aged ≥ 16 years) will be recruited from 12 hospitals and general practitioner (GP) surgeries and followed up for 24 months; the results from this study will be available in 2017.[78]

Current usage in the NHS

The UK National Screening Committee decided that TB screening should be organised locally rather than as a national programme.[79] Therefore, the implementation of NICE guidelines on LTBI testing using the TST and IGRAs has been very ad hoc across the NHS. In London, for example, it is reported that it has not been fully implemented and that current practice is not effective in detecting LTBI.[50]

More recently, in March 2014, a tri-borough Joint Strategic Needs Assessment (JSNA) report[80] stated that 'However, GP screening has to date been inconsistent and no clear assessment and patient pathway exists for latent TB'. Leicester, Leicestershire and Rutland's *Tuberculosis Summary Needs Assessment* from December 2013[81] mentions expanding numbers of cases of LTBI from IGRA testing but calls for a more systematic testing process for testing new entrants to make an impact on active TB cases. In addition, Kirklees's JSNA[82] mentions exploring funding to develop IGRA testing and Manchester City Council JSNA[83] reports needing to improve LTBI screening.

Commissioners are currently looking at models for local service provision. This is in line with the suggested approach of TB control boards in the recent PHE consultation document *Collaborative Tuberculosis Strategy for England 2014 to 2019*.[7] There is not one agreed service model and PHE has recently sponsored several pilot projects, which are ongoing at present, looking at the feasibility of screening in different settings. These include the identification of eligible individuals from GP practice lists followed by an invitation for screening at the GP surgery by IGRA (Dr Huda Mohammed, PHE, West Midlands, 12 May 2014, personal communication) and a more innovative approach in which screening for LTBI was carried out using an IGRA at a college of further education among self-selected individuals taking part in English for Speakers of Other Languages classes following a campaign of education.[84] Neither of these studies has reported yet but they are expected to show positive result rates of between 17% and 20% (Dr Huda Mohammed, personal communication).

It is difficult to know how many GPs are identifying new entrants and organising testing for them or how many new entrants are contacting TB services directly for testing. The websites of several community TB[85] teams list testing new entrants for LTBI as part of their remit and give a contact number or e-mail address. The Birmingham and Solihull Tuberculosis Service[86] has a full page on its website with eligibility criteria for screening, whereas the Liverpool Community Health NHS Trust Tuberculosis Service[87] excludes testing of new entrants who are students.

Taking the Coventry and Warwickshire area as a case study, the Meridian Practice in Coventry, a specialist service that cares for refugees and asylum seekers, offers IGRA testing to all registered patients (Najeeb Wai, practice manager, Meridian Practice, 8 July 2014, personal communication). The Coventry and Warwickshire Tuberculosis Service reports that it 'indirectly tr[ies] to identify high TB risk individuals other than identified contacts and offer screening' (Debbie Crisp, lead TB nurse specialist and primary care services for the Arden Community TB Service, 9 July 2014, personal communication). Apart from supporting the work at the Meridian Practice, it also supports the Warwickshire programme for looked-after children, which has an established TB screening programme incorporated into its medical review, and has plans to discuss the programme with the Coventry team. In addition, the Coventry and Warwickshire Partnership Trust commenced a TB screening programme for HIV-infected individuals in July 2013 and supports the LTBI treatment programme.

In summary, it is difficult to know how much awareness there is for LTBI screening in the primary care setting in the NHS. Pathways are not widely available, if they exist at all. Secondary care specialist services are more aware, but do not employ standard criteria for testing. There is great variability within the system. There is a clear need for new evidence to provide information on the most appropriate strategies available for identifying LTBI in the three subgroups of interest: children, immunocompromised individuals and recently arrived immigrants from high-incidence countries. This evidence will aid in the decision-making process on whether IGRAs should be used as a replacement or as an adjunct to the TST for the diagnosis of LTBI in these populations.

The next chapter discusses the decision problem and outlines the key clinical questions and objectives of this work.

Chapter 2 Definition of the decision problem

Tuberculosis is a major cause of morbidity and mortality worldwide. The timely identification and prophylactic treatment of people with LTBI is of public health and clinical importance. Unfortunately, there is no diagnostic gold standard for the identification of individuals with LTBI who would benefit from such prophylactic treatment. Instead, the available screening tests provide indirect and imperfect assessment of the presence of LTBI. There are two types of tests used to identify LTBI in the UK: (1) the TST and (2) IGRAs.

In light of new evidence since 2009, this systematic review aimed to compare the clinical effectiveness and cost-effectiveness of screening tests for LTBI (IGRAs and TST) in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of TB. To do this we updated the searches since 2009 to identify relevant evidence and incorporate both pre- and post-2009 evidence into the analysis. This review also attempted to determine the most cost-effective approach for identifying LTBI.

The key clinical questions to be considered were:

1. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in children?
2. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in people who are immunocompromised or at risk of immunosuppression?
3. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in people who are recent arrivals from countries with a high incidence of TB?

Chapter 3 Clinical effectiveness review methods

A protocol to which we adhered was developed for undertaking this systematic review of the clinical effectiveness literature. The presentation of our systematic review is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Identification and selection of studies

Search strategy for clinical effectiveness

Scoping searches were undertaken to inform the development of the overall search strategy. An iterative procedure was used, with input from the searches and studies included in NICE clinical guideline 117 (CG117)[10] and methods manuals.[88,89] The bibliographic database search strategies focused on the diagnosis of LTBI using IGRAs compared with other methods and were limited to articles in English that had been added to databases since searches for the equivalent questions in CG117[10] were run (7–14 December 2009; see *Appendix 1*). The searches automatically picked up comparisons in performance between IGRAs and TSTs and therefore it was not necessary to search independently for comparator technologies (e.g. TSTs). The search strategies used in the major databases are provided in *Appendix 2*. Bibliographic database searches were undertaken on 9 and 10 April 2014 and were updated on 2 December 2014 using the same strategies. Supplementary searches were undertaken between 10 June 2014 and 5 August 2014 (see *Appendix 2* for exact dates).

The search strategy included the following main elements:

- searching of electronic bibliographic databases
- contact with experts in the field
- scrutiny of references of included studies and relevant systematic reviews
- screening of manufacturers' and other relevant websites.

The bibliographic databases searched were MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library incorporating the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment database (Wiley); Science Citation Index and Conference Proceedings Citation Index (Web of Science); and Medion. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were searched for ongoing and recently completed trials.

Specific conference proceedings selected with input from a clinical expert were checked for the last 5 years. The online resources of relevant organisations were also searched. Further details of these searches are provided in *Appendix 2*.

Citation searches of included studies were undertaken using the Web of Science and Scopus citation search facilities. The reference lists of included studies and relevant systematic reviews were checked. Included papers were checked for errata using PubMed. Identified references were downloaded to bibliographic management software (EndNote X7; Thomson Reuters, CA, USA).

Inclusion and exclusion of studies

Inclusion criteria

Primary studies evaluating and comparing the head-to-head effectiveness of commercially available approaches/tests used for identifying people with LTBI:

- IGRAs, for example:
  - QFT-GIT (old version: QFT-G)
  - T-SPOT.*TB*.
- TST (i.e. Mantoux test).

Head-to-head studies involving a direct comparison between an IGRA and TST only were included.

Type and language of publication

- Full-text reports published in English.
- Abstracts (only if they were companion publications to full-text included studies).

Study design

- Longitudinal studies (randomised controlled trials, retrospective or prospective cohort studies).
- Cross-sectional or case–control studies.

Population

- Children (both sexes, aged < 18 years, immunocompetent) (research question 1).
- People (both sexes, any age) who were immunocompromised or at risk from immunosuppression (e.g. transplant recipients or those with HIV infection, renal disease, diabetes, liver disease, haematological disease, cancer or autoimmune disease or those who were on or about to start antiTNF-α treatment, steroids or ciclosporins) (research question 2).
- People (both sexes, any age, immunocompetent) who had recently arrived from regions with a high incidence/prevalence of TB (countries/territories with an estimated incidence rate of $\geq$ 40 per 100,000, e.g. those in Africa, Central/South America, Eastern Europe and Asia) (research question 3).

Intervention

- Two IGRAs (one- or two-step testing):
  - QFT-GIT (old version: QFT-G)
  - T-SPOT.*TB*.

Comparator

- TST (Mantoux test) alone or plus IGRA (one- or two-step testing).

Construct validity measures (as a proxy for outcomes)

- Progression to active TB.
- Exposure to MTB defined by proximity, duration, geographical location or dose–response gradient.
- People at low risk of MTB infection or healthy populations.

Exclusion criteria

- Studies not comparing IGRAs with the TST with regard to the prespecified construct validity (i.e. incidence of TB, exposure to MTB defined by proximity, duration, geographical location, dose–response gradient).
- Studies not comparing the accuracy of tests (IGRAs with TSTs) in a head-to-head comparison to identify people with LTBI.
- Studies (involving children, recently arrived immigrants or immunocompromised people) not reporting subgroup data separately for each relevant population.
- Studies comparing the IGRAs with each other (e.g. QFT-G-IT vs. T-SPOT.*TB*) in identifying people with LTBI.
- Studies applying non-commercial IGRAs, in-house IGRAs, older-generation IGRAs [e.g. PPD-based first-generation QuantiFERON-TB (QFT)] or tests unavailable in the UK.
- Studies assessing the effects of TB treatment on IGRA/TST test results.
- Studies evaluating and/or comparing the reproducibility (test and retest) of tests for identifying LTBI.
- Studies not focusing specifically on LTBI [e.g. studies in which the presence of blood culture-positive TB (active TB) was used to estimate sensitivity – 'active TB' is assumed as the reference standard for the 'true presence of LTBI'; however, given that active TB and LTBI are two clinically and immunologically distinct forms of TB, this assumption is problematic].
- Studies using serial testing (e.g. health-care staff/students, military personnel or prisoners) of IGRAs (or TST) to detect LTBI.
- Studies focusing on a specific biomarker (e.g. IFN-γ-inducible protein 10).
- Systematic/narrative reviews, meta-analyses, case reports, case series, abstracts (see *Type and language of publication*), commentaries, letters or editorials.

Review outcomes

Diagnostic accuracy measures

- Measures of association between test (IGRAs, TST) results and construct validity – I [i.e. prognostic value of tests in predicting the development/risk of active TB (sensitivity, specificity, false-negative and false-positive rates, PPVs and NPVs, incidence density rate ratios (IDRRs), CIRs].
- Measures of association between test (IGRAs, TST) results and construct validity – II {i.e. exposure status/level with regard to MTB defined by proximity, length of time and type of contact and including the dose–response gradient if applicable [sensitivity, specificity, false-negative and false-positive rates, DORs, regression-based odds ratios (ORs) of test positivity]}.
- Measures of association between test (IGRAs, TST) results and other construct(s) of validity – III [e.g. people at low risk for LTBI, e.g. healthy people, residents of low-incidence countries (specificity and false-positive rate)].

Measures of concordance and discordance

- Agreement (inter-rater, intrarater) (kappa statistic, 95% CI).
- Concordance between tests (%, 95% CI).
- Discordance between tests (%, 95% CI).

Other outcomes

- Dependence of test positivity (IGRAs, TST) on previous BCG vaccination.
- Adverse events.
- Likelihood of an indeterminate result.
- Health-related quality of life.

Study selection strategy

Two independent reviewers screened all identified bibliographic records on title/abstract (screening level I) using a prespecified and piloted questionnaire form. Full-text reports of all potentially relevant records passing screening level I were then retrieved and independently reviewed using the same study eligibility criteria (screening level II). Any disagreements over inclusion/exclusion were resolved by discussion between two reviewers or by recourse to a third-party reviewer.

Data extraction strategy

Two reviewers independently extracted relevant data using an a priori defined pre-piloted data extraction sheet (see *Appendix 3*). Data extracted were cross-checked and any disagreements were resolved by discussion or by recourse to a third-party reviewer. Data extracted included information on the study [e.g. author, country, publication year, design, setting, sample size, follow-up duration, risk of bias (ROB) items such as blinding or incomplete outcome data], participants (e.g. age, sex, study eligibility criteria, comorbidities, BCG vaccination status/time, immune status), intervention/comparator tests (type of test/assay used for identification of LTBI, definition of positivity/negativity thresholds/cut-off values for each test, methods of laboratory analysis used for the derivation of test results, repeat testing), construct validity (e.g. definition of exposure to MTB in terms of proximity, length of time and/or type of contact; incidence of progression to active TB; timing of exposure to MTB/incidence of active TB; definition of low-risk populations; type of summary effect measures).

For individual studies, 2 × 2 contingency tables were constructed by cross-tabulating test results (separately for IGRAs and TST) with construct validity responses in relation to exposure level or incidence of progression to active TB. The proportions of subjects with positive and negative test results were extracted. For each test, all summary parameters of interest (see the list of outcomes) with corresponding measures of variability (95% CIs, *p*-values) were ascertained or calculated, if reported data permitted. A value of 0.5 was imputed for incidence studies with zero events for one of the compared tests to allow the calculation of CIRs and their ratios (R-CIRs). The R-CIRs were rendered indeterminate in the case of zero events in the 2 × 2 tables of both tests compared (no imputation was carried out). All relevant summary parameters were entered into the data extraction sheets and evidence and summary tables. Calculated parameters were marked as 'calculated'.

Study quality assessment

The methodological quality of the incidence and exposure studies included in the current review was assessed using the Quality in Prognosis Studies (QUIPS) tool[90] and a modified tool reported by Dinnes *et al.*,[44] respectively (see *Appendix 4*).

The QUIPS tool[90] (also referred to as the 'Methodology checklist: prognostic studies', developed by Hayden *et al.*,[90] in the NICE *Guidelines Manual*[89]) was used to assess studies reporting the diagnostic performance/validation of tests (e.g. sensitivity, specificity, incidence density rate/CIRs, PPVs/NPVs, DORs, regression-based ORs). The QUIPS tool assesses the ROB in the six domains of patient selection/participation, study sample attrition, index test measurement, outcome/construct validity measurement, confounding and statistical analysis/outcome reporting. According to responses to prompting items, each of the six domains is rated as high, moderate or low ROB. The overall summary ROB rating for each study is then derived based on the domain-specific ROB ratings.

We used a modified tool reported by Dinnes *et al.*[44] to assess the quality of retrospective/cross-sectional studies reporting associations between test results and exposures. The QUIPS tool is not directly applicable to assessing the quality of retrospective/cross-sectional studies of association between test results and

exposure because of the non-prognostic nature of their design (exposure is ascertained retrospectively, which is then correlated with test results). *Appendix 4* outlines the criteria used to appraise these exposure studies. Each study was assessed for blinding of test results from exposure, description of index test and threshold (TST and IGRA), definition/description of exposure, completeness of verification of exposure and sample attrition. Each study was then awarded an overall quality score defined as:

- low quality: studies with 0–2 satisfied (yes response) quality features
- moderate quality: studies with three satisfied (yes response) quality features
- high quality: studies with 4–5 satisfied (yes response) quality features.

Study quality was assessed independently by two reviewers (PS and KF). Any disagreements were resolved by discussion or by a third reviewer. The evidence across studies was summarised qualitatively using the overall ROB ratings (low, moderate, high).

Data synthesis and analysis

Given the absence of a gold standard for diagnosing LTBI, the performance of tests was compared using alternative methodologies that rely on validation of test results against predetermined validity constructs (i.e. proxies for a reference standard). Thus, our analyses focused on the following recommended approaches: (1) we evaluated and compared predictive values of IGRAs and the TST in relation to construct validity I (i.e. progression rate to active TB); (2) we evaluated and compared the degree of association/correlation of IGRA and TST results with construct validity II (i.e. exposure to MTB defined by proximity, duration or dose–response gradient); (3) we estimated and compared the specificity (or false positives) of IGRAs and the TST in relation to construct validity III (i.e. people at low risk of MTB or healthy populations); and (4) we measured the degree of concordance/discordance between IGRA and TST results.[44,91–94]

For each index test (TST, IGRAs), if data permitted (either directly reported or, if not reported, calculated if possible), relevant statistical parameters of diagnostic test accuracy are presented per individual study. For statistics measuring agreement/disagreement between two tests, values for concordant (both tests positive or negative) and discordant (one test negative, the other test positive or vice versa) test results are presented or calculated if data permitted. Moreover, when possible, the likelihood of indeterminate test results was calculated.

The performance of the tests (in terms of diagnostic accuracy and concordance) was compared (e.g. IGRA vs. TST) using sensitivity, specificity, PPVs/NPVs, ratio of diagnostic odds ratios (R-DOR), ratio of incidence density rate ratios (R-IDRR) (or CIRs), regression-based ORs, kappa statistics, per cent discordance and likelihood of indeterminate test results. Note that, as there is no gold standard for the diagnosis of LTBI, specificity and sensitivity does not have the same meaning as in the conventional paradigm (i.e. against a gold standard) but reflects the performance of tests in relation to predetermined proxy constructs of validity (i.e. past exposure to TB or future progression to active TB).

The association between BCG vaccination and test performance in terms of specificity was explored by comparing false-positive rates (or odds of false positivity) of the TST and IGRAs in both BCG-vaccinated and unvaccinated individuals (i.e. dependence of false-positive rates on BCG vaccination status).

Summary measures of effectiveness (e.g. sensitivity, specificity, DOR, R-DOR, R-CIR) were pooled when deemed appropriate and feasible (based on the absence of clinical/methodological heterogeneity, the same cut-off values of a test or the absence of a test threshold effect on the DOR) using univariate[95] and/or bivariate random-effects meta-analysis models.[19] The presence of heterogeneity across studies was determined using visual inspection of forest plots (of individual study ORs and R-DOR estimates and degree of overlap across 95% CIs) and chi-squared tests (two tailed, $p \leq 0.10$).[96,97] A series of subgroup and sensitivity analyses (see below) was undertaken to explore potential reasons for statistical

heterogeneity, if present. When pooling was not feasible, because of a lack of sufficient data or important clinical/statistical heterogeneity across studies (e.g. significant test threshold effect),[98] the findings from individual studies were summarised qualitatively.

Data synthesis for the summary outcome measures is presented in evidence/summary tables and text overall and/or stratified by demographic characteristics (e.g. age), TST thresholds (≥ 5 mm, ≥ 10 mm, ≥ 15 mm), intervention (T-SPOT.*TB* vs. QFT) and prevalence/burden of TB in country of origin (high burden vs. low burden).[1] In addition, for people who were immunocompromised or at risk from immunosuppression (research question 2), when possible outcomes have been stratified by type of immunosuppression, use of immunosuppressive drugs (e.g. steroids, antiTNF-α treatment, antirheumatic drugs) and comorbidity condition (e.g. HIV infection, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, transplant recipients).

It was planned to conduct subgroup analysis according to BCG vaccination status, TST threshold (≥ 5 mm, ≥ 10 mm, ≥ 15 mm) and prevalence of TB in country of origin, if data permitted.

Calculations were performed using Meta-DiSc version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain)[99] and Stata version 14 (StataCorp LP, College Station, TX, USA).[100]

Overall quality of evidence

There is no formally accepted and validated approach for the assessment of the overall quality of evidence that would be appropriate to the type of evidence synthesised in this review. Work on the formulation of this approach is still ongoing [Grading of Recommendations Assessment, Development and Evaluation Working Group; see www.gradeworkinggroup.org (accessed 15 December 2015)].[101]

Derivation of summary measures of diagnostic accuracy

We used Bayesian meta-analysis to derive the sensitivity and specificity for various testing strategies for LTBI in the various population subcategories. The methods and results for this are reported in *Chapter 6* [see *Performance of screening texts (sensitivity and specificity)*].

Chapter 4 Clinical effectiveness results

Number of studies identified

A total of 6687 bibliographic records were identified through electronic database searches. After removing duplicates, 3757 records were screened for inclusion. On the basis of title/abstract, 3279 records were excluded. The remaining 478 records were included for full-text screening. A further 424 records were excluded at the full-text stage. The remaining 54 records[102–155] (53 unique studies) were considered relevant to the review since the previous NICE clinical guidance work in 2011 (CG117).[10] One study by Rutherford *et al.*[110,111] was presented in two publications. In addition, 37 studies[156–192] from CG117[10] were included in the current evidence synthesis (see *Appendix 5*). The study flow and the reasons for exclusion are shown in *Figure 2* and *Appendix 6*. A search for ongoing trials was undertaken in different databases (Clinical Trials.gov, WHO ICTRP) up to August 2014. A total of 50 ongoing trials were identified, of which 30 were excluded; the reasons for exclusion are presented in *Appendix 7*. Twenty ongoing trials were therefore considered relevant for inclusion in our review (see *Appendix 8*).

Description of included studies and synthesis

In the following sections we describe the baseline characteristics and study quality for the incidence and exposure studies of the three populations of interest: (1) children, (2) immunocompromised individuals and (3) those recently arrived from countries with a high TB incidence. Full data-extraction sheets including baseline characteristics for all recently identified studies since CG117[10] are provided in *Appendix 9*. For each of the three populations we present the synthesis of the evidence in terms of the comparative performance of tests (diagnostic accuracy indices for identifying LTBI) and between-test concordance, discordance and agreement. *Appendix 10* provides the incidence rates of TB for each included study since CG117.[10]

Children and adolescents

Description of baseline characteristics

This section included 27 studies (28 publications[102–113,148,150–152,154,156–166]) in children and adolescents, of which 11 studies[156–166] had already been reviewed in CG117[10] (see *Appendix 5*). Our searches identified 16 additional studies (in 17 publications[102–113,148,150–152,154]), five[102–104,150,152] of which investigated the incidence of active TB following testing for LTBI (incidence studies) and 11 of which (in 12 publications[105–113,148,151,154]) investigated levels of exposure in relation to LTBI test outcomes (exposure studies). Two publications[110,111] reported data on the same population and were therefore considered as one study. See *Appendix 9* for the full data-extraction sheets for all new included studies.

Incidence studies

Three[102,104,152] of the five incidence studies included close contacts of TB cases and one study[150] included only TST-positive (≥ 15 mm) children with no history of close contact with a TB case. Mahomed *et al.*[103] recruited low-risk high-school students in a high TB burden country, of whom 25% had current or past household contact with TB. Four studies were carried out in countries with TB vaccination: South Africa,[104] Iran,[103] Turkey[150] and South Korea.[152] One study[102] was carried out in Germany, in which only 35.7% of participants were BCG vaccinated. Four studies[102–104,152] investigated the agreement of a QFT test with the TST. Four studies compared QFT-GIT with the TST in community settings[102,103,150,152] whereas Noorbakhsh *et al.*[104] investigated the agreement between QFT-G and TST (≥ 10 mm) in a hospital setting. Follow-up to confirm active TB across the five studies ranged from 1 year[104] to 3.8–4 years.[102,103] *Table 2* provides further details on these studies.

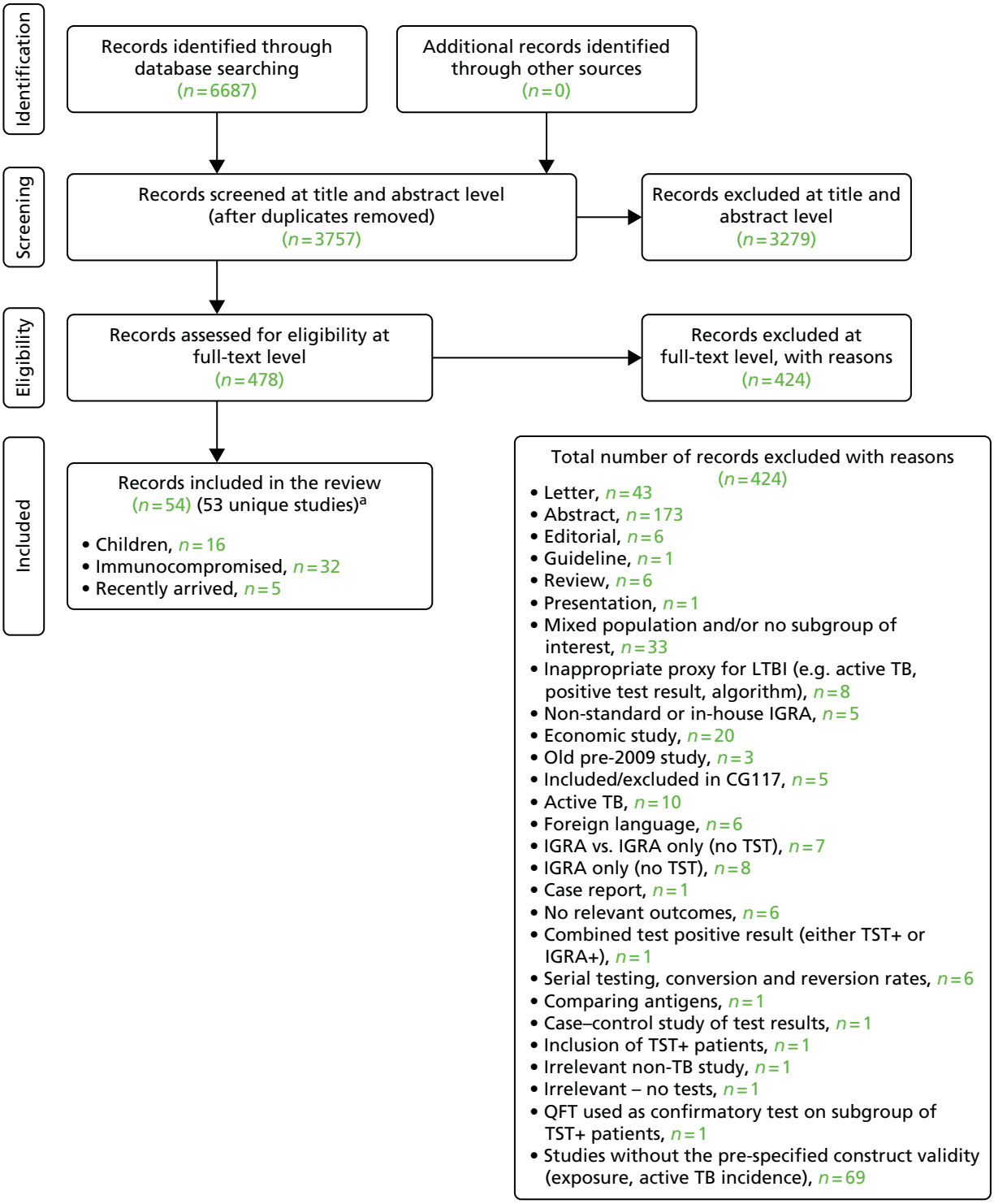


FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow diagram of studies identified since 2011. a, An additional 37 studies were included from CG117.[10]

TABLE 2 Baseline characteristics of studies in children and adolescents: incidence studies

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Diel 2011,[102] Germany (low)	Aim: to compare QFT-GIT with the TST in close contacts of patients with TB and evaluate progression to active TB for up to 4 years Setting: community-based contact study Design: prospective cohort study Follow-up: 2–4 years Funding source: NR (none of the authors had a financial relationship with a commercial entity that had an interest in the subject of this manuscript)	CXR (and CT), identification of AFB in sputum samples by bronchoscopy or lavage of gastric secretions, conventional culture of MTB, nucleic acid amplification assays and/or histopathology, assessment of preceding clinical suspicion of TB. In culture-negative cases, and given a CXR consistent with TB, subsequent clinical and radiographic response to multidrug therapy over an appropriate time course (1–3 months) was considered sufficient to confirm the diagnosis of TB	Inclusion criteria: close contacts of smear-positive and subsequently culture-confirmed source MTB index cases; aggregate exposure time of the contact in the 3 months before the diagnosis of the respective index case (presumed period of infectiousness) > 40 hours indoors with shared air Exclusion criteria: contacts with an exposure time of < 40 hours to the source	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA: IFN-γ ≥ 0.35 IU/ml; TST: induration of > 5 mm or > 10 mm	Mean (SD) age: 10.4 (4.3) years Female, *n* (%): NR Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): Germany 84 (66.7) BCG vaccination, *n* (%): 45 (35.7) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n/N* (%): 6/104 (5.7) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR	Total number of recruited patients: 141; total number of excluded patients: 15	Assessors of the TST were blinded to the QFT results and vice versa. Induration was read by trained and well-experienced public health nurses. If there was a borderline result (e.g. 5 mm exactly), a second reading was performed by a different nurse to verify the result. If there was disagreement, a third nurse read the TST and the consensus result was used

continued

TABLE 2 Baseline characteristics of studies in children and adolescents: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Mahomed 2011,[103] South Africa (high)	Aim: to compare the predictive value of a baseline TST with that of the QFT-GIT for subsequent microbiologically confirmed TB disease among adolescents Setting: high school (TB vaccine trial site in the town of Worcester and surrounding villages; high burden of TB) Design: longitudinal cohort study Follow-up: 3.8 years Funding source: Aeras Global TB Vaccine Foundation with some support from the Gates Grand Challenge 6 and Gates Grand Challenge 12 grants for QFT testing	Two sputum samples for smear microscopy on two separate occasions. If any single sputum sample was smear positive, a mycobacterial culture, chest radiography, and HIV test were performed	Inclusion criteria: adolescents aged 12–18 years Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA: IFN-γ ≥ 0.35 IU/ml; TST: induration of ≥ 5 mm	Mean (range or SD) age: NR Female, *n* (%): 2842 (54.2) Race/ethnicity, *n* (%): black 995 (19.0); mixed race: 3839 (73.2); Indian/white: 410 (7.8) BCG vaccination, *n* (%): yes 4917 (93.8); unknown 281 (5.4) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): 52 (1.0) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 6363; total number of excluded patients: 1119	People with a recent household contact, TB-related symptoms, a positive TST of ≥ 10-mm induration or a positive QFT were referred for two sputum smears. If the results of either or both were sputum positive for AFB, the sputum samples were cultured and chest radiography and a HIV test were undertaken

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Metin Timur 2014,[150] Turkey (intermediate)	Aim: to compare QFT-GIT and TST for the diagnosis of LTBI in children who have been vaccinated with the BCG vaccine Setting: community based Design: prospective cohort study Follow-up: 3 years as an outpatient with 3-month intervals between assessments Funding source: NR	Active TB disease was defined as both TST and QFT-GIT test positive in a child who had symptoms of TB disease and/or abnormal findings on chest radiography or CT, or proven MTB culture, polymerase chain reaction or histopathological examination	Inclusion criteria: children with positive TST results, children without a history of contact with a TB case, active TB case in the household not detected through family screening, no medical reason for immunosuppression, diagnosed with TB disease without a contact with an active TB case Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT) and TST Cut-off values/ thresholds: IGRA: NR; TST: induration of ≥ 15 mm	Mean (SD) age: 94.8 (51.9) months Female, *n* (%): 33 (40.7) Race/ethnicity, *n* (%): NR BCG vaccination, *n* (%): one BCG scar 69 (85.2); two BCG scars 12 (14.8) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): none Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): acute appendicitis 1 (1.2) Type of during-study treatment, *n* (%): no treatment *n* = 69 children with TST+/QFT– results; isoniazid *n* = 8 children with TST+/QFT+ results but no symptoms (assumed with LTBI); isoniazid, rifampicin and pyrazinamide *n* = 4 children with TST+/QFT+ results with symptoms (with TB)	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 2 Baseline characteristics of studies in children and adolescents: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Noorbakhsh 2011,[104] Iran (intermediate)	Aim: to detect the agreement between TST and QFT-G in young household contacts of cases of proven active pulmonary TB in a BCG-vaccinated population in Tehran, Iran, and to compare subjects progressing to TB with non-progressive subjects Setting: pulmonary and infectious diseases department of Rasul Hospital in Tehran Design: cross-sectional study Follow-up: 1 year Funding source: Research Centre of Paediatric Infectious Diseases, Iran University of Medical Sciences	Person diagnosed by an internist in the pulmonary and infectious ward of Rasul Hospital. The index cases were confirmed by positive culture for MTB or sputum smear-positive TB	Inclusion criteria: all young (age < 20 years) close or household contacts of people (any person who had lived with the index case for > 3 months) with confirmed active pulmonary TB and previous BCG vaccination received at birth. The subjects were invited to the research centre for clinical and laboratory follow-up Exclusion criteria: household contacts were excluded if they had been treated for TB in the past year or had a known immunodeficiency status according to history or clinical signs (malignancy, corticosteroid therapy, HIV infection, etc.)	Type of tests: IGRA (QFT-G), TST Cut-off values/ thresholds: IGRA: NR; TST: induration of ≥ 10 mm	Mean (range or SD) age: NR Female, *n* (%): 34 (57.6) Race/ethnicity, *n* (%): NR BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): 10 (16.9) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Song 2014,[152] South Korea (high)	Study aim: to determine the agreement between QFT-GIT and TST, and identify the relationships between the results of these tests and the development of active TB in middle- and high-school students in close contact with TB patients in South Korea Setting: community based Design: prospective cohort study Follow-up: 24 months Funding source: Research of Korea Centers for Disease Control and Prevention	NR	Inclusion criteria: close contacts of identified smear-positive TB cases with normal chest radiography aged 11–19 years Exclusion criteria: participants showing abnormal findings on simple chest radiography, taken immunosuppressive agents or anticancer drugs previously and been treated with antiTB drugs or chemoprophylaxis previously	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA: IFN-γ 0.35 IU/ml; TST induration of ≥ 10 mm or ≥ 15 mm	Mean (SD) age: 15.1 (1.3) years Female, *n* (%): 1356 (45.5) Race/ethnicity, *n* (%): NR BCG vaccination, *n* (%): 1818 (61.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n/N* (%): 23/2982 (0.77) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n/N* (%): 5/215 (2.32) (isoniazid)	Total number of recruited patients: 3202; total number of excluded patients: 220	To eliminate the possibility of false-positive IGRA results due to PPD reagents, blood samples were collected before PPD injection

AFB, acid-fast bacilli; CT, computerised tomography; CXR, chest radiography; ID, identification; NR, not reported; SD, standard deviation.

Exposure studies

Eleven studies (in 12 publications[105–113,148,151,154]) compared one or more QFT tests with the TST test in children and adolescents by relating test results to previous levels of exposure (exposure studies). Five studies were carried out in countries with a high TB incidence [Gambia,[105] South Africa,[107,108] Indonesia (one study in two publications)[110,111] and Thailand[154]], two studies were carried out in countries with TB of intermediate incidence (Mexico[148] and Brazil[151]) and four studies were carried out in low-incidence countries (USA,[106,112] Croatia[109] and Greece[113]).

The mean and/or median age of the recruited children was reported in eight[106–109,112,148,151,154] of the 11 studies. The populations in the studies by Pavic *et al.*[109] and Perez-Porcuna *et al.*[151] had a mean age of < 4 years. The studies by Laniado-Laborın *et al.*[148] and Tieu *et al.*[154] included children whose mean age was about 8 years. Cruz *et al.*[106] and Kasambira *et al.*[107] recruited children with a median age of 8.6 and 6 years, respectively. Mahomed *et al.*[108] and Talbot *et al.*[112] investigated adolescents with an age range of 12–18 years and a median age of 20 years, respectively. The reported proportion of females was just above 50% in the majority of studies[105–108,112,148,151,154] and was 40% in one study.[109] Eight studies compared QFT-GIT with the TST ≥ 5 mm[107,108,148] or the TST ≥ 10 mm.[109–111,151,154] The T-SPOT.*TB* test was compared with the TST (≥ 10 mm or ≥ 15 mm) in three studies.[106,112,154] Adetifa *et al.*[105] compared three tests [QFT-GIT, T-SPOT.*TB* and TST (≥ 10 mm)] whereas Tsolia *et al.*[113] compared QFT-GIT with TST at two different thresholds (≥ 5 mm and ≥ 10 mm).

Exposure to TB was defined as household contacts in one study[108] and was further categorised by four studies to include sleep proximity[105] (same room/different room), time spent with contact[107,109] (≥ 40 hours in closed rooms; < 6 hours per day or > 7 hours per day, respectively) or both[110,111] (different room/same room/same bed and < 2 hours per day or 2–8 hours per day or > 8 hours per day). One study described exposure only as contact with a source case,[106] another study described it in terms of country of birth, residence and extended visit to a high-incidence country,[112] and a further study distinguished exposure as either non-household but regular contact or household contact.[113] Three studies used a TB contact score[151,154] or duration of exposure to the TB index case.[148,151,154]

Studies were either community based[105,107,108,112,151,154] or hospital based.[106,109–111,113,148] The level of BCG vaccination was high in six studies,[107–109,148,151,154] medium in a further three studies,[105,106,110,111] low in one study[112] and not reported in another study.[113] *Table 3* provides further details on these studies.

Study quality

Incidence of active tuberculosis

Of the five[102–104,150,152] newly identified active TB incidence studies in children, three[102,103,152] were rated as having a moderate ROB and two[104,150] were rated as having a high ROB. Most studies had a moderate ROB for the item misclassification of individuals in relation to construct validity groups. The studies also failed to provide information on prognostic factor and outcome measurement. *Table 4* provides further details.

Exposure levels

The majority of the 11 included exposure studies in children[105–113,148,151,154] identified since the publication of CG117[10] were rated as being of low quality, with only three[109,151,154] studies rated as being of high quality. One study was of moderate quality.[148] *Table 5* provides further details.

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Adetifa 2010,[105] Gambia (high)	Aim: to compare T-SPOT.*TB*, QFT-GIT and TST for the diagnosis of LTBI in Gambian childhood contacts of TB patients Setting: community based Design: retrospective cohort/cross-sectional study Funding source: Medical Research Council (MRC) laboratories, UK	Sleep proximity: non-exposed: different house (reference group); exposed 1: same house, different room; exposed 2: same house, same room	Inclusion criteria: household contacts (< 16 years) of newly diagnosed TB index cases Exclusion criteria: history of treatment for active TB, TB diagnosis within 1 month of recruitment	Type of tests: IGRAs (T-SPOT.*TB*, QFT-GIT), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): ≥ 6 spots in either the ESAT-6 or CFP-10 panel after subtracting the number of spots in the negative control panel; IGRA (QFT-GIT): IFN-γ ≥ 0.35 IU/ml; TST: induration of ≥ 10 mm	Mean (range or SD) age: NR Female, *n* (%): 145 (51) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n*/*N* (%): 127/199 (59.1) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): HIV positive 3 (1.1) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 285; total number of excluded patients: NR	

continued

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Cruz 2011,[106] USA (low)	Study aim: to compare the performance of T-SPOT.*TB* with that of TST in children with different epidemiological risk factors for TB Setting: paediatric TB clinics Design: retrospective cohort/cross-sectional study Funding source: Cellestis Ltd, Oxford Immunotec, Inc.	Non-exposed: no contact with an identifiable source case; exposed 1: contact with an identifiable source case	Inclusion criteria: children (aged 1 month to 18 years) with LTBI or TB disease and children uninfected with TB Exclusion criteria: children on any TB medication for ≥ 2 months were not eligible for enrolment	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): ≥ 8 spots; TST: induration of ≥ 15 mm	Median (range) age: 8.6 years (1 month to 18 years) Female, *n* (%): 9451 Race/ethnicity, *n* (%): Hispanic 115 (62.5), non-Hispanic black 36 (19.6), non-Hispanic white 19 (10.3), Asian 6 (3) Geographical origin, *n* (%): low-prevalence regions (US/UK) 121 (65.7) BCG vaccination, *n* (%): 68 (37) History of antiTB treatment, *n* (%): Total incidence of active TB, *n* (%): none Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	Borderline results (5–7 spots) were excluded from concordance analyses but were analysed separately. A subgroup analysis was performed for specimens with six to seven spots because these specimens are sometimes considered positive internationally

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Kasambira 2011,[107] South Africa (high)	Aim: to determine and compare the prevalence of MTB infection as assessed by TST and QFT-GIT, and to assess agreement between the two test methods and identify factors associated with various patterns of test results Setting: community based Design: retrospective cohort/cross-sectional study (with limited follow-up of 6 months) Funding source: United States Agency for International Development	Adult index case type of TB diagnosis: non-exposed: smear-positive TB; exposed 1: smear-negative, culture-positive TB; exposed 2: clinical TB Adult index case smear grade: non-exposed: negative; exposed 1: scanty; exposed 2: 1+; exposed 3: 2+; exposed 4: 3+ Exposure to index case during the day: non-exposed: minority of day (< 6 hours); exposed: majority of day (> 7 hours)	Inclusion criteria: children aged 6–16 years whose parents and guardians were TB index cases aged ≥ 18 years, with a diagnosis of pulmonary TB within the preceding 3 months, willingness to have their child undergo study testing and provision of informed consent Exclusion criteria: previous diagnosis or treatment of active or latent TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: definition of positive test: IGRA (QFT-GIT): NR; TST: induration of ≥ 5 mm	Median (IQR) age: 6 (3–9) years Female, *n* (%): 141 (52) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 257 (95) History of antiTB treatment, *n* (%): none Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): NR Clinical examination (yes/no): yes Morbidity, *n* (%): HIV 14 (5) Comorbidity, *n* (%): NA Type of during-study treatment, *n* (%): active TB treatment 37 (19), LTBI treatment 19 (10)	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Laniado-Laborın 2014,[148] Mexico (intermediate)	Aim: to compare the prevalence of LTBI between paediatric contacts of drug-resistant cases and drug-susceptible cases Setting: TB clinic Design: cross-sectional/ retrospective cohort study Funding source: NR	Non-exposed: NR; exposed: exposure to source, hours per day exposure, number of cohabitants, number of rooms	Inclusion criteria: family contacts of culture-proven cases aged ≤ 16 years Exclusion criteria: subjects with a history of TB, a previous diagnosis of LTBI or the administration of a TST in the past year	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): IFN-γ ≥ 0.35 IU/ml; TST: induration of ≥ 5 mm	Mean (SD) age: drug susceptible 7.79 (4.28) years; drug resistant 7.36 (4.46) years Female, *n/N* (%): 86/173 (50.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 164 (95) History of antiTB treatment, *n* (%): none Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n/N* (%): 77/173 (44.5) contacts of multidrug-susceptible index cases were treated for LTBI with isoniazid or rifampicin; 96/173 (55.5) contacts of multidrug-resistant cases did not receive treatment for LTBI	Total number of recruited patients: NR; total number of excluded patients: NR	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Mahomed 2011,[108] South Africa (high)	Aim: to determine the prevalence of and predictive factors associated with LTBI in adolescents Setting: high school Design: retrospective cohort/cross-sectional study Funding source: Aeras Global TB Vaccine Foundation and the Gates Grand Challenge 6 and Gates Grand Challenge 12 grants for QuantiFERON testing	Non-exposed: no current or previous TB household contact; exposed: current or previous TB household contact	Inclusion criteria: all adolescents aged 12–18 years Exclusion criteria: diagnosed with active TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): IFN-γ ≥ 0.35 IU/ml TST: induration of ≥ 5mm	Age range: 12–18 years Female, *n* (%): 2842 (54.2) Race/ethnicity, *n* (%): Indian/ white 410 (7.8); mixed race 3839 (73.2); black 995 (19.0) Geographical origin, *n* (%): NR BCG vaccination, *n* (%): no 46 (0.9); yes 4917 (93.8); unknown 281 (5.4) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): no Clinical examination (yes/no): no Morbidity, *n* (%): NR Comorbidity, *n* (%): chronic allergy-related condition, e.g. asthma, hay fever, eczema yes 53 (1.0); no 5191 (99.0) Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 6363 enrolled, 5244 enrolled for analysis Total number of excluded patients: 13 because of indeterminate QFT results, 639 because TST was not performed with past TB, 22 because TST was not performed with current TB, 22 because diagnosed with active TB	

continued

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Pavic 2011,[109] Croatia (low)	Aim: to evaluate an IGRA for the diagnosis of LTBI in BCG-vaccinated children up to 5 years of age with documented exposure to active TB Setting: children's hospital and general hospital Design: retrospective cohort/cross-sectional study Funding source: none	Non-exposed: distant contact was defined as occasional or unclear exposure time or < 40 hours during the presumed period of infectiousness; exposed: close contact was defined as household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms	Inclusion criteria: paediatric patients aged ≤ 5 years with documented exposure (close or distant contact) to a case of active TB Exclusion criteria: children aged > 5 years, immunocompromised children, inadequate blood sampling and diagnosis of active TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): IFN-γ ≥ 0.35 IU/ml as recommended by the manufacturer; TST: induration of ≥ 10 mm	Mean age: 29 ± 16 months Female, *n* (%): 57 (40.1) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 142 (100) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): NR Comorbidity, *n* (%): pneumonia 1 (0.7) Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 142; total number of excluded patients: 1	Blood samples for QFT-GIT were drawn under standardised conditions in hospital on the same day as the TST was carried out. The test was considered indeterminate if the value of the positive control was < 0.5 IU/ml and/or the nil negative control was > 8 IU/l

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Perez-Porcuna 2014,[151] Brazil (intermediate)	Aim: to evaluate the response of the QFT-GIT and TST tests in young children with recent exposure to an index case Setting: community based Design: cross-sectional/ retrospective study Funding source: Brazilian National Council of Scientific and Technological and Development, Foundation for Research Support of the State of Amazonas and University of Barcelona. Cellestis Ltd donated QFT kits	Time of exposure to the index case: non-exposed: NR; exposed: number of months (continuous scale covariate) MTB contact (MTC) score 0–15: non-exposed: NR; exposed: MTC score (continuous scale covariate) was composed of infectivity of the index case (0–4), the duration of exposure in hours per day (0–4), the relationship to the index case (0–4) and the type of exposure (0–3)	Inclusion criteria: children aged 0–6 years with contact with an adult symptomatic TB index case within the last 12 months Exclusion criteria: children receiving treatment or prophylaxis for TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): IFN-γ ≥ 0.35 IU/ml; TST: induration of ≥ 10 mm	Mean (range) age: 46 (28.0–64.5) months Female, *n* (%): 74 (54.8) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 118 (90.8) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 140; total number of excluded patients: 3	Experienced laboratory technicians who were unaware of the data of the study subjects

continued

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Rutherford 2012,[110,111] Indonesia (high)	Aim: to quantify MTB infection in children living with a smear-positive adult TB case and identify risk factors for TST and QFT-GIT positivity Setting: outpatient-based clinic Design: retrospective cohort/cross-sectional study Funding source: NR	Characteristics of TB case smear positivity: non-exposed: scanty and 1+; exposed 1: 2+; exposed 2: 3+ Relationship to child: non-exposed: other; exposed 1: uncle; exposed 2: parent Sleeping proximity to child: non-exposed: different room; exposed 1: same room; exposed 2: same bed Time spent with child (number of hours per day): non-exposed: < 2; exposed 1: 2–8; exposed 2: > 8	Inclusion criteria: child contacts living for > 3 months with newly diagnosed TB cases (index cases) who were smear and CXR positive Exclusion criteria: child contacts who had received a diagnosis of TB disease within the past year or who were aged < 6 months	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): NR; TST: induration of ≥ 10 mm	Median (IQR) age: 58 (31–81) months Female, *n* (%): 152 (50.7) Race/ethnicity, *n* (%): Sudanese 284 (93.7); other 19 (6.3) Geographical origin, *n* (%): NR BCG vaccination, *n* (%): with scar 221 (73.2); unknown BCG status 30 (9.9) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes [children who were symptomatic and test negative (on either IGRA or TST) were referred to the children's clinic for further assessment according to clinic policy] Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 320; total number of excluded patients: 16	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Talbot 2012,[112] USA (low)	Aim: to test the specificity of the TST and T-SPOT.*TB* assay among students at low risk for TB exposure Setting: college health setting Design: retrospective cohort/cross-sectional study Funding source: Oxford Immunotec, Inc.	Non-exposed: low TB exposure risk group; exposed: non-low TB exposure risk [any history of exposure to TB through country of birth, residence or visits of > 3 weeks to high TB burden areas (> 40 cases per 100,000 population) or occupational exposure]	Inclusion criteria: students with a history of exposure to TB Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): 5–7 spots borderline and results with a low mitogen response or a high nil control response are indeterminate TST: induration of > 15 mm for students with no risk factors for TB exposure	Median (range) age: 20 (17–47) years Female, *n* (%): 97 (53.9) Race/ethnicity, *n* (%): US born 165 (91.7); white 135 (75) Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 7 (3.9) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 184; total number of excluded patients: 4	

continued

TABLE 3 Baseline characteristics of studies in children and adolescents: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Tieu 2014,[154] Thailand (high)	Aim: to compare the performances of the IGRAs (T-SPOT.*TB*, QFT-GIT) and TST at two different cut-off thresholds (10 mm and 15 mm) in Thai children who had a recent exposure to an adult index case with TB Setting: community based Design: cross-sectional/ retrospective cohort study Funding source: investigator-initiated research grant from Tibotec REACH Initiative	TB contact score (range 6–19): non-exposed: TB contact score 8–10; exposed 1: TB contact score 11–12; exposed 2: TB contact score 13–14; exposed 3: TB contact score 15–16 TB contact score (range 6–19): non-exposed: TB contact score 8–12; exposed: TB contact score ≥ 13 Relationship to TB index case: non-exposed: relative other contact in household with TB; exposed 1: second caregiver in household with TB; exposed 2: primary caregiver in household with TB Duration of average contact per day with TB index case: non-exposed: 0–7 hours; exposed: ≥ 8 hours Duration of contact with TB index case in last 12 months:	Inclusion criteria: children between the ages of 2 months and 16 years with recent exposure (defined as having lived with and/ or having had close contact with) to adults with active pulmonary TB (confirmed by positive AFB stain, polymerase chain reaction test for TB or TB culture), with or without extrapulmonary TB manifestations Exclusion criteria: children's caregivers refused study participation, were receiving antiTB medications for TB disease (including isoniazid for latent TB) or had recently been diagnosed with active TB	Type of tests: IGRA (T-SPOT.*TB*, QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT, T-SPOT.*TB*): NR TST: induration of 10 mm or ≥ 15 mm	Mean (SD) age: 7.6 (4.3) years Female, *n* (%): 67 (49.3) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 132 (96.4) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): none (for TB exposed)	Total number of recruited patients: 137 (TB exposed); total number of excluded patients: NR	Study investigators, site co-ordinators, and clinicians were blinded to the results of the IGRAs until completion of enrolment and the 9-month follow-up

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
		non-exposed: 0–7 months; exposed: > 7 months Index TB case history: non-exposed: sputum acid-fast smear negative; exposed: sputum acid-fast smear positive					
Tsolia 2010,[113] Greece (low)	Aim: to evaluate and compare the performance of the QFT-GIT assay and the TST among children with active TB or possible LTBI in a low-endemic country Setting: TB clinic Design: retrospective cohort/cross-sectional study Funding source: Bienmoyo Foundation	Contact with an adult TB: non-exposed: non-household occasional contact; exposed 1: non-household regular contact; exposed 2: household contact	Inclusion criteria: adolescents aged ≤ 15 years Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): NR TST: induration of ≥ 10 mm for BCG-immunised children, ≥ 5 mm for non-BCG-immunised children	Mean (range or SD) age: NR Female, *n* (%): NR Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 295; total number of excluded patients: 9 because of refusal, lost specimen and sample processing delay	Indeterminate results on the QFT-GIT were excluded from the analysis

AFB, acid-fast bacilli; CXR, chest radiography; ID, identification; IQR, interquartile range; NR, not reported; SD, standard deviation.

TABLE 4 Summary assessment of ROB for included incidence studies in children and adolescents

Study ID (burden)	Study design	Study participation (risk of selection bias)	Study attrition (risk of selection bias)	Prognostic factor measurement (risk of exposure measurement bias)	Outcome/construct measurement (ROB in misclassification of individuals in relation to construct validity groups)	Study confounding (ROB from confounding)	Statistical analysis and reporting (ROB from analysis and selective reporting)	Total ROB (high, moderate, low)
Diel 2011[102] (low)	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Mahomed 2011[103] (high)	Low	Moderate	Moderate	Moderate	Moderate	High	Low	Moderate
Metin Timur 2014[150] (intermediate)	Low	High	High	Moderate	Moderate	High	High	High
Noorbakhsh 2011[104] (intermediate)	Moderate	High	High	High	Moderate	High	High	High
Song 2014[152] (high)	Low	Low	Moderate	Low	High	Moderate	Low	Moderate

ID, identification.
Source: adapted from Hayden *et al.*[90]

TABLE 5 Summary assessment of ROB for the included exposure studies in children and adolescents

Study ID (burden)	Recruitment of subjects [consecutive (yes), arbitrary or unreported (no)]	Blinding of test results from exposure [blinded (yes), not blinded or unreported (no)]	Description of index test and threshold [adequate (yes), inadequate or unreported (no)]	Definition and description of exposure [adequate (yes), inadequate or unreported (no)]	Sample attrition [adequate (yes),[a] inadequate or unreported (no)]	Overall quality score of satisfactory features[b]
Adetifa 2010[105] (high)	No	No	Yes	Yes	No	Low
Cruz 2011[106] (low)	No	No	No	No	Yes	Low
Kasambira 2011[107] (high)	No	No	No	Yes	Yes	Low
Laniado-Laborın 2014[148] (intermediate)	Yes	Yes	Yes	No	No	Moderate
Mahomed 2011[108] (high)	No	No	No	No	No	Low
Pavic 2011[109] (low)	Yes	No	Yes	Yes	Yes	High
Perez-Porcuna 2014[151] (intermediate)	Yes	Yes	Yes	Yes	No	High
Rutherford 2012[110,111] (high)	No	No	No	Yes	Yes	Low
Talbot 2012[112] (low)	No	No	Yes	No	No	Low
Tieu 2014[154] (high)	Yes	Yes	No	Yes	Yes	High
Tsolia 2010[113] (low)	Yes	No	No	No	Yes	Low

ID, identification.
a ≥ 90% of participants were included in the follow-up analysis (yes response) and < 90% were classified as 'no response'.
b Studies with one or two 'yes' ratings = low quality; studies with three 'yes' ratings = moderate quality; studies with four or five 'yes' ratings = high quality.
Source: adapted from Dinnes *et al.*[44] The item 'study design' was removed from the original checklist as all studies were considered to be retrospective; furthermore, the item 'sample attrition' was added.

Comparative performance of tests (diagnostic accuracy indices for identifying latent tuberculosis infection): children

Incidence of active tuberculosis

Ratios of cumulative incidence ratios

This analysis included seven studies: two studies[161,162] reviewed in CG117[10] (see *Appendix 5*) and five more recent studies, three published in 2011[102–104] and two published in 2014[150,152] (see *Appendix 9*). For three[150,161,162] of the studies, R-CIRs could not be calculated because none of the children developed active TB. The R-CIRs in the remaining four studies[102–104,152] were pooled (*Table 6*), with one analysis comparing QFT-GIT with TST 5 mm and the other comparing QFT-GIT with TST 10 mm (they were pooled separately because TST performance differs according to its threshold). The pooled estimates indicated that there was no significant difference in performance between QFT-GIT and TST 5 mm (pooled R-CIR 1.12, 95% CI 0.72 to 1.75) (*Figure 3*),[102,103] whereas QFT-GIT was better than TST 10 mm in identifying/predicting LTBI (pooled R-CIR 4.33, 95% CI 1.32 to 14.23) (*Figure 4*).[102,104,152]

Sensitivity and specificity

There was wide variability in the sensitivity and specificity of IGRAs (QFT-GIT/G) and the TST (5 mm or 10 mm) across newly identified studies.[102–104,150,152] TST sensitivity was higher at 5 mm than at 10 mm/15 mm and, vice versa, specificity was better at 10 mm/15 mm than at 5 mm. IGRAs (QFT-GIT/G) demonstrated a similar sensitivity (range 48–100%) to that of TST 5 mm (sensitivity range 57–100%) and slightly better specificity (range 49–90%) than that of TST 5 mm (range 45–65%). Although the sensitivities of the IGRAs and TST 5 mm were higher than those for TST 10 mm/15 mm (range 30–56%), the corresponding specificities of these tests were lower than those for TST 10 mm/15 mm (range 63–93%). Forest plots of sensitivities and specificities were generated and because of high unexplained heterogeneity (not explained by IGRA type and TST threshold, different methods for diagnosing active TB), no meta-analysis could be performed (*Figures 5–8*).

TABLE 6 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (incidence studies) – children and adolescents

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Diel 2011,[102] Germany (low)	Number of test results: QFT-GIT 106; T-SPOT.*TB* NA; TST 106 Test (+/–): QFT-GIT 23/83; T-SPOT.*TB* NA; TST ≥ 5 mm 40/66; TST ≥ 10 mm 20/86 Number of indeterminate results: QFT-GIT NR; T-SPOT.*TB* NA; TST NR Number lost to follow-up: NR	QFT-GIT: SN 100 (60.97 to 100); SP 84.69 (76.27 to 90.5); PPV 28.57 (13.81 to 49.96); NPV 100 (95.58 to 100)	TST ≥ 5 mm: SN 100 (60.97 to 100); SP 65.31 (55.47 to 73.99); PPV 15.00 (7.06 to 29.07); NPV 100 (94.34 to 100) TST ≥ 10 mm: SN 66.67 (30.00 to 90.32); SP 63.27 (53.39 to 72.14); PPV 10.00 (3.96 to 23.05); NPV 96.88 (89.3 to 99.14)	QFT-GIT: CI (+) 28.57 (13.81 to 49.96); CI (–) 1.20 (0.03 to 6.53); CIR 23.7 (2.57 to 110.3)	TST ≥ 5 mm: CI (+) 15.00 (7.06 to 29.07); CI (–) 1.55 (0.04 to 8.4); CIR 9.6 (1.08 to 448.2) TST ≥ 10 mm: CI (+) 10.00 (3.95 to 23.05); CI (–): 3.12 (0.22 to 11.33); CIR 3.20 (0.61 to 16.67)	R-CIR (QFT-GIT vs. TST ≥ 5 mm): 2.47 (0.40 to 15.12) R-CIR (QFT-GIT vs. TST ≥ 10 mm): 7.41 (2.06 to 26.57)
Mahomed 2011,[103] South Africa (high)	Number of test results: QFT-GIT 5244; T-SPOT.*TB* NA; TST 5244 Test (+/–): QFT-GIT 2669/2575; T-SPOT.*TB* NA; TST ≥ 5 mm 2894/2350 Number of indeterminate results: QFT-GIT NR; T-SPOT.*TB* NA; TST NR Number lost to follow-up: 18%	QFT-GIT: SN 75.00 (61.79 to 84.77); SP 49.35 (47.99 to 50.71); PPV 1.46 (1.07 to 1.99); NPV 99.50 (99.14 to 99.7)	TST ≥ 5 mm: SN 76.92 (63.87 to 86.28); SP 45.03 (43.68 to 46.39); PPV 1.38 (1.02 to 1.88); NPV 99.49 (99.11 to 99.71)	QFT-GIT: CI (+) 1.46 (1.07 to 1.99); CI (–) 0.50 (0.28 to 0.87); CIR 2.89 (1.55 to 5.40); IDR (+) 0.64 (0.45 to 0.87) per 100 person-years; IDR (–) 0.22 (0.12 to 0.38) per 100 person-years; IDRR 2.92 (1.58 to 5.67)	TST ≥ 5 mm: CI (+) 1.38 (1.02 to 1.87); CI (–) 0.51 (0.28 to 0.90); CIR 2.71 (1.42 to 5.14); IDR (+) 0.60 (0.43 to 0.82) per 100 person-years; IDR (–) 0.22 (0.11 to 0.39) per 100 person-years; IDRR 2.73 (1.45 to 5.42)	R-CIR (QFT-GIT vs. TST ≥ 5 mm): 1.07 (0.68 to 1.68); R-IDRR (QFT-GIT vs. TST ≥ 5 mm): 1.07 (0.67 to 1.71)

continued

TABLE 6 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (incidence studies) – children and adolescents (*continued*)

		Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		
Study ID, country (burden)	Test results	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
Metin Timur 2014,[150] Turkey (intermediate)	Number of test results: QFT-GIT 81; T-SPOT.*TB* NA; TST 81 Test (+/–): QFT-GIT 12/69; T-SPOT.*TB* NA; TST ≥ 15 mm 81/0 Number of indeterminate results: QFT-GIT 0; T-SPOT.*TB* NA; TST 0 Number lost to follow-up: NR	QFT-GIT: SN NA; SP 100 (NR); PPV NA; NPV 100 (NR)	TST ≥ 15 mm: SN NA; SP 0.0 (NR); PPV 0.0 (NR); NPV NA	QFT-GIT: CI (+) NA; CI (–) 0.0 (NR); CIR NA	TST ≥ 15 mm: CI (+) 0.0 (NR); CI (–) NA; CIR: NA	R-CIR (QFT-GIT vs. TST ≥ 15 mm): NA
Noorbakhsh 2011,[104] Iran (intermediate)	Number of test results: QFT-G 59; T-SPOT.*TB* NA; TST 58 Test (+/–): QFT-G 18/41; T-SPOT.*TB* NA; TST ≥ 10 mm 8/50 Number of indeterminate results: QFT-G NR; T-SPOT.*TB* NA; TST 1 Number lost to follow-up: NR	QFT-G: SN 100 (72.25 to 100); SP 83.67 (70.96 to 91.49); PPV 55.56 (33.72 to 75.44); NPV 100 (91.43 to 100)	TST ≥ 10 mm: SN 30.00 (10.78 to 60.32); SP 89.58 (77.83 to 95.47); PPV 37.50 (13.68 to 69.43); NPV 86.00 (73.81 to 93.05)	QFT-G: CI (+) 55.56 (33.72 to 75.44); CI (–) 2.41 (0.06 to 12.9); CIR 22.78 (2.75 to 101.1)	TST ≥ 10 mm: CI (+) 37.5 (13.49 to 69.62); CI (–) 14.00 (6.63 to 26.50); CIR 2.68 (0.86 to 8.27)	R-CIR (QFT-G vs. TST ≥ 10 mm): 8.50 (2.87 to 25.17)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Song 2014,[152] South Korea (high)	Number of test results: QFT-GIT 2966; T-SPOT.*TB* NA; TST 2982 Test (+/–): QFT-GIT 317/2649; T-SPOT.*TB* NA; TST ≥ 10 mm 663/2319; TST ≥ 15 mm 231/2751 Number of indeterminate results: QFT-GIT 16; T-SPOT.*TB* NA; TST 0 Number lost to follow-up: NR	QFT-GIT: SN 47.83 (29.24 to 67.04); SP 89.6 (88.45 to 90.65); PPV 3.47 (1.94 to 6.10); NPV 99.55 (99.21 to 99.74)	TST ≥ 10 mm: SN 56.52 (36.81 to 74.37); SP 78.03 (76.51 to 79.49); PPV 1.96 (1.14 to 3.32); NPV 99.57 (99.21 to 99.77) TST ≥ 15 mm: SN 56.52 (36.81 to 74.37); SP 92.63 (91.64 to 93.52); PPV 5.62 (3.31 to 9.38); NPV 99.64 (99.33 to 99.80)	QFT-GIT: CI (+) 3.47 (1.87 to 6.17); CI (–) 0.45 (0.24 to 0.79); CIR 7.66 (3.41 to 17.21); OR 7.90 (3.46 to 18.06)	TST ≥ 10 mm: CI (+) 1.96 (1.11 to 3.36); CI (–) 0.43 (0.22 to 0.80); CIR 4.55 (2.00 to 10.32) ; OR 4.62 (2.02 to 10.58) TST ≥ 15 mm: CI (+) 5.62 (3.23 to 9.47); CI (–) 0.36 (0.18 to 0.67); CIR 15.48 (6.86 to 34.92); OR 16.35 (7.08 to 37.71)	R-CIR (QFT-GIT vs. TST ≥ 10 mm): 1.68 (0.94 to 3.03); R-OR (QFT-GIT vs. TST ≥ 10 mm): 1.71 (0.94 to 3.11) R-CIR (QFT-GIT vs. TST ≥ 15 mm): 0.49 (0.28 to 0.89); R-OR (QFT-GIT vs. TST ≥ 15 mm): 0.48 (0.27 to 0.88)

CI (–), cumulative incidence in those who tested negative; CI (+), cumulative incidence in those who tested positive; ID, identification; IDR, incidence density rate; NA, not applicable; NR, not reported; R-OR, ratio of odds ratios; SN, sensitivity; SP, specificity.

Study or subgroup	Log-risk ratio	SE	IGRA total *n*	TST 5 mm total *n*	Weight	Risk ratio IV, random, 95% CI
Diel 2011[102]	0.903	0.924	104	104	6.0%	2.47 (0.40 to 15.09)
Mahomed 2011[103]	0.064	0.233	5244	5244	94.0%	1.07 (0.68 to 1.68)
Total (95% CI)			**5348**	**5348**	**100.0%**	**1.12 (0.72 to 1.75)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.78$, df = 1 ($p = 0.38$); $I^2 = 0\%$
Test for overall effect: $z = 0.51$ ($p = 0.61$)

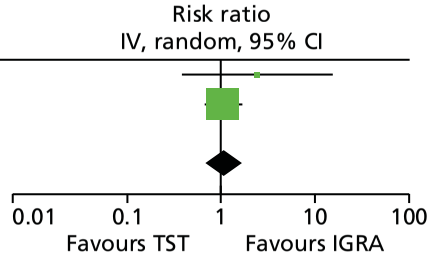


FIGURE 3 Pooled R-CIR (QFT-GIT vs. TST 5 mm) in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-risk ratio	SE	IGRA total *n*	TST 10 mm total *n*	Weight	Risk ratio IV, random, 95% CI
Diel 2011[102]	2.002	0.651	104	104	28.9%	7.40 (2.07 to 26.52)
Noorbakhsh 2011[104]	2.14	0.553	59	59	31.9%	8.50 (2.88 to 25.12)
Song 2014[152]	0.52	0.3	2966	2982	39.2%	1.68 (0.93 to 3.03)
Total (95% CI)			**3129**	**3145**	**100.0%**	**4.33 (1.32 to 14.23)**

Heterogeneity: $\tau^2 = 0.85$; $\chi^2 = 9.14$, df = 2 ($p = 0.01$); $I^2 = 78\%$
Test for overall effect: $z = 2.41$ ($p = 0.02$)

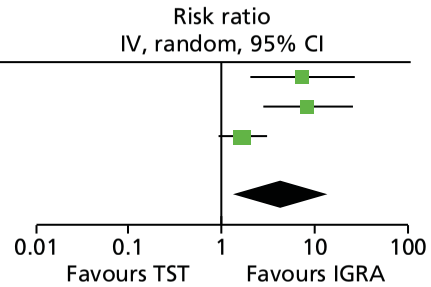


FIGURE 4 Pooled R-CIR (QFT-GIT vs. TST 10 mm) in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

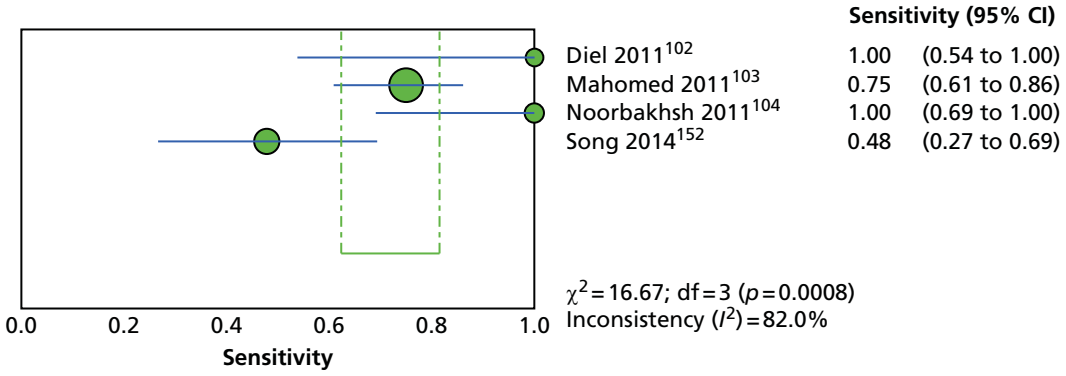


FIGURE 5 Forest plot of sensitivity based on incidence of active TB (QFT-GIT/G) in children and adolescents. df, degrees of freedom.

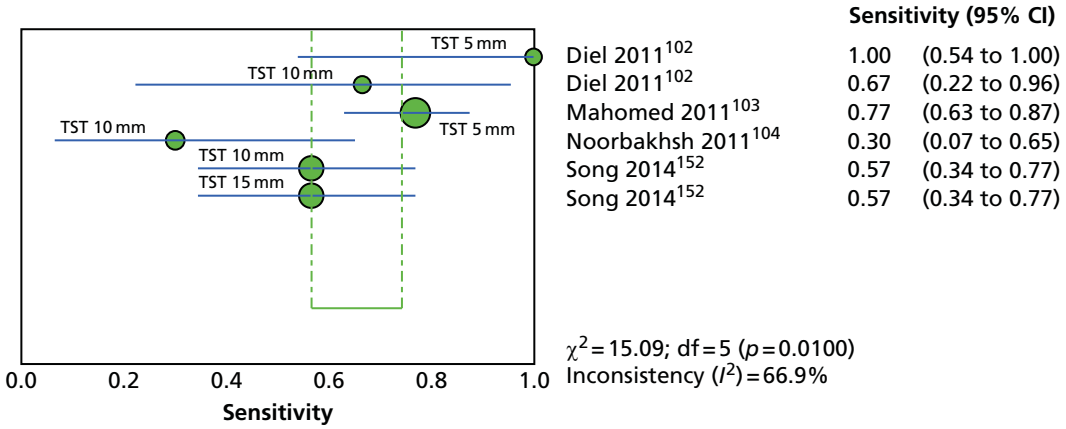


FIGURE 6 Forest plot of sensitivity based on incidence of active TB (TST) in children and adolescents. df, degrees of freedom.

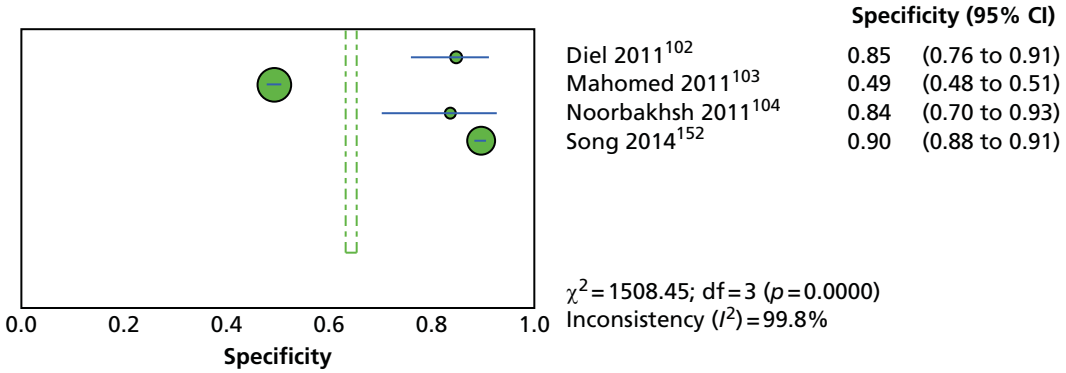


FIGURE 7 Forest plot of specificity based on incidence of active TB (QFT-GIT/G) in children and adolescents. df, degrees of freedom.

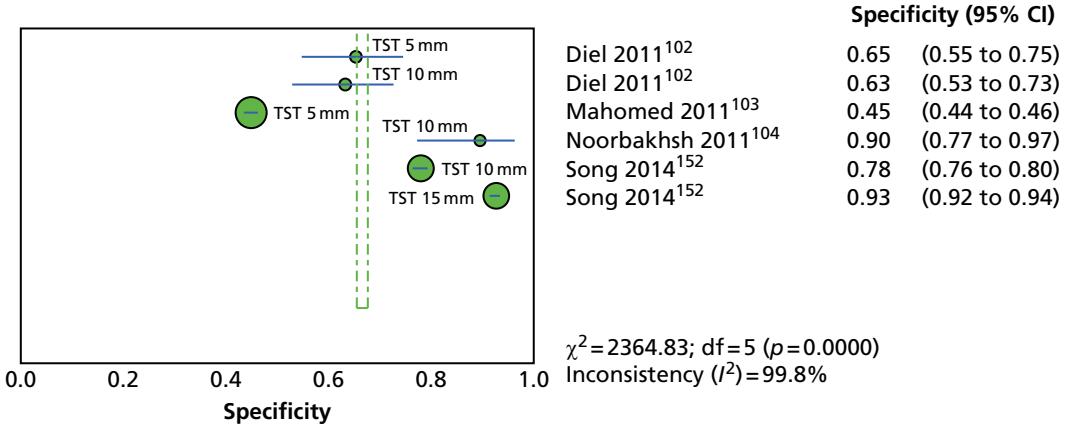


FIGURE 8 Forest plot of specificity based on incidence of active TB (TST) in children and adolescents. df, degrees of freedom.

Exposure levels

Ratios of diagnostic odds ratios

This analysis included 17 studies: six studies[156,157,160,162–164] from CG117[10] (see *Appendix 5*) and 11 studies[105–113,148,151,154] from the updated review (see *Appendix 9*). The association between the screening test results and the risk of LTBI/exposure level measured using the R-DORs (IGRA vs. TST) in individual studies ranged from 0.27[105] to 11.01[113] (*Table 7*).

The updated meta-analysis included 14 studies: six studies[156,157,160,162–164] from CG117[10] (see *Appendix 5*) and eight more recent studies[105–111,113,154] published from 2009 onwards (see *Appendix 9*). One study[112] did not provide sufficient information to calculate the R-DOR and therefore this study could not be included in the meta-analysis. In a random-effects meta-analysis of the 14 studies,[105–111,113,154,156,157,160,162–164] of which two studies[106,160] used T-SPOT.*TB* and the remaining 12 studies used QFT-GIT [or QuantiFERON-Gold (QFT-G)], the pooled R-DOR showed a significantly stronger association for the IGRAs than for the TST in relation to a risk of LTBI/exposure level (pooled R-DOR 1.98, 95% CI 1.19 to 3.28; $I^2 = 89\%$) (*Figure 9*).

Heterogeneity was high ($I^2 = 89\%$) and the sources of heterogeneity were explored through subgroup analyses with regard to burden of TB incidence, IGRA type, TST threshold and study setting. The simultaneous meta-analytical stratification by IGRA type (QFT-GIT/G and T-SPOT.*TB*) and TST threshold (5 mm, 10–15 mm) (*Figures 10–12*) as well as study setting (community-based contact and hospital-based studies) (*Figures 13* and *14*) did not help to explain the presence of heterogeneity (i.e. heterogeneity persisted in these analyses). The study by Adetifa *et al.*[105] displayed a very aberrant result (see *Figure 9*; R-DOR 0.27, 95% CI 0.12 to 0.59) indicating a significant superiority of TST (10 mm) over IGRA (QFT-GIT), which could not be readily explained. The report did not provide the raw data needed for the calculation and verification of the correctness of the reported DORs for the IGRA and TST. The authors explained this finding by the delayed presentation of TB cases (mean time 9 weeks) with early reversion of the IGRA and about 30% of TB cases in the Gambia being infected with *Mycobacterium africanum* (Castets *et al.* 1969), which has a reduced response to ESAT-6.

However, the subgroup analysis by country of burden explained some (but not all) of the observed heterogeneity and revealed an interesting trend, showing no difference between IGRAs and the TST in identifying LTBI across studies conducted in countries of high TB burden (pooled R-DOR 1.13, 95% CI 0.78 to 1.65; $I^2 = 71\%$) (*Figure 15*).

In contrast, IGRAs were significantly superior to the TST in identifying LTBI in the settings of low TB burden (pooled R-DOR 4.74, 95% CI 2.15 to 10.44; $I^2 = 67\%$) (*Figure 16*).

TABLE 7 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (exposure studies) – children and adolescents

		Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
Study ID, country (burden)	Test results	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Adetifa 2010,[105] Gambia (high)	Number of test results: QFT-GIT 215; T-SPOT.*TB* 215; TST 215 Test (+/–): QFT-GIT 72/143; T-SPOT.*TB* 71/144; TST ≥ 10 mm 57/158 Number of indeterminate results: QFT-GIT/G 2; T-SPOT.*TB* 0; TST 0	QFT-GIT: Same house/different room vs. different house: SN NR; SP NR; PPV NR; NPV NR Same house/same room vs. different house: SN NR; SP NR; PPV NR; NPV NR T-SPOT.*TB*: Same house/different room vs. different house: SN NR; SP NR; PPV NR; NPV NR Same house/same room vs. different house: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm: Same house/different room vs. different house: SN NR; SP NR; PPV NR; NPV NR Same house/same room vs. different house: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Same house/different room vs. different house: DOR 1.20 (0.60 to 2.60); DORa 1.50 (0.70 to 3.10) Same house/same room vs. different house: DOR 3.20 (1.20 to 9.10); DORa 4.00 (1.40 to 11.40) T-SPOT.*TB*: Same house/different room vs. different house: DOR 2.00 (0.80 to 5.10); DORa 2.60 (0.90 to 7.10) Same house/same room vs. different house: DOR 5.30 (1.50 to 18.50); DORa 6.60 (1.70 to 25.20)	TST ≥ 10 mm: Same house/different room vs. different house: DOR 2.40 (1.00 to 5.80) DORa: 2.90 (1.30 to 6.70) Same house/same room vs. different house: DOR 10.10 (3.20 to 32.10); DORa 15.00 (4.70 to 47.20) T-SPOT.*TB*: Same house/different room vs. different house: DOR 2.40 (1.00 to 5.80); DORa 2.90 (1.30 to 6.70) Same house/same room vs. different house: DOR 10.10 (3.20 to 32.10); DORa 15.00 (4.70 to 42.20)	QFT-GIT vs. TST ≥ 10 mm: Same house/different room: R-DOR 0.58 (0.28 to 0.90); R-DORa 0.52 (0.29 to 0.91) Same house/same room: R-DOR 0.32 (0.14 to 0.69); R-DORa 0.27 (0.12 to 0.59) T-SPOT vs. TST ≥ 10 mm: Same house/different room: R-DOR 0.83 (0.43 to 1.60); R-DORa 0.90 (0.46 to 1.76) Same house/same room: R-DOR 0.52 (0.22 to 1.25); R-DORa 0.44 (0.18 to 1.09)

continued

TABLE 7 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (exposure studies) – children and adolescents (*continued*)

		Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
Study ID, country (burden)	**Test results**	**IGRA: QFT-GIT/G and/or T-SPOT.*TB***	**TST (by threshold)**	**IGRA: QFT-GIT/G and/or T-SPOT.*TB***	**TST (by threshold)**	**R-DOR (95% CI), IGRA vs. TST (by threshold)**
Cruz 2011,[106] USA (low)	Number of test results: T-SPOT.*TB* 163; TST 163 Test (+/–): T-SPOT.*TB* 94/69; TST ≥ 15 mm 94/69 Number of indeterminate results: T-SPOT.*TB* 22; TST 22	T-SPOT.*TB*: Contact with an identifiable source case vs. no such contact: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 15 mm: Contact with an identifiable source case vs. no such contact: SN NR; SP NR; PPV NR; NPV NR	T-SPOT.*TB*: Contact with an identifiable source case vs. no such contact: DOR NR; DORa 4.41 (1.78 to 10.94)	TST ≥ 15 mm Contact with an identifiable source case vs. no such contact: DOR NR; DORa 0.48 (0.26 to 0.91)	T-SPOT vs. TST ≥ 15 mm Contact with an identifiable source case: R-DOR NR; R-DORa 9.19 (5.23 to 16.3)
Kasambira 2011,[107] South Africa (high)	Number of test results: QFT-GIT 251; TST 254 Test (+/–): QFT-GIT 79/172; TST ≥ 5 mm 71/183 Number of indeterminate results: QFT-GIT 19; TST 16	QFT-GIT: Exposure to index case during the majority of the day (> 7 hours) vs. minority of the day (< 6 hours): SN 29.87 (23.2 to 37.52); SP 71.68 (62.77 to 79.17); PPV 58.97 (47.89 to 69.22); NPV 42.86 (36.01 to 49.99)	TST ≥ 5 mm: Exposure to index case during the majority of the day (> 7 hours) vs. minority of the day (< 6 hours): SN 29.79 (22.86 to 37.79); SP 73.64 (64.71 to 80.97); PPV 59.15 (47.54 to 69.83); NPV 45.00 (37.91 to 52.30)	QFT-GIT: Exposure to index case during the majority of the day (> 7 hours) vs. minority of the day (< 6 hours): DOR 1.10 (0.63 to 1.80); DORa 1.30 (0.69 to 2.30) Adult index case smear grade (vs. negative): scanty: DOR 0.30 (0.05 to 1.60), DORa NR; 1+: DOR 1.50 (0.70 to 3.60), DORa 5.50 (0.89 to 34.70); 2+: DOR 1.50 (0.50 to 4.90), DORa 8.70 (1.20 to 62.00); 3+: DOR 3.20 (1.40 to 7.40), DORa 11.40 (1.80 to 72.00)	TST ≥ 5 mm: Exposure to index case during the majority of the day (> 7 hours) vs. minority of the day (< 6 hours): DOR 1.20 (0.67 to 2.10); DORa 1.10 (0.58 to 2.10) Adult index case smear grade (vs. negative): scanty: DOR NR, DORa NR; 1+: DOR 2.81 (1.20 to 6.70), DORa 7.90 (1.50 to 41.00); 2+: DOR 2.90 (0.80 to 10.60), DORa 15.70 (2.60 to 92.0); 3+: DOR 4.10 (1.50 to 11.10), DORa 11.70 (2.20 to 62.00)	QFT-GIT vs. TST ≥ 5 mm: Exposure to index case during the majority of the day (> 7 hours): R-DOR 0.92 (0.62 to 1.36); R-DORa 1.18 (0.75 to 1.85) Adult index case smear grade (3+): R-DOR 0.78 (0.40 to 1.52); R-DORa 0.97 (0.27 to 3.47)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Laniado-Laborin 2014,[148] Mexico (intermediate)	Number of test results: QFT-GIT 172; TST 172 Test (+/–): QFT-GIT 71/101; TST ≥ 5 mm 136/36 Number of indeterminate results: QFT-GIT 1; TST 1	QFT-GIT: Exposure to source, hours per day exposure, number of cohabitants, number of rooms: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 5 mm: Exposure to source, hours per day exposure, number of cohabitants, number of rooms: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT : Exposure to source: DORa 0.91 (0.57 to 1.45) Hours per day exposure: DORa 1.03 (0.96 to 1.10) Number of cohabitants: DORa 0.91 (0.79 to 1.05) Number of rooms: DORa 1.12 (0.77 to 1.61)	TST ≥ 5 mm: Exposure to source: NR (p = NR) Hours per day exposure: NR (p = NR) Number of cohabitants: NR (p = NR) Number of rooms: NR (p = NR)	QFT-GIT vs. TST ≥ 5 mm: R-DORa NR
Mahomed 2011,[108] South Africa (high)	Number of test results: QFT-GIT 5244; TST 5244 Test (+/–): QFT-GIT 2669/2562; TST ≥ 5 mm 2894/2350 Number of indeterminate results: QFT-GIT 13; TST 0	QFT-GIT: Current or previous TB household contact vs. no such contact: SN 66.67 (64.09 to 69.15); SP 54.32 (52.75 to 55.88); PPV 33.27 (31.51 to 35.08); NPV 82.67 (81.16 to 84.09)	TST ≥ 5 mm: Current or previous TB household contact vs. no such contact: SN 71.32 (68.83 to 73.69); SP 50.31 (48.74 to 51.87); PPV 32.83 (31.14 to 34.56); NPV 83.74 (82.2 to 85.18)	QFT-GIT: Current or previous TB household contact vs. no such contact: DOR 2.40 (2.11 to 2.74); DORa 1.90 (1.70 to 2.20)	TST ≥ 5 mm: Current or previous TB household contact vs. no such contact: DOR 2.52 (2.20 to 2.88); DORa 2.00 (1.70 to 2.30)	QFT-GIT vs. TST ≥ 5 mm: Current or previous TB household contact: R-DOR 0.94 (0.86 to 1.04); R-DORa 0.95 (0.86 to 1.05)

continued

TABLE 7 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (exposure studies) – children and adolescents (*continued*)

		Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
Study ID, country (burden)	Test results	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Pavic 2011,[109] Croatia (low)	Number of test results: QFT-GIT 141; TST 142 Test (+/–): QFT-GIT 18/123; TST ≥ 10 mm 24/118 Number of indeterminate results: QFT-GIT 1; TST 0	QFT-GIT: Close contact (household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms) vs. distant contact (occasional or unclear exposure time or < 40 hours of exposure during the presumed period of infectiousness): SN 19.54 (12.57 to 29.08); SP 98.15 (90.23 to 99.67); PPV 94.44 (74.24 to 99.01); NPV 43.09 (34.68 to 51.92)	TST ≥ 10 mm: Close contact (household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms) vs. distant contact (occasional or unclear exposure time or < 40 hours of exposure during the presumed period of infectiousness): SN 26.44 (18.31 to 36.56); SP 98.18 (90.39 to 99.68); PPV 95.83 (79.76 to 99.26); NPV 45.76 (37.05 to 54.74)	QFT-GIT: Close contact (household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms) vs. distant contact (occasional or unclear exposure time or < 40 hours of exposure during the presumed period of infectiousness): DOR 12.87 (1.66 to 99.80); DORa NR	TST ≥ 10 mm: Close contact (household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms) vs. distant contact (occasional or unclear exposure time or < 40 hours of exposure during the presumed period of infectiousness): DOR 19.41 (2.53 to 148.40); DORa NR	QFT-GIT vs. TST ≥ 10 mm: Close contact (household contact with aggregate exposure to a patient with active TB of ≥ 40 hours in closed rooms): R-DOR 0.66 (0.15 to 2.89); R-DORa NR
Perez-Porcuna 2014,[151] Brazil (intermediate)	Number of test results: QFT-GIT 116; TST 135 Test (+/–): QFT-GIT 36/80; TST ≥ 10 mm 47/88 Number of indeterminate results: QFT-GIT 19; TST 0	QFT-GIT: Time of exposure to the index case (number of months): SN NR; SP NR; PPV NR; NPV NR MTC score 0–15: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm: Time of exposure to the index case (number of months): SN NR; SP NR; PPV NR; NPV NR MTC score 0–15: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Time of exposure to the index case (number of months): DOR NR ($p = 0.024$); DORa NR ($p = 0.537$) MTC score 0–15: DOR NR ($p = 0.021$); DORa 1.16 (1.01 to 1.33; $p = 0.035$)	TST ≥ 10 mm: Time of exposure to the index case (number of months): DOR NR ($p < 0.001$); DORa 1.15 (1.04 to 1.27; $p = 0.009$) MTC score 0–15: DOR NR ($p < 0.001$); DORa 1.29 (1.08 to 1.54; $p = 0.005$)	QFT-GIT vs. TST ≥ 10 mm: Time of exposure to the index case (number of months): R-DOR NR; R-DORa NR MTC score 0–15: R-DOR NR; R-DORa 0.90 (0.80 to 1.01)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Rutherford 2012,[110,111] Indonesia (high)	Number of test results: QFT-GIT 290; TST 302 Test (+/–): QFT-GIT 152/138; TST ≥ 10 mm 145/157 Number of indeterminate results: QFT-GIT 14; TST 2	QFT-GIT: Characteristics of TB case smear positivity (3+ vs. scanty/1+): SN 62.5 (53.58 to 70.65); SP 59.6 (49.75 to 68.73); PPV 65.22 (56.15 to 73.3); NPV 56.73 (47.14 to 65.85) Relationship to child (parent vs. other): SN 61.19 (54.59 to 67.4); SP 77.27 (63.01 to 87.16); PPV 93.06 (87.69 to 96.18); NPV 28.57 (21.22 to 37.26) Sleeping proximity to child (same bed vs. different room): SN 59.24 (51.42 to 66.61); SP 59.05 (49.48 to 67.97); PPV 68.38 (60.15 to 75.6); NPV 49.21 (40.63 to 57.83) Time spent with child (number of hours per day: > 8 vs. < 2): SN 52.00 (44.06 to 59.85); SP 42.55 (29.51 to 56.72); PPV 74.29 (65.17 to 81.68); NPV 21.74 (14.54 to 31.21)	TST ≥ 10 mm: Characteristics of TB case smear positivity (3+ vs. scanty/1+): SN 61.9 (53.19 to 69.91); SP 68.27 (58.81 to 76.43); PPV 70.27 (61.21 to 77.98); NPV 59.66 (50.68 to 68.04) Relationship to child (parent vs. other): SN 55.9 (49.42 to 62.18); SP 90.71); PPV 94.12 (88.82 to 96.99); NPV 26.81 (20.12 to 34.76) Sleeping proximity to child (same bed vs. different room): SN 51.52 (43.94 to 59.02); SP 56.88 (47.51 to 65.79); PPV 64.39 (55.92 to 72.05); NPV 43.66 (35.78 to 51.88) Time spent with child (number of hours per day: > 8 vs. < 2): SN 47.47 (39.83 to 55.22); SP 41.67 (28.85 to 55.72); PPV 72.82 (63.52 to 80.47); NPV 19.42 (12.94 to 28.1)	QFT-GIT: Characteristics of TB case smear positivity (2+ vs. scanty/1+): DOR 1.56 (0.78 to 3.11); DORa NR Characteristics of TB case smear positivity (3+ vs. scanty/1+): DOR 2.43 (1.21 to 4.86); DORa 2.28 (1.06 to 4.90) Relationship to child (aunt/uncle vs. other): R-DOR 1.51 (0.44 to 5.17); R-DORa NR Relationship to child (parent vs. other): R-DOR 5.61 (2.40 to 13.12); R-DORa 4.30 (1.48 to 12.45) Sleeping proximity to child (same room vs. different room): R-DOR 1.87 (0.70 to 5.02); R-DORa NR Sleeping proximity to child (same bed vs. different room): R-DOR 2.01 (1.12 to 3.61); R-DORa 1.45 (0.70 to 2.99)	TST ≥ 10 mm: Characteristics of TB case smear positivity (2+ vs. scanty/1+): DOR 1.80 (0.89 to 3.63); DORa NR Characteristics of TB case smear positivity (3+ vs. scanty/1+): DOR 3.35 (1.81 to 6.21); DORa 2.93 (1.59 to 5.39) Relationship to child (aunt/uncle vs. other): R-DOR 2.31 (0.77 to 6.79); R-DORa NR Relationship to child (parent vs. other): R-DOR 5.85 (2.56 to 13.38); R-DORa 7.04 (2.23 to 22.28) Sleeping proximity to child (same room vs. different room): R-DOR 1.21 (0.41 to 3.53); R-DORa NR Sleeping proximity to child (same bed vs. different room): R-DOR 1.35 (0.79 to 2.32); R-DORa NR	QFT-GIT vs. TST ≥ 10 mm: Characteristics of TB case smear positivity (3+): R-DOR 0.73 (0.45 to 1.17); R-DORa 0.78 (0.47 to 1.28) Relationship to child (parent vs. other): R-DOR 0.96 (0.52 to 1.61); R-DORa 0.78 (0.47 to 1.28) Sleeping proximity to child (same bed): R-DOR 1.47 (1.05 to 2.16); R-DORa NR Time spent with child (> 8 hours per day): R-DOR 1.30 (0.75 to 2.24); R-DORa NR

continued

TABLE 7 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (exposure studies) – children and adolescents (*continued*)

		Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
Study ID, country (burden)	Test results	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
				Time spent with child (number of hours per day: 2–8 vs. < 2): R-DOR 0.78 (0.33 to 1.80); R-DORa NR Time spent with child (number of hours per day: > 8 vs. < 2): R-DOR 0.83 (0.38 to 1.79); R-DORa NR	Time spent with child (number of hours per day: 2–8 vs. < 2): R-DOR 0.55 (0.24 to 1.24); R-DORa NR Time spent with child (number of hours per day: > 8 vs. < 2): R-DOR 0.64 (0.31 to 1.36); R-DORa NR	
Talbot 2012,[112] USA (low)	Number of test results: T-SPOT.*TB* 143; TST 143 Test (+/–): T-SPOT.*TB* 5/138; TST ≥ 15 mm 6/137 Number of indeterminate results: T-SPOT.*TB* 15; TST 22	T-SPOT.*TB*: Non-low TB exposure risk group vs. low TB exposure risk group: SN NR; SP 100 (97.00 to 100); PPV NR; NPV NR	TST ≥ 15 mm: Non-low TB exposure risk group vs. low TB exposure risk group: SN NR; SP 98.39 (94.31 to 99.56); PPV NR; NPV NR	T-SPOT.*TB*: Non-low TB exposure risk group vs. low TB exposure risk group: DOR NR; DORa NR	TST ≥ 15 mm: Non-low TB exposure risk group vs. low TB exposure risk group: DOR NR; DORa NR	T-SPOT.*TB* vs. TST ≥ 15 mm: Non-low TB exposure risk group vs. low TB exposure risk group: R-DOR NR; R-DORa NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Tieu 2014,[154] Thailand (high)	Number of test results: QFT-GIT 136; T-SPOT.*TB* 136; TST 136 Test (+/–): QFT-GIT 40/96; T-SPOT.*TB* 36/100; TST ≥ 10 mm 88/48; TST ≥ 15 mm 48/88 Number of indeterminate results: QFT-GIT 0; T-SPOT.*TB* 0; TST 0	QFT-GIT, T-SPOT.*TB*: TB contact score: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm, TST ≥ 15 mm: TB contact score: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: TB contact score (≥ 13 vs. 8–12): DOR 4.04 (1.81 to 8.99); DORa 1.98 (0.64 to 6.11) T-SPOT.*TB*: TB contact score (≥ 13 vs. 8–12): DOR 3.50 (1.57 to 7.81); DORa 3.15 (1.35 to 7.34)	TST ≥ 10 mm: TB contact score (≥ 13 vs. 8–12): DOR 2.59 (1.28 to 5.23); DORa 2.21 (0.99 to 4.98) TST ≥ 15 mm: TB contact score (≥ 13 vs. 8–12): DOR 2.19 (1.09 to 4.43); DORa 0.83 (0.35 to 1.99)	QFT-GIT vs. TST ≥ 10 mm: TB contact score (≥ 13 vs. 8–12): R-DOR 1.56 (0.91 to 2.69); R-DORa 0.90 (0.44 to 1.82) QFT-GIT vs. TST ≥ 15 mm: TB contact score (≥ 13 vs. 8–12): R-DOR 1.84 (1.07 to 3.18); R-DORa 2.39 (1.15 to 4.93) T-SPOT.*TB* vs. TST ≥ 10 mm: TB contact score (≥ 13 vs. 8–12): R-DOR 1.35 (0.78 to 2.33); R-DORa 1.43 (0.78 to 2.59) T-SPOT.*TB* vs. TST ≥ 15 mm: TB contact score (≥ 13 vs. 8–12): R-DOR 1.60 (0.93 to 2.75); R-DORa 3.80 (2.04 to 7.05)

continued

TABLE 7 Comparison of test performance: diagnostic accuracy indices for identifying LTBI (exposure studies) – children and adolescents (*continued*)

		Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
Study ID, country (burden)	**Test results**	**IGRA: QFT-GIT/G and/or T-SPOT.*TB***	**TST (by threshold)**	**IGRA: QFT-GIT/G and/or T-SPOT.*TB***	**TST (by threshold)**	**R-DOR (95% CI), IGRA vs. TST (by threshold)**
Tsolia 2010,[113] Greece (low)	Number of test results: QFT-GIT 95; TST 99 Test (+/–): QFT-GIT 32/63; TST ≥ 5 mm 55/44 Number of indeterminate results: QFT-GIT 4; TST 0	QFT-GIT: Contact with an adult TB case (non-household regular vs. non-household occasional): SN 33.33 (18.64 to 52.18); SP 90.91 (62.26 to 98.38); PPV 90.00 (59.58 to 98.21); NPV 35.71 (20.71 to 54.17) Contact with an adult TB case (household vs. non-household occasional): SN 38.6 (27.06 to 51.57); SP 90.91 (62.26 to 98.38); PPV 95.65 (79.01 to 99.23); NPV 22.22 (12.54 to 36.27)	TST ≥ 5 mm: Contact with an adult TB case (non-household regular vs. non-household occasional): SN 64.29 (45.83 to 79.29); SP 36.36 (15.17 to 64.62); PPV 72.00 (52.42 to 85.72); NPV 28.57 (11.72 to 54.65) Contact with an adult TB case (household vs. non-household occasional): SN 50.00 (37.73 to 62.27); SP 36.36 (15.17 to 64.62); PPV 81.08 (65.79 to 90.52); NPV 11.76 (4.67 to 26.62)	QFT-GIT: Contact with an adult TB case (non-household regular vs. non-household occasional): DOR 5.00 (0.55 to 45.39); DORa NR Contact with an adult TB case (household vs. non-household occasional): DOR 6.28 (0.75 to 52.56); DORa NR	TST ≥ 5 mm: Contact with an adult TB case (non-household regular vs. non-household occasional): DOR 1.03 (0.24 to 4.39); DORa NR Contact with an adult TB case (household vs. non-household occasional): DOR 0.57 (0.15 to 2.15); DORa NR	QFT-GIT vs. TST ≥ 5 mm: Contact with an adult TB case (non-household regular): R-DOR 4.85 (1.26 to 18.69); R-DORa NR Contact with an adult TB (household regular): R-DOR 11.02 (3.07 to 39.60); R-DORa NR

DORa, adjusted diagnostic odds ratio; ID, identification; MTC, *M. tuberculosis* contact; NR, not reported; R-DORa, adjusted ratio of diagnostic odds ratios; SN, sensitivity; SP, specificity.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Adetifa 2010[105]	–1.321	0.405	215	215	7.9%	0.27 (0.12 to 0.59)
Brock 2004[156]	0.657	0.712	85	85	5.6%	1.93 (0.48 to 7.79)
Chun 2008[157]	0.113	0.609	71	71	6.3%	1.12 (0.34 to 3.69)
Cruz 2011[106]	2.217	0.286	163	163	8.7%	9.18 (5.24 to 16.08)
Hansted 2009[160]	0.939	0.541	97	97	6.8%	2.56 (0.89 to 7.38)
Higuchi 2009[161]	1.498	0.6	313	306	6.4%	4.47 (1.38 to 14.50)
Kasambira 2011[107]	–0.025	0.647	267	251	6.0%	0.98 (0.27 to 3.47)
Lighter 2009[163]	2.311	0.603	174	174	6.4%	10.08 (3.09 to 32.88)
Mahomed 2011[108]	–0.051	0.051	5231	5244	9.7%	0.95 (0.86 to 1.05)
Okada 2008[164]	0.737	0.556	195	195	6.7%	2.09 (0.70 to 6.21)
Pavic 2011[109]	–0.41	0.751	141	142	5.3%	0.66 (0.15 to 2.89)
Rutherford 2012[110,111]	0.4	0.182	290	302	9.3%	1.49 (1.04 to 2.13)
Tieu 2014[154]	0.444	0.277	136	136	8.8%	1.56 (0.91 to 2.68)
Tsolia 2010[113]	2.399	0.652	68	71	6.0%	11.01 (3.07 to 39.52)
Total (95% CI)			**7446**	**7452**	**100.0%**	**1.98 (1.19 to 3.28)**

Heterogeneity: $\tau^2 = 0.68$; $\chi^2 = 116.16$, df = 13 ($p < 0.00001$); $I^2 = 89\%$
Test for overall effect: $z = 2.64$ ($p = 0.008$)

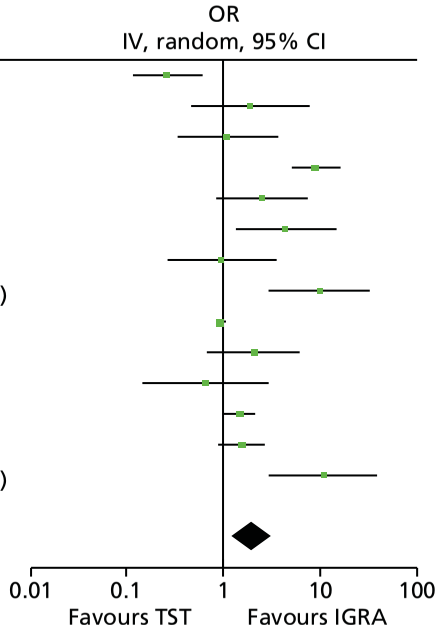


FIGURE 9 Pooled R-DOR of IGRA vs. TST based on high- and low-risk exposure in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Chun 2008[157]	0.113	0.609	71	71	18.6%	1.12 (0.34 to 3.69)
Higuchi 2009[161]	1.498	0.6	313	306	18.8%	4.47 (1.38 to 14.50)
Kasambira 2011[107]	–0.025	0.647	267	251	17.9%	0.98 (0.27 to 3.47)
Mahomed 2011[108]	–0.051	0.051	5231	5244	26.9%	0.95 (0.86 to 1.05)
Tsolia 2010[113]	2.399	0.652	68	71	17.8%	11.01 (3.07 to 39.52)
Total (95% CI)			**5950**	**5943**	**100.0%**	**2.04 (0.81 to 5.13)**

Heterogeneity: $\tau^2 = 0.82$; $\chi^2 = 20.58$, df = 4 ($p = 0.0004$); $I^2 = 81\%$
Test for overall effect: $z = 1.51$ ($p = 0.13$)

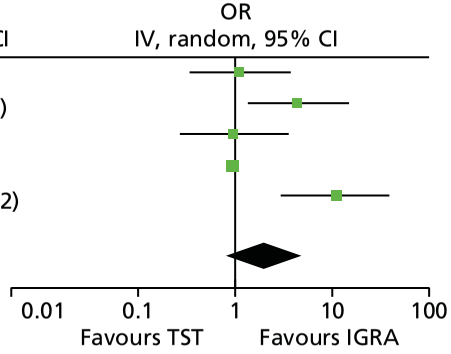


FIGURE 10 Pooled R-DOR of QFT vs. TST 5 mm based on high- and low-risk exposure in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Adetifa 2010[105]	−1.321	0.405	215	215	15.8%	0.27 (0.12 to 0.59)
Brock 2004[156]	0.657	0.712	85	85	11.0%	1.93 (0.48 to 7.79)
Lighter 2009[163]	2.311	0.603	174	174	12.6%	10.08 (3.09 to 32.88)
Okada 2008[164]	0.737	0.556	195	195	13.3%	2.09 (0.70 to 6.21)
Pavic 2011[109]	−0.41	0.751	141	142	10.4%	0.66 (0.15 to 2.89)
Rutherford 2012[110,111]	0.4	0.182	290	302	19.0%	1.49 (1.04 to 2.13)
Tieu 2014[154]	0.612	0.277	136	136	17.8%	1.84 (1.07 to 3.17)
Total (95% CI)			**1236**	**1249**	**100.0%**	**1.48 (0.75 to 2.95)**

Heterogeneity: $\tau^2 = 0.61$; $\chi^2 = 30.26$, df = 6 ($p < 0.0001$); $I^2 = 80\%$
Test for overall effect: $z = 1.13$ ($p = 0.26$)

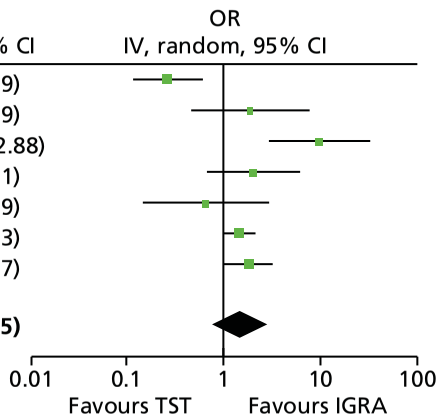


FIGURE 11 Pooled R-DOR of QFT vs. TST 10–15 mm based on high- and low-risk exposure in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Adetifa 2010[105]	−0.82	0.461	215	215	24.3%	0.44 (0.18 to 1.09)
Cruz 2011[106]	2.217	0.286	163	163	26.2%	9.18 (5.24 to 16.08)
Hansted 2009[160]	0.939	0.541	97	97	23.3%	2.56 (0.89 to 7.38)
Tieu 2014[154]	0.301	0.277	136	136	26.3%	1.35 (0.79 to 2.33)
Total (95% CI)			**611**	**611**	**100.0%**	**1.97 (0.53 to 7.27)**

Heterogeneity: $\tau^2 = 1.61$; $\chi^2 = 39.80$, df = 3 ($p < 0.00001$); $I^2 = 92\%$
Test for overall effect: $z = 1.02$ ($p = 0.31$)

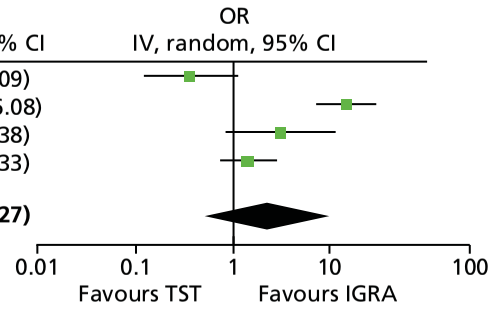


FIGURE 12 Pooled R-DOR of T-SPOT.*TB* vs. TST 10–15 mm based on high- and low-risk exposure in children and adolescents. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Adetifa 2010[105]	−1.321	0.405	215	215	12.2%	0.27 (0.12 to 0.59)
Brock 2004[156]	0.657	0.712	85	85	6.2%	1.93 (0.48 to 7.79)
Higuchi 2009[161]	1.498	0.6	313	306	7.9%	4.47 (1.38 to 14.50)
Kasambira 2011[107]	−0.025	0.647	267	251	7.1%	0.98 (0.27 to 3.47)
Mahomed 2011[108]	−0.051	0.051	5231	5244	22.4%	0.95 (0.86 to 1.05)
Okada 2008[164]	0.737	0.556	195	195	8.7%	2.09 (0.70 to 6.21)
Rutherford 2012[110,111]	0.4	0.182	290	302	19.3%	1.49 (1.04 to 2.13)
Tieu 2014[154]	0.444	0.277	136	136	16.2%	1.56 (0.91 to 2.68)
Total (95% CI)			**6732**	**6734**	**100.0%**	**1.22 (0.81 to 1.83)**

Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 27.87$, df = 7 ($p = 0.0002$); $I^2 = 75\%$
Test for overall effect: $z = 0.95$ ($p = 0.34$)

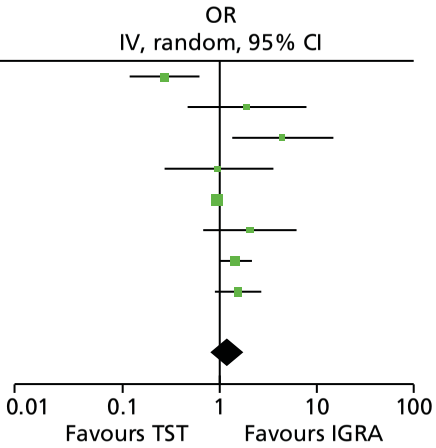


FIGURE 13 Pooled R-DOR of IGRA vs. TST based on high- and low-risk exposure in children and adolescents: community-based contact studies only. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Chun 2008[157]	0.113	0.609	71	71	16.2%	1.12 (0.34 to 3.69)
Cruz 2011[106]	2.217	0.286	163	163	20.7%	9.18 (5.24 to 16.08)
Hansted 2009[160]	0.939	0.541	97	97	17.2%	2.56 (0.89 to 7.38)
Lighter 2009[163]	2.311	0.603	174	174	16.3%	10.08 (3.09 to 32.88)
Pavic 2011[109]	−0.41	0.751	141	142	14.1%	0.66 (0.15 to 2.89)
Tsolia 2010[113]	2.399	0.652	68	71	15.5%	11.01 (3.07 to 39.52)
Total (95% CI)			**714**	**718**	**100.0%**	**3.78 (1.53 to 9.39)**

Heterogeneity: $\tau^2 = 0.95$; $\chi^2 = 22.07$, df = 5 ($p = 0.0005$); $I^2 = 77\%$
Test for overall effect: $z = 2.87$ ($p = 0.004$)

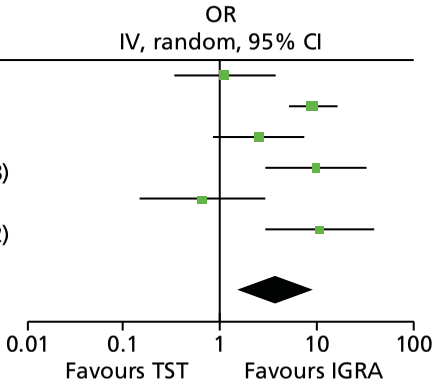


FIGURE 14 Pooled R-DOR of IGRA vs. TST based on high- and low-risk exposure in children and adolescents: hospital-based studies only. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Adetifa 2010[105]	–1.321	0.405	215	215	11.5%	0.27 (0.12 to 0.59)
Chun 2008[157]	0.113	0.609	71	71	6.9%	1.12 (0.34 to 3.69)
Hansted 2009[160]	0.939	0.541	97	97	8.2%	2.56 (0.89 to 7.38)
Kasambira 2011[107]	–0.025	0.647	267	251	6.4%	0.98 (0.27 to 3.47)
Mahomed 2011[108]	–0.051	0.051	5231	5244	23.6%	0.95 (0.86 to 1.05)
Okada 2008[164]	0.737	0.556	195	195	7.9%	2.09 (0.70 to 6.21)
Rutherford 2012[110,111]	0.4	0.182	290	302	19.7%	1.49 (1.04 to 2.13)
Tieu 2014[154]	0.444	0.2777	136	136	15.9%	1.56 (0.90 to 2.69)
Total (95% CI)			**6502**	**6511**	**100.0%**	**1.13 (0.78 to 1.65)**

Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 23.80$, df = 7 ($p = 0.001$); $I^2 = 71\%$
Test for overall effect: $z = 0.66$ ($p = 0.51$)

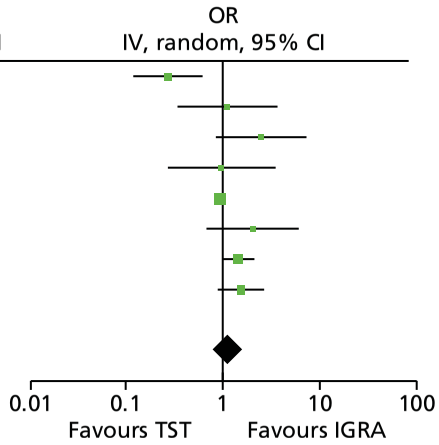


FIGURE 15 Pooled R-DOR of IGRA vs. TST based on high- and low-risk exposure in children and adolescents: studies conducted in high-burden countries. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Brock 2004[156]	0.657	0.712	85	85	14.4%	1.93 (0.48 to 7.79)
Cruz 2011[106]	2.217	0.286	163	163	23.2%	9.18 (5.24 to 16.08)
Higuchi 2009[161]	1.498	0.6	313	306	16.6%	4.47 (1.38 to 14.50)
Lighter 2009[163]	2.311	0.603	174	174	16.5%	10.08 (3.09 to 32.88)
Pavic 2011[109]	–0.41	0.751	141	142	13.7%	0.66 (0.15 to 2.89)
Tsolia 2010[113]	2.399	0.652	68	71	15.6%	11.01 (3.07 to 39.52)
Total (95% CI)			**944**	**941**	**100.0%**	**4.74 (2.15 to 10.44)**

Heterogeneity: $\tau^2 = 0.62$; $\chi^2 = 15.14$, df = 5 ($p = 0.010$); $I^2 = 67\%$
Test for overall effect: $z = 3.86$ ($p = 0.0001$)

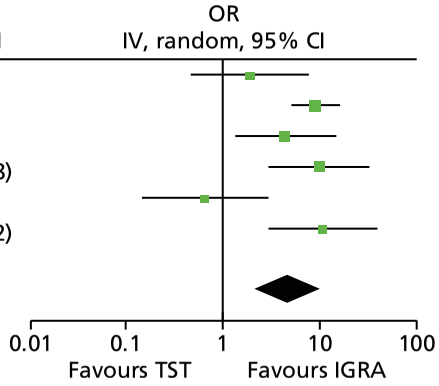


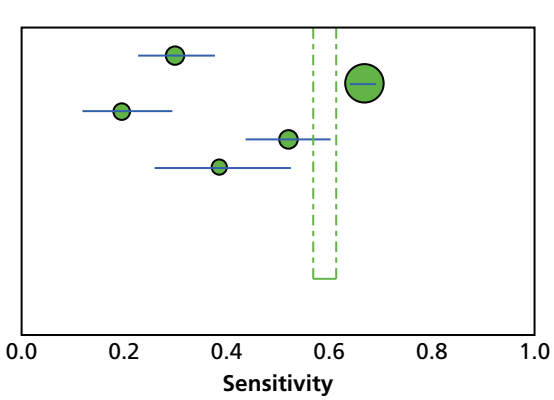
FIGURE 16 Pooled R-DOR of IGRA vs. TST based on high- and low-risk exposure in children and adolescents: studies conducted in low-burden countries. df, degrees of freedom; IV, inverse variance; SE, standard error.

In five studies, trends for exposure gradient (across more than two ordinal exposure groups) for IGRAs and the TST were explored with respect to sleeping proximity (same house/same room, same house/different room, different house),[105,110,111] adult index case type of TB diagnosis,[107] adult index case smear grade (negative, scanty, 1+, 2+, 3+),[107,110,111] duration of exposure to index case (time spent with child),[107,110,111,154] relationship to index case (parent, aunt/uncle, other),[110,111,154] TB contact score (score-based categories)[154] and type of contact (household, non-household regular, occasional).[113] In general, for both IGRAs and the TST there was an increasing trend in DOR across the exposure groups. In two studies this trend was absent for both tests in relation to duration of exposure to the index case[110,111] and for the TST in relation to type of contact.[113] See *Appendix 9* for full extraction sheets.

Sensitivity and specificity

In this analysis, six[105,106,112,148,151,154] of the included 11 recent studies[105–113,148,151,154] failed to provide sufficient information for calculating both sensitivity and specificity. There was wide variability in the sensitivity and specificity of the IGRAs (QFT-GIT/G) and TST (5 mm or 10 mm), with overlapping values across the five remaining studies[107–111,113] (*Figures 17–24*).

Both the QFT-GIT/G and TST (5 mm or 10 mm) demonstrated better specificity (range 36–98%) than sensitivity (range 20–71%). There was no clear numerical pattern indicating the superiority of the IGRA over the TST (or vice versa) with respect to sensitivity and specificity. Forest plots of sensitivities and specificities showed a great extent of heterogeneity that was not explained by IGRA type and/or TST threshold and therefore a meta-analysis was not performed.



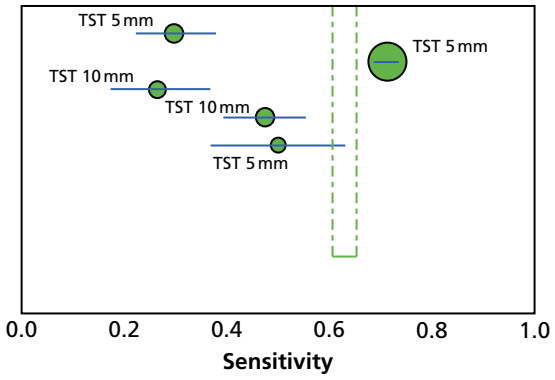
	Sensitivity (95% CI)	
Kasambira 2011[107]	0.30	(0.23 to 0.38)
Mahomed 2011[108]	0.67	(0.64 to 0.69)
Pavic 2011[109]	0.20	(0.12 to 0.29)
Rutherford 2012[110,111]	0.52	(0.44 to 0.60)
Tsolia 2010[113]	0.39	(0.26 to 0.52)

$\chi^2 = 155.87$; df = 4 ($p = 0.0000$)
Inconsistency (I^2) = 97.4%

Reference standard (exposure groups) in studies

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 17 Forest plot of sensitivity based on exposure groups (QFT-GIT) in children and adolescents.
df, degrees of freedom.



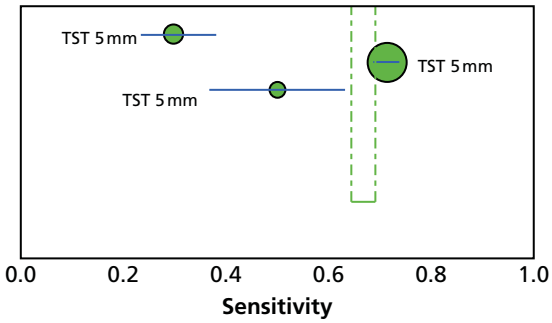
	Sensitivity (95% CI)	
Kasambira 2011[107]	0.30	(0.22 to 0.38)
Mahomed 2011[108]	0.71	(0.69 to 0.74)
Pavic 2011[109]	0.26	(0.18 to 0.37)
Rutherford 2012[110,111]	0.47	(0.39 to 0.56)
Tsolia 2010[113]	0.50	(0.37 to 0.63)

$\chi^2 = 172.94$; df = 4 ($p = 0.0000$)
Inconsistency (I^2) = 97.7%

Reference standard (exposure) groups in studies

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 18 Forest plot of sensitivity based on exposure groups (TST) in children and adolescents.
df, degrees of freedom.



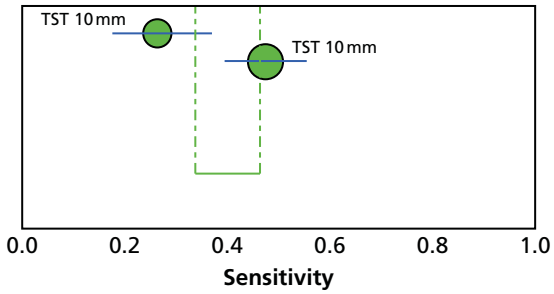
	Sensitivity (95% CI)	
Kasambira 2011[107]	0.30	(0.22 to 0.38)
Mahomed 2011[108]	0.71	(0.69 to 0.74)
Tsolia 2010[113]	0.50	(0.37 to 0.63)

$\chi^2 = 100.22$; df = 2 ($p = 0.0000$)
Inconsistency (I^2) = 98.0%

Reference standard (exposure) groups in studies

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 19 Forest plot of sensitivity based on exposure groups (TST 5 mm) in children and adolescents.
df, degrees of freedom.



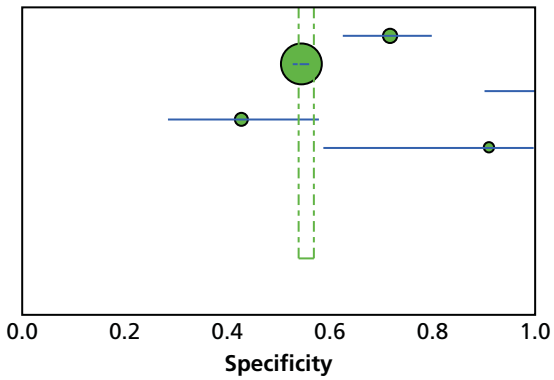
	Sensitivity (95% CI)	
Pavic 2011[109]	0.26	(0.18 to 0.37)
Rutherford 2012[110,111]	0.47	(0.39 to 0.56)

$\chi^2 = 10.65$; df = 1 ($p = 0.0011$)
Inconsistency (I^2) = 90.6%

Reference standard (exposure) groups in studies

Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)

FIGURE 20 Forest plot of sensitivity based on exposure groups (TST 10 mm) in children and adolescents.
df, degrees of freedom.



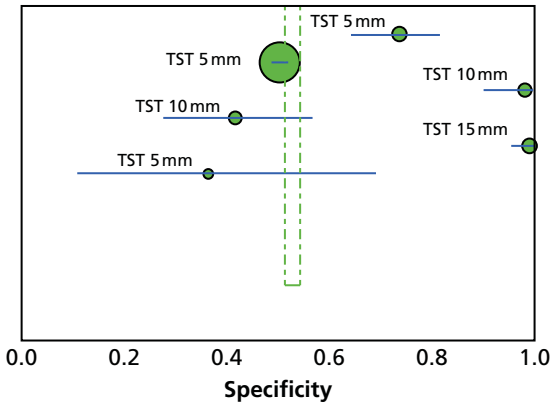
	Specificity (95% CI)	
Kasambira 2011[107]	0.72	(0.62 to 0.80)
Mahomed 2011[108]	0.54	(0.53 to 0.56)
Pavic 2011[109]	0.98	(0.90 to 1.00)
Rutherford 2012[110,111]	0.43	(0.28 to 0.58)
Tsolia 2010[113]	0.91	(0.59 to 1.00)

$\chi^2 = 78.59$; df = 4 ($p = 0.0000$)
Inconsistency (I^2) = 94.9%

Reference standard (exposure groups) in studies

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 21 Forest plot of specificity based on exposure groups (QFT-GIT) in children and adolescents.
df, degrees of freedom.



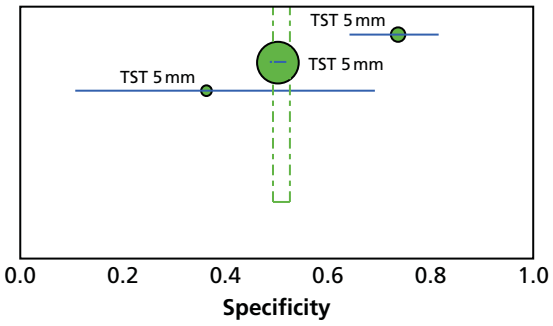
	Specificity (95% CI)	
Kasambira 2011[107]	0.74	(0.64 to 0.82)
Mahomed 2011[108]	0.50	(0.49 to 0.52)
Pavic 2011[109]	0.98	(0.90 to 1.00)
Rutherford 2012[110,111]	0.42	(0.28 to 0.57)
Talbot 2012[112]	0.99	(0.96 to 1.00)
Tsolia 2010[113]	0.36	(0.11 to 0.69)

$\chi^2 = 239.64$; df = 5 ($p = 0.0000$)
Inconsistency (I^2) = 97.9%

Reference standard (exposure) groups

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)
Talbot 2012:[112] non-low-TB exposure risk vs. low-TB exposure risk group
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 22 Forest plot of specificity based on exposure groups (TST) in children and adolescents.
df, degrees of freedom.



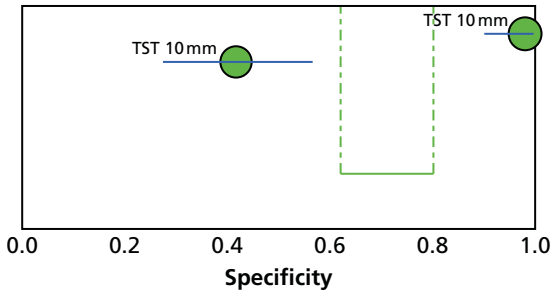
	Specificity (95% CI)	
Kasambira 2011[107]	0.74	(0.64 to 0.82)
Mahomed 2011[108]	0.50	(0.49 to 0.52)
Tsolia 2010[113]	0.36	(0.11 to 0.69)

$\chi^2 = 25.25$; df = 2 ($p = 0.0000$)
Inconsistency (I^2) = 92.1%

Reference standard (exposure) groups

Kasambira 2011:[107] exposure to index case (>7 hours vs. <6 hours)
Mahomed 2011:[108] current or prior TB household contact vs. no such contact
Tsolia 2010:[113] contact with an adult TB case (household vs. non-household occasional)

FIGURE 23 Forest plot of specificity based on exposure groups (TST 5 mm) in children and adolescents.
df, degrees of freedom.



	Specificity (95% CI)	
Pavic 2011[109]	0.98	(0.90 to 1.00)
Rutherford 2012[110,111]	0.42	(0.28 to 0.57)

$\chi^2 = 47.25$; df = 1 ($p = 0.0000$)
Inconsistency (I^2) = 97.9%

Reference standard (exposure) groups

Pavic 2011:[109] household contact with active TB (≥40 hours) vs. occasional or unclear contact (<40 hours)
Rutherford 2012:[110,111] time spent with child (number of hours/day; >8 vs. <2)

FIGURE 24 Forest plot of specificity based on exposure groups (TST 10 mm) in children and adolescents. df, degrees of freedom.

Influence of bacillus Calmette–Guérin vaccination status on test positivity

In this analysis, four[109,112,148,154] of the included 11 recent studies[105–113,148,151,154] did not report any information needed to determine whether or not BCG vaccination status influenced the odds of test positivity differentially for the IGRAs and TST. Of the seven remaining studies reporting this evidence, only three[106,108,113] demonstrated significantly increased ORs for TST positivity in relation to BCG vaccination status (range of ORs 1.16–20.34). The odds of test positivity for IGRAs across the seven studies were not significantly different between the BCG-vaccinated group and the non-vaccinated group (*Table 8*). One study with a relatively large sample size and narrow CIs demonstrated more conclusively that BCG vaccination status was associated with an increased odds of test positivity for TST (OR 1.16, 95% CI 1.0 to 1.33) but not for IGRA (OR 0.99, 95% CI 0.86 to 1.12).[108]

Between-test concordance, discordance and agreement

This section included five studies[156–159,164] reviewed in CG117[10] (see *Appendix 5*) and 16 more recent studies[102–113,148,150–152,154] (see *Appendix 9*). The agreement kappa statistic was not available for four studies.[102,104,106,150] There was a wide variation in the kappa statistic across the remaining studies, ranging from 0.13[113] to 0.91[113] (*Table 9*). In the post-2009 studies,[103,105,107–113,148,151,152,154] the ranges of the kappa statistic according to specific TST threshold and IGRA type were as follows: QFT-GIT compared with TST 5 mm – range 0.27–0.91; QFT-GIT compared with TST 10 mm – range 0.13–0.64; and T-SPOT.*TB* compared with TST 10 mm – range 0.53–0.71. According to one study, both between-test per cent concordance and the kappa statistic were lower among participants with a BCG vaccination history (concordance 46.5%, kappa 0.16) than among those without such history (concordance 96.20%, kappa 0.91).[113]

Summary of studies in children and adolescents

Although there is a limited amount of evidence, the three prospective studies suggested no significant difference between QFT-GIT and TST 5 mm (pooled R-CIR 1.12, 95% CI 0.72 to 1.75). QFT-GIT performed significantly better than TST 10 mm in identifying LTBI or predicting risk of active TB (pooled R-CIR 4.33, 95% CI 1.32 to 14.23). In five newly identified prospective studies investigating the incidence of active TB, there was a wide variability in sensitivity and specificity of IGRAs (QFT-GIT/G) and TST (5 mm or 10 mm). Because of high unexplained heterogeneity (not explained by IGRA type and TST threshold, similar diagnostic methods of active TB), no meta-analysis could be performed. IGRAs (QFT-GIT/G) demonstrated similar sensitivity (range 48–100%) and slightly better specificity (range 49–90%) than TST 5 mm (sensitivity range 57–100%; specificity range 45–65%). Although the sensitivities of the IGRAs and TST 5 mm were higher than that for TST 10 mm/15 mm (range 30–56%), the corresponding specificities of these tests were lower than that of TST 10 mm/15 mm (range 63–93%).

TABLE 8 Association between test positivity and BCG vaccination status in children and adolescents: exposure studies

Study ID, country (burden)	Sample size, *n*	Type of IGRA/TST induration threshold	Association between test positivity and BCG vaccination status: OR (95% CI)	
			Crude/unadjusted	Adjusted
Adetifa 2010,[105] Gambia (low)	199	QFT-GIT	1.10 (0.60 to 2.00)	NR
	199	T-SPOT.*TB*	1.10 (0.61 to 2.09)	NR
	199	TST 10 mm	0.89 (0.50 to 1.70)	NR
Cruz 2011,[106] USA (low)	NR	T-SPOT.*TB*	0.69 (0.37 to 1.31)	NR
	NR	TST 15 mm	4.32 (1.02 to 18.35)	NR
Kasambira 2011,[107] South Africa (high)	262	QFT-GIT	0.62 (0.08 to 4.76)	0.83 (0.08 to 8.33)
	247	TST 5 mm	0.38 (0.05 to 2.85)	0.52 (0.06 to 4.00)
Laniado-Laborın 2014,[148] Mexico (intermediate)	172	QFT-GIT	NR	NR
	172	TST 5 mm	NR	NR
Mahomed 2011,[108] South Africa (high)	3554	QFT-GIT	0.99 (0.86 to 1.12)	NR
	3554	TST 5 mm	1.16 (1.00 to 1.33)	NR
Pavic 2011,[109] Croatia (low)	NR	QFT-GIT	NR	NR
	NR	TST 10 mm	NR	NR
Perez-Porcuna 2014,[151] Brazil (intermediate)	116	QFT-GIT	3.89 (0.46 to 32.33)	NR
	135	TST 10 mm	1.85 (0.36 to 9.36)	NR
Rutherford 2012,[110,111] Indonesia (high)	260	QFT-GIT	0.51 (0.26 to 1.00)	0.60 (0.26 to 1.38)
	272	TST 10 mm	0.68 (0.35 to 1.35)	NR
Talbot 2012,[112] USA (low)	NR	T-SPOT.*TB*	NR	NR
	NR	TST 15 mm	NR	NR
Tieu 2014,[154] Thailand (high)	136	QFT-GIT	NR	NR
	136	TST 10 mm	NR	NR
	136	T-SPOT.*TB*	NR	NR
	136	TST 15 mm	NR	NR
Tsolia 2010,[113] Greece (low)	NR	QFT-GIT	0.19 (0.06 to 0.60)	NR
	NR	TST 5 mm	20.34 (5.60 to 73.89)	NR

ID, identification; NR, not reported.

TABLE 9 Between-test concordance and discordance in children and adolescents: exposure and incidence studies

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Adetifa 2010,[105] Gambia (low)	217	QFT-GIT vs. TST 10 mm	80.00 (74.15 to 84.80)	20.00 (15.2 to 25.85)	0.52 (0.39 to 0.65)
	215	T-SPOT.*TB* vs. TST 10 mm	80.47 (74.65 to 85.21)	19.53 (14.79 to 25.35)	0.53 (0.40 to 0.66)
Cruz 2011,[106] USA (low)	NR	T-SPOT.*TB* vs. TST 15 mm	NR	NR	NR
Diel 2011,[102] Germany (low)	NR	QFT-GIT vs. TST 5/10 mm	NR	NR	NR
Kasambira 2011,[107] South Africa (high)	254	QFT-GIT vs. TST 5 mm	86.86 (81.96 to 90.59)	13.14 (9.41 to 18.04)	0.68 (0.56 to 0.81)
	254	QFT-GIT vs. TST 10 mm	85.59 (80.54 to 89.5)	14.41 (10.5 to 19.46)	0.64 (0.51 to 0.76)
Laniado-Laborın 2014,[148] Mexico (intermediate)	172	QFT-GIT vs. TST 5 mm	59.88 (52.42 to 66.92)	40.12 (33.08 to 47.58)	0.27 (0.17 to 0.38)
Mahomed 2011,[108] South Africa (high)	NR	QFT-GIT vs. TST 5 mm	84.8 (NR)	NR	0.70 (0.68 to 0.71)
	NR	QFT-GIT vs. TST 10 mm	81.4 (NR)	NR	0.63 (0.61 to 0.65)
	NR	QFT-GIT vs. TST 15 mm	64.3 (NR)	NR	0.30 (0.27 to 0.32)
Mahomed 2011,[103] South Africa (high)	5244	QFT-GIT vs. TST 5 mm	84.80 (83.80 to 85.75)	15.20 (14.25 to 16.20)	0.69 (0.66 to 0.72)
Metin Timur 2014,[150] Turkey (intermediate)	81	QFT-GIT vs. TST 15 mm	NR	NR	NR
Noorbakhsh 2011,[104] Iran (intermediate)	NR	QFT-GIT vs. TST 10 mm	NR	NR	NR
Pavic 2011,[109] Croatia (low)	141	QFT-GIT vs. TST 10 mm	89.36 (83.19 to 93.45)	10.64 (6.554 to 16.81)	0.59 (0.42 to 0.75)
Perez-Porcuna 2014,[151] Brazil (intermediate)	116	QFT-GIT vs. TST 10 mm	71.55 (62.75 to 78.97)	28.44 (21.03 to 37.25)	0.35 (0.16 to 0.53)
Rutherford 2012,[110,111] Indonesia (high)	292	QFT-GIT vs. TST 10 mm	80.48 (75.55 to 84.62)	19.52 (15.38 to 24.45)	0.61 (0.49 to 0.72)
Song 2014,[152] South Korea (high)	2982	QFT-GIT vs. TST 10 mm	82.6 (81.2 to 83.92)	17.4 (16.08 to 18.80)	0.38 (0.34 to 0.42)
	2982	QFT-GIT vs. TST 15 mm	92.52 (91.51 to 93.41)	7.48 (6.59 to 8.48)	0.55 (0.50 to 0.61)

continued

TABLE 9 Between-test concordance and discordance in children and adolescents: exposure and incidence studies (*continued*)

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Talbot 2012,[112] USA (low)	143	T-SPOT.*TB* vs. TST 15 mm	97.9 (94.01 to 99.28)	2.01 (0.72 to 5.99)	0.71 (0.55 to 0.88)
Tieu 2014,[154] Thailand (high)	131	QFT-GIT vs. TST 10 mm	59.54 (50.98 to 67.56)	40.46 (32.44 to 49.02)	0.29 (0.18 to 0.40)
	131	QFT-GIT vs. TST 15 mm	79.39 (71.67 to 85.43)	20.61 (14.57 to 28.33)	0.53 (0.38 to 0.69)
	131	T-SPOT.*TB* vs. TST 10 mm	55.73 (47.18 to 63.95)	44.27 (36.05 to 52.82)	0.23 (0.12 to 0.34)
	131	T-SPOT.*TB* vs. TST 15 mm	78.63 (70.84 to 84.78)	21.37 (15.22 to 29.16)	0.51 (0.35 to 0.66)
Tsolia 2010,[113] Greece (low)	99	QFT-GIT vs. TST NR	71.58 (61.81 to 79.67)	28.42 (20.33 to 38.19)	0.45 (0.27 to 0.63)
	43 with BCG history[a]	QFT-GIT vs. TST 10 mm	46.50 (NR)	NR	0.13 ($p = 0.06$)
	52 no BCG history[a]	QFT-GIT vs. TST 5 mm	96.20 (NR)	NR	0.91 ($p = 0.06$)

ID, identification; NR, not reported.
a For four people BCG status was unknown.

The updated meta-analysis of 14 studies showed a significantly stronger association for IGRAs than for the TST in relation to risk of LTBI/exposure level (pooled R-DOR 1.98, 95% CI 1.19 to 3.28; $I^2 = 89\%$). The subgroup analysis by country of burden explained some (but not all) of the observed heterogeneity and revealed a trend showing no difference between the IGRAs and the TST in identifying LTBI across studies conducted in countries of high TB burden (pooled R-DOR 1.13, 95% CI 0.78 to 1.65; $I^2 = 71$). In contrast, IGRAs were significantly superior to the TST in identifying LTBI in the settings of low TB burden (pooled R-DOR 4.74, 95% CI 2.15 to 10.44; $I^2 = 67\%$). In five studies both tests revealed strong associations of increasing strength across the exposure gradient for most exposures (sleeping proximity, adult index case type of TB diagnosis, adult index case smear grade, TB contact score and relationship to index case).

There was limited evidence of whether or not BCG vaccination status influenced the odds of test positivity differentially for IGRAs and TST. Out of seven studies reporting relevant data, only three demonstrated a significantly increased OR for TST positivity in relation to BCG vaccination status (range of ORs 1.16–20.34). The odds of test positivity for IGRAs across six studies were not significantly different between the BCG vaccinated and the non-vaccinated groups. One large study showed that there was a statistically significant association between BCG vaccination status and an increased odds of test positivity for TST (OR 1.16, 95% CI 1.0 to 1.33) but not for IGRA (OR 0.99, 95% CI 0.86 to 1.12).

There was a wide variation in the kappa statistic across 17 studies (five studies from CG117[10] and 12 more recent studies), ranging from 0.13 to 0.91. In the post-2009 studies,[103,105,107–113,148,151,152,154] the ranges of the kappa statistic according to specific TST threshold and IGRA type were as follows: QFT-GIT vs. TST 5 mm – range 0.27–0.91 mm; QFT-GIT vs. TST 10 mm – range 0.13–0.64 mm; and T-SPOT.*TB* vs. TST 10 mm – range 0.53–0.71 mm.

Immunocompromised people

Description of baseline characteristics: qualitative synthesis in text and tables

This section included 48 studies.[114–142,149,153,155,167–182] Our searches identified 32 studies[114–142,149,153,155] in immunocompromised patients, of which eight investigated the incidence of active TB following testing for LTBI (incidence studies) and 24[120–142,153] investigated levels of exposure in relationship to LTBI test outcomes (exposure studies). An additional 16 studies[167–182] in immunocompromised patients were identified in CG117.[10]

Incidence studies

Eight studies[114–119,149,155] compared an IGRA test with the TST in immunocompromised people. Reasons for immunodeficiency (condition and procedure) varied across studies. We identified the following subpopulations: (1) HIV patients, (2) haematopoietic stem cell transplantation candidates or recipients, (3) post-kidney transplantation patients, (4) patients undergoing haemodialysis in end-stage renal disease (ESRD) and (5) patients with immune-mediated inflammatory disease before antiTNF-α therapy. The included studies are described below according to these subpopulations. *Table 10* provides further details on these studies.

One study compared the T-SPOT.*TB* with the TST (≥ 5 mm) in a retrospective case study of HIV patients (31.1% female) with a median age of 33 years.[114] The study was carried out in a community setting in Switzerland with a follow up of 2 years. The proportion of BCG-vaccinated participants was not reported.

Moon *et al.*[115] compared QFT-GIT with TST (≥ 5 mm) in haematopoietic stem cell transplantation candidates in a prospective cohort study in a hospital setting in South Korea. The mean age of patients was 47 years and 44% were female. The median (interquartile range) follow-up time to assess patients for active TB was 0.8 (0.1–2.6) years. BCG vaccination was high at 82%. Another study by Lee *et al.*[149] compared QFT-GIT with TST (≥ 5 mm or ≥ 10 mm) in haematopoietic stem cell transplant recipients who were followed up for a median of 1.3 years. The patients' mean age was 42.3 years, 47% were female and 91% had a BCG immunisation scar.

Post-kidney transplantation patients were investigated by Kim *et al.*[116] in a prospective cohort study comparing T-SPOT.*TB* with TST (≥ 10 mm). The setting was a tertiary care hospital in South Korea. The age range reported was 40–46 years, 46% of the participants were female and 79% were BCG vaccinated. Patients were followed up for a median of 14 months.

Three studies[117,118,155] investigated IGRA and TST in haemodialysis patients with ESRD. Tests compared were QFT-GIT and TST (≥ 5 mm),[117] T-SPOT.*TB* and TST (≥ 10 mm),[155] and QFT-G, T-SPOT.*TB* and TST (two step; ≥ 10 mm).[118] Anibarro *et al.*[117] undertook a prospective cohort study in a Spanish dialysis unit following a TB outbreak in the dialysis centre. Lee *et al.*[118] carried out a prospective, matched cohort study in Taiwan. The setting was unreported. The mean age and proportion of female patients was 62 years and 40% in the study by Anibarro *et al.*,[117] 44 years and 66% in the study by Sherkat *et al.*[155] and 54 years and 38% in the study by Lee *et al.*[118] The follow-up across the three studies ranged from 1.5 years[117] to 2 years.[118] The proportion of BCG-vaccinated patients was low (13.5%) in the study by Anibarro *et al.*,[117] intermediate (27.3%) in the study by Sherkat *et al.*[155] and high (82.8%) in the study by Lee *et al.*[118]

Chang *et al.*[119] compared QFT-GIT with TST (≥ 10 mm) in a prospective cohort study in patients with immune-mediated inflammatory diseases investigated for LTBI before treatment with antiTNF-α. The study setting was a hospital in South Korea. Patients were followed up for a median of 18 months. The median age of patients was 39 years, 41% were female and 59% were BCG vaccinated.

TABLE 10 Baseline characteristics of studies in immunocompromised patients: incidence studies

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
HIV infection							
Elzi 2011,[114] Switzerland (Low)	Aim: to evaluate the sensitivity of T-SPOT.*TB* in comparison to TST in identifying HIV-infected individuals with LTBI Setting: community-based cohort Design: retrospective case-only study (no control group) Follow-up: 2 years Funding source: grants/honoraria received from private manufacturers (Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche, Janssen, Pfizer)	NR	Inclusion criteria: NR Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/thresholds: IGRA (T-SPOT.*TB*): ≥ 6 spots in either or both of panel A and panel B – when the positive control was < 20 spots or the negative control was ≥ 10 spots, the test was scored as indeterminate; TST: induration of ≥ 5 mm	Median (IQR) age: 33 (31–42) years Female, *n/N* (%): 20/64 (31) Race/ethnicity, *n/N* (%): white 29/64 (45.3) Geographical origin, *n/N* (%): NR BCG vaccination, *n/N* (%): NR History of antiTB treatment, *n/N* (%): NR Total incidence of active TB, *n/N* (%): NR Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n/N* (%): HIV Co-morbidity, *n/N* (%): NR	Total number of recruited patients: 64; total number of excluded patients: 0 – however, the total number of patients with valid results for both IGRA and TST was 44	T-SPOT.*TB* was retrospectively performed using frozen viable lymphocytes of HIV-infected individuals stored within 6 months before culture-confirmed TB occurred. This retrospective case-only study does not allow an estimate of the incidence of active TB in test-positive and test-negative groups from baseline (no denominators provided)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Haematopoietic stem cell transplantation candidates							
Moon 2013,[115] South Korea (high)	Aim: to compare QFT-GIT with the TST in HCT candidates for detecting LTBI Setting: Asan Medical Center, Seoul Design: prospective cohort study Follow-up: median (IQR) 0.8 (0.1–2.6) years Funding source: Basic Science Research Program through the National Research Foundation (NRF) funded by the Ministry of Education, Science and Technology (MEST) (grant 2010–0005898)	NR	Inclusion criteria: all adult patients admitted for HCT Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): according to manufacturer; TST: induration of ≥ 5mm	Mean (range) age: 47 (35–55) Female, *n* (%): 107 (44) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 201 (82) History of antiTB treatment, *n* (%): 10 (4) Total incidence of active TB, *n* (%): 2 (0.80) Chest radiography (yes/no): yes Clinical examination (yes/no): yes	Total number of recruited patients: NR; total number of excluded patients: 52 patients died and 2 were lost to follow-up	Blood samples were collected before performing the TST to avoid a possible boosting effect of the TST on the QFT-GIT test. The laboratory technicians did not know the results of the TST

continued

TABLE 10 Baseline characteristics of studies in immunocompromised patients: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
					Morbidity, *n* (%): acute myelogenous leukaemia 72 (30), acute lymphoblastic leukaemia 28 (11), chronic myelogenous leukaemia 4 (2), aplastic anaemia 17 (7), myelodysplastic syndrome 19 (8), non-Hodgkin's lymphoma 58 (24), Hodgkin's lymphoma 3 (1), multiple myeloma 38 (16), plasmacytoma 2 (1), others 3 (1) Comorbidity, *n* (%): diabetes mellitus 25 (10), hypertension 38 (16), chronic kidney disease 21 (9), ESRD with dialysis 1 (0.4), hepatitis 16 (7), HIV infection 0 (0), non-haematological malignancy 9 (4) Type of during-study treatment, *n* (%): ciclosporin 71 (29), ciclosporin–MTX 65 (27), ciclosporin–corticosteroid 8 (3), corticosteroid therapy 111 (46)		

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Haematopoietic stem cell transplantation recipients							
Lee 2014,[149] South Korea (high)	Aim: to test the hypothesis that HCT recipients who are QFT-TB positive develop active TB more frequently than QFT-TB-negative or indeterminate patients and to evaluate if the QFT-TB assay can predict active TB development in HCT recipients without any clinical risk factors for LTBI Setting: tertiary hospital based Design: prospective cohort study Follow-up: median (IQR) 1.3 (0.6–2.3) years Funding source: supported by a grant from the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning	Chest radiography, a sputum AFB smear and CT scan (pulmonary TB)	Inclusion criteria: adult patients admitted for allogeneic HCT Exclusion criteria: history of close contact with active TB, history of untreated or inadequately treated TB, radiographic evidence of old TB, refused informed consent, presence of active TB, presence of skin disease that precluded the TST (between January 2010 and December 2011) and paediatric HCT candidates (aged < 16 years)	Type of tests: IGRA (QFT-GIT) and TST Cut-off values/ thresholds: QFT-GIT: NR; TST: induration of ≥ 5 mm or ≥ 10 mm	Mean (SD) age: 42.3 (13.8) years Female, *n* (%): 183 (46.8) Race/ethnicity, *n* (%): Asian 409 (100) Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 353 (90.7) History of antiTB treatment, *n* (%): 0 Total incidence of active TB, *n/N* (%): 8/391 (2.04) Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): HCT recipients Comorbidity, *n* (%): acute or chronic graft-versus-host disease 151 (38.6); diabetes mellitus 32 (8.2); liver cirrhosis 4 (1.0); solid organ transplant 2 (0.5); HIV 0	Total number of recruited patients: 409; total number of excluded patients: 18	

continued

TABLE 10 Baseline characteristics of studies in immunocompromised patients: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Post-kidney transplantation							
Kim 2011,[116] South Korea (high)	Aim: to assess whether an ELISPOT assay is capable of predicting active TB development in KT recipients with negative TST results and without LTBI risk factors Setting: tertiary-care hospital Design: prospective cohort study Follow-up: median (IQR) 14 (8–19) months Funding source: basic Science Research Program through National Research Foundation funded by the Ministry of Education, Science and Technology (MEST) (grant 2008-E00136)	Symptoms/signs, sputum AFB smear and a CT scan	Inclusion criteria: KT patients aged ≥ 16 years with TST (< 10 mm) and without LTBI risk factors (history of close contact with TB case, abnormal chest radiography, history of untreated or inadequately treated TB, newly infected) Exclusion criteria: refusal of informed consent, presence of active TB, presence of skin disease that precluded TST, paediatric renal transplant candidates (aged < 16 years), TB risk factors and presence of any contraindication for KT (e.g. malignancy)	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): NR; TST: induration of ≥ 10 mm 48–72 hours after injection and in accordance with Korea Centers for Disease Control and Prevention guidelines	Age range: 40.4–46.0 years Female, *n* (%): 126 (46.3) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 215 (79.0) History of anti-TB treatment, *n* (%): 0 Total incidence of active, *n/N* (%): 4/272 (1.47) (incidence rate 0.83 per person-years, 95% CI 0.23 to 2.12 per person-years) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): glomerulonephritis 72 (26.5), hypertension 65 (23.9), diabetes mellitus 48 (17.6), unknown 58 (21.3), polycystic kidney 12 (4.4), other 11 (4.0) Comorbidity, *n* (%): NR	Total number of recruited patients: 324; total number of excluded patients: 52 – the total number of patients with valid results for both IGRA and TST was 242	The development of TB after KT was observed by attending surgeons, nephrologists and infectious disease specialists blind to the results of the ELISPOT assays, to avoid verification bias

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Haemodialysis in ESRD							
Anibarro 2012,[117] Spain (low)	Aim: to compare IGRA with TST in patients with ESRD after a TB outbreak at a dialysis centre Setting: outbreak investigation Design: prospective cohort study Follow-up: 18 months Funding source: University of Vigo and Sudoefeder (IMMUNONET-SOE1/P1/E014)	Microscopic examination of sputum and sputum culture	Inclusion criteria: all patients who attended the dialysis unit while index case was on duty Exclusion criteria: patients who had had a previous positive TST test	Type of tests: IGRA (QFT-GIT), TST Cut-off values/thresholds: IGRA (QFT-GIT): 0.35 IU/ml; TST: induration of ≥ 5 mm (a second test was performed 5 days later if the first TST was < 5 mm)	Mean (SD) age: 62 (16.8) years Female, *n* (%): 21 (40.4) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 7 (13.5) History of anti-TB treatment, *n* (%): NR Total incidence of active TB, *n* (%): 0 Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD 58 (100) Comorbidity, *n* (%): diabetes mellitus 8 (15.4)	Total number of recruited patients: 58; total number of excluded patients: 6	The second test was performed 5 days after the initial test but it is not stated when the result of the second test was read

continued

TABLE 10 Baseline characteristics of studies in immunocompromised patients: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Lee 2009,[118] Taiwan (high)	Aim: to compare QFT-G, T-SPOT.*TB* and TST in terms of their ability to diagnose LTBI in ESRD patients and to determine the prevalence of LTBI in ESRD patients compared with healthy control subjects, the risk factors for QFT-G and TST positivity and the predictive value of a positive QFT-G, T-SPOT.*TB* or TST for active TB disease over a 2-year period Setting: NR Study design: prospective, matched, double-cohort study Follow up: 2-year follow-up Funding source: National Health Research Institutes, Department of Health, Executive Yuan, Republic of China (NHRI-CN-CL-094-PP13) and Kaohsiung Veterans General Hospital, Kaohsuing, Taiwan (VGHKS95–012)	Asymptomatic cases were diagnosed by chest radiography and symptomatic cases were diagnosed with a sputum TB smear, culture and chest radiography	Inclusion criteria: patients with ESRD Exclusion criteria: NR	Type of tests: IGRA (QFT-G, T-SPOT.*TB*), TST (two step) Cut-off values/ thresholds: IGRA (QFT-G): according to analysis software, available for download from the Cellestis Ltd website; IGRA (T-SPOT.*TB*): NR; TST: ≥ 10-mm induration for ESRD patients and BCG-unvaccinated individuals, ≥ 15-mm induration for BCG-vaccinated, healthy individuals	Mean (range) age: 53.8 (34.4–77.7) years Female, *n* (%): 24 (37.5) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): Kaohsiung BCG vaccination, *n* (%): 53 (82.8) History of anti-TB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): ESRD Comorbidity, *n* (%): NR	Total number of recruited patients: 64; total number of excluded patients: 0	

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Sherkat 2014,[155] Iran (intermediate)	Aim: to compare the IGRA (T-SPOT.*TB*) and TST in the detection of LTBI in KT candidates and evaluate the agreement between the two tests Setting: hospital based Design: prospective cohort study Follow-up: 21 months (follow-up included 9 months of prophylactic treatment and 12 months post transplantation) Funding source: none	NR	Inclusion criteria: candidates for KT Exclusion criteria: active TB, history of previous TB or isoniazid prophylactic treatment, refusal to continue prophylactic treatment, symptoms of isoniazid-induced hepatitis or drug reaction	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: T-SPOT.*TB*: NR; TST: induration of ≥ 10 mm	Mean (SD) age: 44 (15.5) years Female, *n* (%): 15 (66) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 12 (27.3) History of anti-TB treatment, *n* (%): 0 Total incidence of active TB, *n/N* (%): 1/44 (2.27) Chest radiography (yes/no): NR Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD Comorbidity, *n* (%): dialysis 30 (68.2), hypertension 10 (22.7), diabetes 10 (22.7), obstructive uropathy 6 (13.6), polycystic kidney 6 (13.6), other renal etiologies 17 (38.6), other 3 (6.8)	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 10 Baseline characteristics of studies in immunocompromised patients: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Number of recruited and excluded study participants	Comments
Immune-mediated inflammatory diseases before antiTNF-α therapy							
Chang 2011,[119] South Korea (high)	Aim: to evaluate the usefulness of IGRA for the diagnosis of LTBI in arthritis patients who received TNF antagonists in South Korea Setting: hospital based Design: prospective cohort study Follow-up: 18 months (median) Funding source: IN-SUNG Foundation for Medical Research (CA98051)	Medical history (current symptoms, previous history of treatment for TB and recent history of contact with a case of active TB) and TST (according to the recommendation of the Korea Food and Drug Administration)	Inclusion criteria: patients with inflammatory arthritis including rheumatoid arthritis and ankylosing spondylitis who visited the facility to evaluate LTBI before starting TNF antagonists Exclusion criteria: active TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml; TST: induration of ≥ 10 mm after 48–72 hours	Median age: 39 years Female, *n* (%): 44 (41) Race/ethnicity, *n* (%): Asian Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 63 (59) History of anti-TB treatment, *n* (%): 4 (3.8) Total incidence of active TB, *n* (%): 1 (0.9%) (patient had active TB at recruitment and was excluded from the study) Chest radiography (yes/no): NR Clinical examination (yes/no): yes Morbidity, *n* (%): rheumatoid arthritis 46 (43), ankylosing spondylitis 61 (57) Comorbidity, *n* (%): NR	Total number of recruited patients: 108; total number of excluded patients: 1	Both the TST and QFT-GIT were performed on the same day as the screening examination in all patients before initiating TNF antagonists

AFB, acid-fast bacillus; CT, computerised tomography; HCT, haematopoietic stem cell transplant; IQR, interquartile range; KT, kidney transplant; MTX, methotrexate; NR, not reported; SD, standard deviation.

Exposure studies

Twenty-four newly identified studies[120–142,153] compared an IGRA test with the TST in immunocompromised people, relating test outcome to previous level of exposure. All studies within this group were therefore classed as having either a retrospective cohort or a cross-sectional design. Reasons for immunodeficiency (condition and procedure) varied across studies. We identified the following subpopulations: (1) HIV patients, (2) solid organ transplantation candidates, (3) post-kidney transplantation patients, (4) patients on haemodialysis for ESRD, (5) patients with immune-mediated inflammatory diseases before antiTNF-α therapy, (6) patients with hepatitis C and (7) lupus erythematosus patients. The included studies are described below according to these subpopulations. *Table 11* provides further details on these studies.

Three studies[125,136,153] assessed the test performance of different IGRA tests compared with that of the TST in patients with HIV. Chkhartishvili *et al.*[125] compared QFT-GIT and T-SPOT.*TB* with TST (≥ 5 mm) in HIV patients recruited from a national referral centre for HIV in Georgia, with the non-exposed group having no household member treated for TB and the exposed group having a household member treated for active TB. Mutsvangwa *et al.*[136] compared T-SPOT.*TB* with TST at the ≥ 10 mm cut-off value in HIV-positive household contacts of TB cases identified in a factory in Zimbabwe. The non-exposed control group consisted of contacts of factory workers without TB. Souza *et al.*[153] compared QFT-GIT with TST (≥ 5 mm) in adults living with HIV and/or acquired immune deficiency syndrome (AIDS) in outpatient sexually transmitted disease public clinics in a low TB incidence urban area (11.1 per 100,000 inhabitants). The rate of BCG vaccination across the three studies ranged from 76%[153] to 94%[125] and the proportion of women ranged from 28%[153] to 89%.[136] The median age was reported for only two studies and ranged from 38[125] to 40 years.[153]

Four studies compared either QFT-GIT[120,124,131] or T-SPOT.*TB*[130] with TST at the cut-off level of ≥ 5 mm,[124] ≥ 10mm[120,131] or both[130] in solid organ transplantation candidates. All four studies were hospital based. Two studies were undertaken in South Korea,[130,131] one in Iran[120] and one in Spain.[124] The mean age was 39.9 years,[120] 47 years,[131] 56.4 years[124] or not reported.[130] The proportion of women was close to 50% in two studies[120,131] and < 25% in one study.[124] One study did not report sex.[130] BCG vaccination was high in studies from Korea (78%[130] and 91%[131]) as well as in the study from Iran (91%)[120] but low in the Spanish study (31.6%).[124] Exposure to TB was universally defined as a history of (close) contact with active TB. Two studies also included newly acquired TB[130] or a history of active TB[130,131] as a risk factor for LTBI. The non-exposed groups consisted of participants without contact with or at a low risk of LTBI.

Hadaya *et al.*[128] and Kim *et al.*[132] compared one or more IGRA tests with the TST in patients post-kidney transplantation. Hadaya *et al.*[128] compared QFT-GIT, T-SPOT.TB and TST (≥ 5 mm) in the setting of a Swiss hospital and Kim *et al.*[132] compared QFT-GIT with TST (≥ 10 mm) in South Korean kidney transplant recipients. Exposure was defined as close contact with a TB patient or previous TB according to (1) chest radiography[128] or (2) a history of treated TB or abnormal chest radiography.[132]

Four studies[121,122,126,139] investigated the agreement between IGRA and TST tests in patients on haemodialysis for ESRD. Three studies[121,122,126] compared QFT-GIT with TST (≥ 10 mm) and one study[139] compared QFT-G with TST (≥ 10 mm). Chung *et al.*[126] additionally investigated the T-SPOT.*TB*. Three studies[121,122,126] reported the setting to be hospital based whereas one study[139] did not report the study setting. The rate of BCG vaccination of the study participants was low in the study from Saudi Arabia (14%)[121] and intermediate in the two studies from Turkey (49%[122] and 72%[139]) and the study from South Korea (67%).[126] The mean age of study participants was similar across all four studies (58,[121] 52,[122] 54[126] and 56[139] years) and the sex distribution within the studies was balanced (52%,[121] 50%,[122] 43%[126] and 53%[139] female). Exposure to TB was not well defined. Three studies[121,122,126] described exposure as (close) contact with a TB case whereas one study[139] specified the contact as household contact or working in the same room with the TB case. History of active TB was included as a risk factor in the exposure group in two studies.[126,139] The comparison group included people who were at low risk of LTBI.

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
HIV infection							
Chkhartishvili 2013,[125] Georgia (high)	Aim: to assess the performance of two commercially available IGRAs (QFT-GIT and T-SPOT.*TB*) compared with that of the TST for the diagnosis of LTBI in HIV-infected patients and to identify risk factors for LTBI in an effort to improve TB prevention and care among HIV patients Setting: national referral institution for HIV diagnosis, treatment and care Design: retrospective/ cross-sectional study Funding source: the US Civilian Research and Development Foundation award; the National Institutes of Health Fogarty International Center through the Emory AIDS International Training and Research Program award and the Emory–Georgia Tuberculosis Research Training Program award	Non-exposed: no household member treated for TB; exposed 1: household member treated for TB; exposed 2: NA	Inclusion criteria: age ≥ 18 years, confirmed HIV infection and ability to provide written informed consent Exclusion criteria: patients with a history of active TB disease	Type of tests: IGRA (QFT-GIT), IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (QFT-GIT): IFN-γ response to TB antigens minus the negative control was ≥ 0.35 IU/ml and also > 25% of the negative control, indeterminate if either the negative control was > 8 IU/ml or the positive control was < 0.5 IU/ml; IGRA (T-SPOT.*TB*): six or more spot-forming cells or twice the nil control, indeterminate if the nil control spot count was > 10 spot-forming cells or if the reading in the positive control was < 20 spot-forming cells; TST: induraton of ≥ 5 mm	Median (range) age: 38.0 (32.8–43.8) years Female, *n* (%): 81 (33.75) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 219 (94%) History of anti-TB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n* (%): HIV infection Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	Blood was drawn for the IGRAs prior to placement of the TST

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Mutsvangwa 2010,[136] Zimbabwe (high)	Aim: to test for LTBI using T-SPOT.*TB* and TST, correlate test results with TB exposure in household contacts of TB cases and assess the impact of HIV co-infection on test results in these contacts Setting: NR Design: retrospective cohort/cross-sectional study Funding source: the Wellcome Trust	Non-exposed: contact of index control (no TB); exposed 1: contact of index TB case; exposed 2: NA	Inclusion criteria: all consenting individuals over the age of 10 years living with the TB cases (index case household contacts) and those living with control subjects (no TB); TB cases were sampled from factories in Harare and control samples were sampled randomly from the same factories Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): NR; TST: induration of ≥ 10 mm (if < 10 mm second TST after 7–14 days)	Mean (range or SD) age: NR Female, *n* (%): 65 (89.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): sub-Saharan Africa BCG vaccination, *n* (%): 63 (86.0) History of anti-TB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n* (%): HIV infection Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	Persons performing and reading the assays were blind to all personal identifiers and TST results

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Souza 2014,[153] Brazil (intermediate)	Aim: to evaluate the added value of QFT-GIT over the TST for detecting LTBI among those living with HIV/AIDS and to explore the factors associated with a positive QFT-GIT and with discordant QFT-GIT/TST results Setting: outpatient clinics Design: retrospective cohort/cross-sectional study Funding source: Fundação de Apoio ā Pesquisa do Distrito Federal	Non-exposed: no history of contact with index case; exposed: history of contact with index case	Inclusion criteria: people with HIV/AIDS aged > 17 years who had not had a TST in the previous 5 weeks Exclusion criteria: patients with a history of other immunosuppressive conditions (severe AIDS-related opportunistic infections, acute viral infections, those undergoing any vaccination in the previous 2 months and those using immunosuppressive drugs), patients with present or past active TB and those with a history of a previous positive TST	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 UI/ml; TST: induration of ≥ 5 mm	Median (IQR) age: 40 (32–46) years Female, *n* (%): 85 (28.3) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 228 (76.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n* (%): HIV/AIDS 300 (100) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
SOT candidates							
Ahmadinejad 2013,[120] Iran (intermediate)	Aim: to compare the QFT and TST in the diagnosis of LTBI in SOT candidates (kidney, liver, lung) Setting: tertiary care teaching hospital Design: cross-sectional/ retrospective cohort study Funding source: Tehran University of Medical Sciences and Health Services grant	Non-exposed: no history of exposure to active TB; exposed 1: exposure history to active TB; exposed 2: NA	Inclusion criteria: SOT candidates referred to the transplant clinic Exclusion criteria: failure to return to the clinic to read the results of the TST within 5 days of the initial intradermal injection or unwillingness to continue the study at any stage	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): NR; TST: induration of ≥ 10 mm	Mean (SD) age: 39.9 (12.7) years Female, *n* (%): 76 (46.3) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 151 (92.1) History of antiTB treatment, *n/N* (%): 1/164 (0.6) Total incidence of active TB, *n/N* (%): 1/164 (0.6) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD 64 (39.0), chronic hepatic failure 97 (59.2), pulmonary failure 3 (1.8) Comorbidity, *n* (%): NA Type of during-study treatment, *n* (%): patients with positive TST received chemoprophylaxis with 300 mg of isoniazid for 9 months; immunosuppressive medication 24 (14.6)	Total number of recruited patients: 187; total number of excluded patients: 23 (dropouts)	For prevention of potential boosting effect of TST on QFT, blood sampling and PPD injection were carried out simultaneously for all patients

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Casas 2011,[124] Spain (low)	Aim: to compare the performance of the TST and the QFT-GIT test in detecting LTBI in patients with ESLD requiring LT Setting: hospital based Study design: retrospective/cross-sectional study Funding source: grants from the Spanish Ministry for Health and Consumer Affairs and the Carlos III Health Institute through the Fund for Health Investigations (PI070810, 2007–2010) and from the Carlos III Health Institute and Spanish Federation for Rare Diseases through the Spanish Network for Research in Infectious Diseases; research grant from the University of Barcelona	Non-exposed: no risk factors for TB; exposed 1: risk factors for TB (previous contact with TB, abnormal chest radiography, birth or prolonged residence in a country with a high TB burden, alcoholism, drug abuse, a previous stay in prison and involvement with health care); exposed 2: NA	Inclusion criteria: all patients with ESLD being considered for LT were invited to participate in the study Exclusion criteria: patients aged < 18 years, patients with a previous history of TB, patients who had recently been tested with the TST and patients with a known immunosuppressive condition	Type of tests: IGRA (QFT-GIT), TST (two step) Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml (the MTB-specific antigen tube minus the nil tube), indeterminate < 0.5 IU/ml (the mitogen tube minus the nil tube) or > 8.0 IU/ml (the nil tube) (plasma samples with indeterminate results were retested); TST: induration of ≥ 5 mm at 48–72 hours in accordance with the national transplant guidelines	Mean (SD) age: 56.4 (7.6) years Female, *n* (%): 23 (24.2) Race/ethnicity, *n* (%): Spanish 89 (93.7) Geographical origin, *n* (%): born or residing in a country with a high TB burden 6 (6.3) BCG vaccination, *n* (%): 30 (31.6) History of antiTB treatment, *n* (%): 0 Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): cirrhosis 52 (54.7), hepatocellular carcinoma 35 (36.8), other hepatopathies 8 (8.4) Comorbidity, *n* (%): diabetes mellitus 28 (29.5), chronic pulmonary obstructive disease 3 (3.2), renal failure 12 (12.6) Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 110; total number of excluded patients: 15 (previous TB infection, HIV infection, dropouts, antiTNF-α agents, incomplete IGRA results)	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Kim 2010,[130] South Korea (high)	Aim: to compare the results of T-SPOT.*TB* with those of the TST in renal transplant candidates before transplantation in a country with an intermediate TB burden[a] Setting: clinic based Design: retrospective/ cross-sectional study Funding source: Korea Research Foundation	Non-exposed: no LTBI group; exposed 1: (i) close contact with a person with TB within the last year, (ii) abnormal chest radiography, (iii) a history of untreated or inadequately treated TB or (iv) newly acquired infection (recent conversion of the TST to positive status); exposed 2: NA	Inclusion criteria: kidney transplant adult candidates before transplantation Exclusion criteria: if abnormal chest radiograph findings were observed, a sputum acid-fast bacilli smear and a CT scan were performed to rule out active pulmonary TB	Type of tests: IGRA (T-SPOT.*TB*), TST (≥ 5 mm), TST (≥ 10 mm) Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): as recommended by manufacturer; TST: induration of ≥ 10 mm 48–72 hours after injection	Mean (range or SD) age: NR Female, *n* (%): NR Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 163 (78.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): isoniazid for 9 months immediately after renal transplantation 5 (19)	Total number of recruited patients: 213; total number of excluded patients: 4 (*n* = 1 refusal, *n* = 1 active TB, *n* = 2 cancer)	All blood samples were collected before the TST to avoid the possible boosting effect of the TST on the ELISPOT assay

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Kim 2013,[131] South Korea (high)	Aim: to compare the results of the TST and QFT-GIT as methods for screening for LTBI and determine the agreement between the TST and QFT-GIT in renal transplant candidates before transplantation in a country with an intermediate TB burden[a] Setting: clinic based Study design: retrospective/cross-sectional study Funding source: grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea	Non-exposed: no LTBI group; exposed 1: (i) patients with a history of LTBI or active TB, (ii) patients with abnormal chest radiography findings consistent with previously healed TB and (iii) patients with a history of close contact with active pulmonary TB patients within the past year; exposed 2: NA	Inclusion criteria: kidney transplant adult candidates before transplantation Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/thresholds: IGRA (QFT-GIT): IFN-γ response of TB antigen minus that of the nil tube ≥ 0.35 IU/ml and ≥ 25% of the negative control value; TST: induration of ≥ 10 mm after 48–72 hours	Mean (range) age: 47 (20–69) years Female, *n* (%): 55 (43.6) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 115 (91.3) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD/haemodialysis 100 (79.4), peritoneal dialysis 12 (9.5), no dialysis 14 (11.1) Comorbidity, *n* (%): hypertension 60 (47.6), diabetes mellitus 31 (24.6) Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Post-kidney transplantation							
Hadaya 2013,[128] Switzerland (low)	Aim: to compare the diagnostic performance of the TST and two IGRAs (T-SPOT.*TB* and QFT-GIT) in renal transplant recipients under stable immunosuppression Setting: Geneva University Hospital Design: retrospective cohort/cross-sectional study Funding source: Ligue Pulmonaire Genevoise (a non-profit organisation)	Non-exposed: no risk for LTBI; exposed 1: risk for LTBI [chest radiography suggestive of previous infection (calcified granuloma or adenopathy, suggestive fibrotic scars) and/or close contact with TB patient]; exposed 2: NA	Inclusion criteria: aged > 18 years, able to provide informed consent, had a renal transplant at least 12 months before inclusion and having stable immunosuppression Exclusion criteria: treatment for acute rejection within the preceding 3 months and signs or symptoms of acute infection	Type of tests: IGRA (QFT-GIT), IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (QFT-GIT): according to manufacturer; IGRA (T-SPOT.*TB*): according to manufacturer; TST: ≥ 5 mm transverse diameter, measured 48–72 hours after injection	Mean (SD) age: 59.0 (13.2) years Female, *n* (%): 84 (42.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): high incidence of TB in country of origin 24 (12.0) BCG vaccination, *n* (%): 155 (77.5) History of antiTB treatment, *n* (%): active therapy 9 (4.5), LTBI treatment 12 (6.0) Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): renal transplant recipients Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): prednisone 88 (44.0), tacrolimus 127 (63.5), ciclosporin 41 (20.5), mycophenolate mofetil 159 (79.5), azathioprine 17 (8.5), sirolimus 12 (6.0)	Total number of recruited patients: 205; total number of excluded patients: 5 (indeterminate IGRAs)	Blood sampling for the two IGRAs was performed simultaneously

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Kim 2013,[132] South Korea (high)	Aim: to compare the QFT-GIT with the TST for screening for LTBI in kidney transplant recipients Setting: NR Design: retrospective cohort/cross-sectional study (with prospective part) Funding source: Korea Health Care Technology R&D project, Ministry for Health, Welfare and Family Affairs, Republic of Korea	Non-exposed: NR; exposed 1: history of treated TB; exposed 2: abnormal chest radiography	Inclusion criteria: kidney transplant recipients Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml and ≥ 25% in the presence of TB-specific antigen minus that of the nil tube; TST: induration of ≥ 10 mm at 48–72 hours after injection	Mean age: 44.7 ± 11.5 years Female, *n* (%): 41 (38) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): 3 (2.8) Total incidence of active TB, *n* (%): 1 (0.9) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): glomerulonephritis 19 (17.4); hypertensive nephrosclerosis 11 (10.1); diabetes mellitus 31 (28.4); unknown 34 (31.2); polycystic kidney disease 2 (1.8); other 12 (11.0) Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 109; total number of excluded patients: 4 with indeterminate QFT-GIT results (excluded for analysis)	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Haemodialysis in patients with ESRD							
Al Jahdali 2013,[121] Saudi Arabia (low)	Aim: to compare the performance of the QTF-GIT test and the TST for detecting LTBI among haemodialysis patients and to investigate the agreement between these two tests in the detection of TB infection in a population showing an intermediate TB prevalence Setting: outpatient haemodialysis unit, hospital based Design: retrospective cohort/cross-sectional study Funding source: none	Non-exposed: no high likelihood of LTBI; exposed 1: high likelihood of LTBI (contact with TB case, abnormal chest radiography, diabetes mellitus, immunosuppressant in the last 12 months, failed kidney transplant or BMI $\leq 20\,kg/m^2$); exposed 2: NA	Inclusion criteria: haemodialysis patients Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml for the relationship [(IFN-γ in the TB antigen tube)–(IFN-γ in the negative control tube)] – if the IFN-γ level was < 0.35 IU/ml in the TB antigen tube and the mitogen control was positive (≥ 0.5 IU/ml), the test was recorded as negative; TST: induration of ≥ 10 mm for LTBI – for results < 10 mm a second TST was carried out within 3–6 weeks (positive if either the first or second test showed a response of ≥ 10 mm)	Mean (SD) age: 58.42 (17.65) years Female, *n* (%): 103 (51.5) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 28 (14.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): haemodialysis patients Comorbidity, *n* (%): diabetic nephropathy 127 (63.5), kidney transplant failed 21 (10.5), NR 52 (26.0) Type of during-study treatment, *n* (%): immunosuppressant in the last 12 months 2 (1.0)	Total number of recruited patients: 215; total number of excluded patients: 15 (active TB)	IGRA blood was collected before the administration of the TST

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Ates 2009,[122] Turkey (intermediate)	Aim: to assess the efficacy of the QTF-GIT test for the detection of LTBI and determine the degree of agreement between the TST and QTF-GIT in haemodialysis patients Setting: outpatient haemodialysis hospital centres Design: retrospective cohort/cross-sectional study Funding source: grant from the University of Dicle	Non-exposed: no TB exposure; exposed 1: TB exposure; exposed 2: NA	Inclusion criteria: haemodialysis patients aged ≥ 18 years Exclusion criteria: patients diagnosed with active TB and receiving treatment for the last 12 months, those taking immunosuppressive medicine or those aged < 18 years	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): according to the QTF-GIT analysis software; TST: induration of ≥ 10 mm	Mean (SD) age: 51.9 (16.2) years Female, *n* (%): 137 (50.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 134 (48.72) History of antiTB treatment, *n* (%): 17 (7.4%) Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): haemodialysis Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 290; total number of excluded patients: 15 (rejected tests, improper blood sampling and unsuccessful phlebotomy)	Observers were blinded to the results of the TST

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Chung 2010,[126] South Korea (high)	Aim: to compare two IGRAs (QFT-GIT and T-SPOT.*TB*) simultaneously with the TST for diagnostic efficacy for LTBI in Korea, an intermediate TB burden country[a] Setting: medical centre Design: retrospective cohort/cross-sectional study Funding source: Gil Medical Centre	Non-exposed: low risk; exposed 1: high-risk group for LTBI consisting of patients with a history of close contact with TB patients, old TB lesions on chest radiography or a history of TB infection; exposed 2: NA	Inclusion criteria: haemodialysis patients with ESRD Exclusion criteria: patients who had taken empirical antiTB medications and patients taking antiTB medication for active TB infection	Type of tests: IGRA (QFT-GIT), IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (QFT-GIT): performed according to manufacturer's instructions; IGRA (T-SPOT.*TB*): as previously described; TST: induration of ≥ 10 mm (mean value of two measurements)	Mean (SD) age: 54.1 (14.4) years Female, *n* (%): 71 (42.5) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 111 (67.3) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): ESRD because of diabetes mellitus 67 (40.1), hypertension 18 (10.8), glomerulonephritis 12 (7.2), other 11 (6.6), unknown 59 (35.3) Comorbidity, *n* (%): history of cancer 12 (7.2), cardiac disease 46 (27.5), cerebrovascular accident 13 (7.8), history of TB infection 21 (12.6) Type of during-study treatment, *n* (%): immunosuppressant medication 9 (5.4)	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Seyhan 2010,[139] Turkey (intermediate)	Aim: to compare the results of the QFT-G with those of the TST for detecting LTBI in haemodialysis patients Setting: NR Design: retrospective cohort/cross-sectional study Funding source: none	(1) History of active TB – non-exposed: no previous history of active TB; exposed 1: previous history of active TB (2) Contact of the patient with TB – non-exposed: no previous contact of the patient with TB cases; exposed 1: previous contact of the patient with TB cases (details of any contact with a person having TB, individuals who had household contact with or who had worked in the same rooms as patients with smear-positive pulmonary TB, elapsed time after the contact) (3) Chest radiograph changes – non-exposed: no chest radiography changes consistent with old TB; exposed 1: chest radiography changes consistent with old TB	Inclusion criteria: haemodialysis patients Exclusion criteria: suspicion of active TB infection, use of immunosuppressive drugs and other known immunodeficiency status (HIV infection, malignancy)	Type of tests: IGRA (QFT-G), TST Cut-off values/ thresholds: IGRA (QFT-G): IFN-γ $\geq$ 0.35 IU/ml in the TB antigen tube minus the negative control tube; TST: induration of $\geq$ 10 mm	Mean age: 56.2 $\pm$ 15.3 years Female, *n* (%): 53 (53) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 72 (72) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	Blood was collected before TST placement. Those with an initial induration of < 10 mm were administered a second TST 1 week later to cause a potential booster response. Results from the two-step testing were used in all further analyses

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Immune-mediated inflammatory diseases before antiTNF-α therapy							
Casas 2011,[123] Spain (low)	Aim: to assess the prevalence of LTBI obtained by the whole blood-based QFT-GIT and the TST in patients with immune-mediated inflammatory diseases and to determine if QFT-GIT performs in the same way as in healthy people Setting: outpatient clinics Design: retrospective cohort/cross-sectional study Funding source: the first author received a research grant from the University of Barcelona (October 2006–January 2010). This study was supported by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III-FEDER, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008)	Non-exposed: no risk factors for TB infection; exposed 1: risk factors for TB infection (birth or residence for ≥ 6 months in a high TB incidence country, TB contact, previous prison stay, intravenous drug abuse, health-care worker, abnormal chest radiography and history of past TB); exposed 2: NA	Inclusion criteria: patients with immune-mediated inflammatory diseases before antiTNF-α therapy Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/thresholds: IGRA QFT-GIT): according to manufacturer, indeterminate results were retested; TST: induration of ≥ 5 mm at 48–72 hours	Mean (SD) age: 49.1 (12.9) years Female, *n* (%): 109 (50.9) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): born in a high TB incidence country 16 (7.5) BCG vaccination, *n* (%): 56 (26.2) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity, *n* (%): rheumatoid arthritis 91 (42.5), cutaneous psoriasis 57 (26.6), spondyloarthropathies 29 (13.6), psoriatic arthropathy 21 (9.8), IBD 14 (6.5), other 2 (0.9) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): immunosuppressive treatment 163 (76.2), corticosteroids 91	Total number of recruited patients: 323; total number of excluded patients: 9 (*n* = 2 no immune-mediated inflammatory disease, *n* = 7 problems with QFT-GIT plasma sample storage)	

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
					(42.5), methotrexate 91 (42.5), leflunomide 36 (16.8), ciclosporin A 22 (10.3), azathioprine/efalizumab 13 (6.1)		
Costantino 2013,[127] France (low)	Aim: to compare TST and IGRA results in screening for LTBI in a large population of patients with chronic inflammatory arthritis requiring biological treatment and to investigate predictive factors of the results of these two tests, with special attention paid to indeterminate IGRA results Setting: rheumatology department of Nancy University Hospital Design: retrospective cohort/cross-sectional study Funding source: NR	Non-exposed: no CRFs of LTBI; exposed 1: CRFs of LTBI (history of active TB treated before 1970 or not treated for at least 6 months including 2 months with a combination of rifampicin and pyrazinamide, close contact with a patient with active TB and chest radiography suggestive of previous TB infection); exposed 2: NA	Inclusion criteria: patients with rheumatoid arthritis and spondyloarthritis requiring TNF antagonists Exclusion criteria: patients with previous antiTB chemoprophylaxis	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): ≥ 6 spots, indeterminate if the negative control spot count yielded > 10 spots or if the positive control spot count yielded < 20 spots; TST: induration of ≥ 5 mm	Mean (range) age: 51.0 (39.0–59.0) years Female, *n* (%): 321 (57.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): birth in endemic zone of TB 52 (9.2) BCG vaccination, *n* (%): 439 (78.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): rheumatoid arthritis 293 (52.0), spondyloarthritis 270 (48.0) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): DMARDs 277 (49.2), corticosteroids 254 (45.1), NSAIDs 255 (45.4)	Total number of recruited patients: NR; total number of excluded patients: NR	To avoid any potential boosting effect of the TST on the IGRA results, all T-SPOT.*TB* assays were performed before initiating the TST

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Hsia 2012,[129] USA (low)	Aim: to evaluate the performance of an IGRA compared with the standard TST as a screening tool for LTBI prior to the initiation of antiTNF therapy in patients with autoimmune inflammatory diseases Setting: NR Design: retrospective cohort/cross-sectional study Funding source: Johnson & Johnson, honoraria from Genentech, Pfizer, Celgene, Corrona, Amgen, Bristol-Myers Squibb and Janssen	Non-exposed: North America; exposed 1: Western Europe; exposed 2: Asia; exposed 3: Eastern Europe; exposed 4: Latin America	Inclusion criteria: no history of latent/active TB prior to screening (except in the GO-AFTER trial, which allowed the inclusion of patients with a history of latent TB who had been treated within the last 3 years) and having no signs or symptoms of active TB or no recent close contact with anyone with active TB. All patients were required to have a chest radiograph, obtained within 3 months before the first dose of study agent, that showed no evidence of active TB or old inactive TB Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): according to manufacturer; TST: according to the local country guidelines for defining an immunosuppressed host or induration of ≥ 5 mm	Mean (SD) age: 48.58 (12.6) years Female, *n* (%): 1515 (65.7) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): North America 962 (41.8), Western Europe 440 (19.1), Eastern Europe 432 (18.8), Latin America 203 (8.8), Asia 266 (11.6) BCG vaccination, *n* (%): 788 (34.2) History of antiTB treatment, *n* (%): 317 (13.8) Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): rheumatoid arthritis 1542 (67.0), psoriatic arthritis 405 (17.6), ankylosing spondylitis 356 (15.5) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): methotrexate 571 (24.8), corticosteroids 1000 (43.4)	Total number of recruited patients: 2303; total number of recruited patients: NR	

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Kleinert 2012,[133] Germany (low)	Aim: to compare the utility of IGRAs and the TST in LTBI screening in a large cohort of patients with rheumatic diseases receiving immunosuppressive therapy Setting: hospital based Design: retrospective cohort study Funding source: Abbott, Pfizer, Roche and Wyeth, Chugai, Cellestis, Oxford Immunotec, Pharmore and Roche	Non-exposed: none of the CRFs present; exposed 1: a CRF defined as the presence of at least one of these three risk factors: (i) history of previous TB, (ii) close contact with a patient with TB or (iii) chest radiography suggestive of LTBI; exposed 2: NA	Inclusion criteria: patients with rheumatic diseases Exclusion criteria: NR	Type of tests: IGRA (QFT-G), IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (QFT-G): NR; IGRA (T-SPOT.*TB*): ≥ 6 spots; TST: induration of ≥ 5 mm	Mean age range: 50.8–59.5 years Female, *n* (%): 937 (61.3) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 204 (13.3) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): rheumatoid arthritis 852 (55.7), ankylosing spondylitis 294 (19.2), psoriatic arthritis 215 (14.0), undifferentiated spondyloarthropathy 92 (6.0), various other rheumatological disorders 76 (5.0) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): immunosuppressive therapy (not specified)	Total number of recruited patients: NR; total number of excluded patients: none	All patients received one type of IGRA, either T-SPOT.*TB* or QFT-G, depending on what was available in the corresponding laboratory

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Laffitte 2009,[134] Switzerland (low)	Study aim: to determine the frequency of LTBI in a population of patients with psoriasis before antiTNF treatment, compare the TST with T-SPOT.*TB* for detecting LTBI evaluate the tolerance and effectiveness of treatment for LTBI for those on antiTNF therapy Setting: hospital based Study design: retrospective cohort/ cross-sectional study Funding source: NR	Non-exposed: no probable LTBI; exposed 1: probable LTBI defined as having a history of definite exposure to a case of active TB and/or chest radiography suggestive of previous TB infection (granulomas, calcified adenopathy) and/or originating from a high-incidence country (defined as > 40 cases in 100,000 per year); exposed 2: NA	Inclusion criteria: patients with moderate to severe psoriasis qualifying for antiTNF-α therapy Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): NR; TST: induration of ≥ 5 mm or ≥ 10 mm	Mean (range) age: 48 (17–74) years Female, *n* (%): 15 (30) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): high TB incidence in country of origin 10 (20) BCG vaccination, *n* (%): 45 (90) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): 0 Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): psoriasis Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): 12 patients treated for LTBI (9 with rifampicin and 3 with isoniazid) before antiTNF therapy	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Maritsi 2011,[135] UK (low)	Aim: to describe the findings of the QFT-GIT test when applied to a paediatric rheumatology population and to assess the efficacy of this test compared with the methods previously used for the exclusion of TB infection prior to starting antiTNF-α treatment Setting: Paediatric Rheumatology Centre Design: retrospective case study Funding source: None	Non-exposed: low-risk group; exposed 1: high-risk group [TB risk evaluation was performed using the questionnaire formulated by the US Pediatric Tuberculosis Collaborative Group (2004)[193]]; exposed 2: NA	Inclusion criteria: children on infliximab since 2007 Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): NR; TST: NR	Median (range) age: 8.9 (1.5–13) years Female, *n* (%): 12 (52.1) Race/ethnicity, *n* (%): Caucasian (55), Afro-Caribbean (19), Asian (26) Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 5 (22) History of antiTB treatment, *n* (%): 5 (22) Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): no Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): methotrexate 5 (22), infliximab 23 (100)	Total number of recruited patients: 27; total number of excluded patients: 4 (no record of the QFT test)	Authors suggested that the results for the QFT-GIT are reported as positive, negative and indeterminate

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Papay 2011,[137] Austria (low)	Aim: to evaluate the impact of immune-modulatory treatment on results from the TST and IGRA in IBD patients before starting therapy with a biological agent Setting: outpatient clinic Design: retrospective cohort/cross-sectional study Funding source: NR	Non-exposed: NR; exposed 1: from a high-prevalence country; exposed 2: history of contact with active TB; exposed 3: chest radiography indicative of LTBI	Inclusion criteria: IBD patients Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml; TST: people with immunomodulators – induration of ≥ 5 mm, people with IBD – induration of > 10 mm	Mean age at screening: 36.6 ± 11.3 years Female, *n* (%): 107 (51.4) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): all subjects underwent BCG vaccination during childhood History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): medically confirmed active TB 1 (0.5) Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): Crohn's disease 152 (73.1), ulcerative colitis 56 (26.9) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): immunotherapy	Total number of recruited patients: 208; total number of excluded patients: NR	

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Ramos 2013,[138] Spain (low)	Aim: to evaluate the performance of QFT-GIT compared with the TST for the diagnosis of LTBI in patients with immune-mediated inflammatory disease before TNF-α antagonist therapy and evaluate the impact of immunosuppressive therapy on QFT-GIT and TST performance in different immune-mediated inflammatory diseases Setting: outpatient infectious diseases clinic of a university hospital Design: retrospective cohort/cross-sectional study Funding source: grants from Conselleria de Sanidad (051/2007) and FIS (PI08/90778)	Non-exposed: not born in a TB-endemic area/no contact with TB patients; exposed 1: born in a TB-endemic area/ contact with TB patients; exposed 2: NA	Inclusion criteria: all adult (aged ≥ 15 years) candidates for antiTNF-a therapy who attended the clinic Exclusion criteria: NR	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): ≥ 0.35 IU/ml, indeterminate if negative control ≥ 8.0 IU/ml or positive control < 0.5 IU/ml or if IFN-γ level ≥ 0.10 IU/ml but < 0.35 IU/ml; TST: induration of > 5 mm	Median (range) age: 52 (16–82) years Female, *n* (%): 73 (47.7) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): born in a TB-endemic area 8 (5.2) BCG vaccination, *n* (%): 29 (19) History of antiTB treatment, *n* (%): 5 (3.3) Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): rheumatoid arthritis 53 (43.6), psoriasis/ psoriatic arthritis 45 (29.4), IBD 25 (16.3), spondyloarthropathy 22 (14.4), severe hidradenitis 3 (2.0), systemic lupus erythematosus 2 (1.3), polymyositis 1 (0.6), sarcoidosis 1 (0.6), mixed connective tissue disease 1 (0.6) Comorbidity, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	The QFT assay and TST were performed simultaneously in a blinded fashion

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
					Type of during-study treatment, *n* (%): immunosuppressive drug 91 (59.5) [methotrexate 57 (37.3), corticosteroids 28 (18.3), leflunomide 21 (13.7), azathioprine 19 (12.4), ciclosporin 6 (3.9)]		
Vassilopoulos 2011,[142] Greece (low)	Aim: to compare the latest IGRAs (QFT-GIT and T-SPOT.*TB*) and the TST for LTBI diagnosis in rheumatic patients starting antiTNF treatment Setting: outpatient rheumatology clinic of Hippokration General Hospital Design: retrospective cohort study/cross-sectional study Funding source: supported in part by research grants from the Hellenic Society for Rheumatology and the Special Account for Research Grants, National and Kapodistrian University of Athens, Athens, Greece	(1) History of TB contact – non-exposed: no history of previous TB contact; exposed 1: history of previous TB contact (2) Chest radiography – non-exposed: chest radiography without signs suggestive of old TB; exposed 1: chest radiography suggestive of old TB (3) Risk factor for TB – non-exposed: no risk factor for TB; exposed 1: any risk factor for TB (≥ 1 risk factor) including aged > 50 years, chest radiography suggestive of old/healed TB, contact with a person with TB and birth or residence in a country with a high TB prevalence (non-Greek nationality)	Inclusion criteria: patients with various rheumatic diseases who were seen at the outpatient rheumatology clinic of Hippokration General Hospital and were scheduled for antiTNF treatment Exclusion criteria: patients with active TB, a history of treatment with antiTB agents including isoniazid for LTBI or a history of previous treatment with antiTNF agents or other biological agents	Type of tests: IGRA (QFT-GIT), IGRA (T-SPOT.*TB*), TST Cut-off values/thresholds: IGRAs: NR; TST: induration of ≥ 5 mm	Mean age: 52 ± 16 years Female, *n* (%): 90 (58) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): 81 (76) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): NR Comorbidity, *n* (%): 15 (21.4) Type of during-study treatment, *n* (%): immunosuppressive therapy (DMARDs/steroids) 98 (63) [DMARDs 80 (52), steroids 66 (43)]	Total number of recruited patients: 157; total number of excluded patients: 2 (indeterminate QFT-GIT results from the analysis: spondyloarthropathy related to ulcerative colitis on high-dose methylprednisolone)	The blood draw for both IGRAs was performed just prior to TST application to avoid potential interference with the IGRA results

continued

TABLE 11 Baseline characteristics of studies in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Hepatitis C							
Shen 2012,[140] China (high)	Aim: to evaluate the diagnostic value of ELISPOT measuring interferon-γ in hepatitis C patients with LTBI Setting: university hospital Design: retrospective study Funding source: none	Non-exposed: no history of TB exposure and no clinical symptoms ($n = 39$); exposed 1: history of exposure to TB (suspected of having TB but no symptoms, $n = 31$); exposed 2: NA	Inclusion criteria: hepatitis patients: TB exposure group – patients who had a history of exposure to TB without a clinical diagnosis of TB and with obvious clinical symptoms; non-TB exposure group – patients who had no history of exposure to TB and no clinical symptoms; TB group – patients who were clinically diagnosed with TB and who had apparent clinical symptoms Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): NR; TST: induration of ≥ 5 mm	Mean age: TB exposure group ($n = 40$) 42.9 ± 18.6; no TB exposure group ($n = 39$) 37.8 ± 17.6 Female, *n* (%): TB exposure group 37 (47); no TB exposure group 17 (45) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): hepatitis C Comorbidity, *n* (%): heart disease, diabetes mellitus, liver cirrhosis, solid tumour, chronic renal failure Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Nos of recruited and excluded study participants	Comments
Lupus erythematosus							
Takeda 2011,[141] Japan (low)	Study aim: to evaluate whether QFT-2G (QFT-G) is useful in detecting LTBI in systemic lupus erythematosus patients Setting: hospital based Design: retrospective cohort/cross-sectional study Funding source: NR	Non-exposed: without risk of LTBI; exposed 1: with risk factors for LTBI [history of household TB contact, chest radiography suggestive of previous TB (nodules, fibrotic scars, calcified granulomas, basal thickening), history of active TB)]; exposed 2: NA	Inclusion criteria: systemic lupus erythematosus patients and those with non-systemic lupus erythematosus connective tissue disease Exclusion criteria: NR	Type of tests: IGRA (QFT-2G), TST Cut-off values/ thresholds: IGRA (QFT-2G): ≥ 0.35 IU/ml; TST: induration of ≥ 10 mm	Mean (SD) age: 38.3 (15.2) years Female, *n* (%): 58 (81.7) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): NR BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): systemic lupus erythematosus Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): corticosteroids 37 (52.1), immunosuppressive drugs 19 (26.8), prednisolone pulse therapy 2 (2.8), NSAIDs or no therapy 13 (18.3)	Total number of recruited patients: NR; total number of excluded patients: NR	

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CRF, compound risk factor; CT, computerised tomography; DMARD, disease-modifying antirheumatic drug; ESLD, end-stage liver disease; GO-AFTER, Golimumab in Patients with Active Rheumatoid Arthritis after Treatment with Tumor Necrosis Factor α Inhibitors; IBD, inflammatory bowel disease; ID, identification; LT, liver transplant; NA, not applicable; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; R&D, research and development; SD, standard deviation; SOT, solid organ transplant.

a By our definition this is a high-incidence country.

Patients with immune-mediated inflammatory diseases before antiTNF-α treatment were recruited in nine studies[123,127,129,133–135,137,138,142] comparing IGRA with TST tests. The combination of tests investigated varied greatly among the studies. Three studies[123,129,138] compared QFT-GIT with TST (≥ 5 mm) with one study[142] additionally including the T-SPOT.*TB*. One study[135] compared the TST with QFT-GIT but did not provide the threshold for a positive TST test, one study[137] compared QFT-GIT with the TST test at two different thresholds (≥ 5 mm and ≥ 10 mm) for different subgroups of patients, one study[133] compared QFT-G with the T-SPOT.*TB* and TST (≥ 5 mm), and two studies compared the T-SPOT.*TB* with the TST at only the ≥ 5 mm threshold[127] or at two different thresholds (≥ 5 mm and ≥ 10 mm).[134] All studies were undertaken in low TB incidence countries in either Europe[123,127,133–135,137,138,142] or the USA[129] and all studies were hospital based. BCG vaccination was low in studies undertaken in Spain (26%[123] and 19%[138]), the USA (34%),[129] Germany (13%)[133] and the UK (22%)[135] but was higher in studies from France (78%)[127] and Greece (76%),[142] and considerably higher in studies from Switzerland (90%)[134] and Austria (100%).[137] Male and female participants were generally well balanced in the studies, with two possible exceptions: the study by Laffitte *et al.*[134] recruited a population with only 30% women and in the study by Hsia *et al.*[129] 66% of the participants were women. One study[135] investigated children with a median age of 8.9 years whereas the participants' mean age in the remaining studies ranged from 37 years[137] to 52 years.[142] Exposure to TB was not well defined in any of the studies. High risk of LTBI was described as a history of contact with a TB case in the majority of studies.[123,127,133–135,137,138,142] Additional risk factors reported were origin or residence in a high-incidence country[129,134,137,138,142] and a history of active TB.[123,127,133] The non-exposed group was generally described as having no history of TB contact.

Shen *et al.*[140] compared a T-SPOT.*TB* test with the TST (≥ 5 mm) in hepatitis C patients in a university hospital in China. The mean age of participants was 40 years and 47% were women. BCG vaccination was not reported in this study and exposure was loosely defined as a history of exposure compared with no exposure to TB.

Takeda *et al.*[141] evaluated the agreement between the QFT-2G (QFT-G) and the TST (≥ 10 mm) in a hospital in Japan in patients with lupus erythematosus. The mean age of participants was 38 years and 82% were women. BCG vaccination of participants was not reported in this study and exposure to TB was defined as a household TB contact. This was combined with other LTBI risk factors and compared with a group without LTBI risk factors.

Study quality

Incidence of active tuberculosis

Of the eight included incidence studies[114–119,149,155] concerning immunocompromised patients identified since the publication of CG117,[10] one [116] had a low ROB rating, three[115,117,149] had a moderate ROB rating and four[114,118,119,155] had a high ROB rating. Potential ROB because of confounding was noted in five studies.[114,117–119,155] Overall, in most of the studies the study design, study attrition, statistical analysis and reporting was appropriate. *Table 12* provides further details of the ROB assessment.

Exposure levels

Of the 24 included exposure studies[120–142,153] concerning immunocompromised patients identified since the publication of CG117,[10] 19 studies[120,122–126,128–136,140–142,153] were identified as being of low quality and the remaining five studies[121,127,137–139] were rated as being of moderate quality. However, all studies failed to blind the test results from exposure and only two studies[126,139] provided an adequate description of exposure. *Table 13* provides further details of the ROB assessment.

TABLE 12 Summary assessment of ROB for included incidence studies in immunocompromised patients

Study ID (burden)	Study design	Study participation (risk of selection bias)	Study attrition (risk of selection bias)	Prognostic factor measurement (risk of exposure measurement bias)	Outcome/construct measurement (ROB in misclassification of individuals in relation to construct validity groups)	Study confounding (ROB from confounding)	Statistical analysis and reporting (ROB from analysis and selective reporting)	Total ROB (high, moderate, low)
Anibarro 2012[117] (low)	Low	Low	Low	Moderate	Moderate	High	Low	Moderate
Chang 2011[119] (high)	Low	Moderate	Low	Moderate	High	High	Low	High
Elzi 2011[114] (low)	High	High	Low	Low	Moderate	High	Low	High
Kim 2011[116] (high)	Low	Low	Low	Low	Low	Moderate	Low	Low
Lee 2009[118] (high)	Low	High	Low	Low	Moderate	High	Low	High
Lee 2014[149] (high)	Low	High	Moderate	Moderate	Moderate	Low	Low	Moderate
Moon 2013[115] (high)	Low	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate
Sherkat 2014[155] (intermediate)	Low	High	High	Moderate	High	High	Moderate	High

ID, identification.
Source: adapted from Hayden *et al.*[90]

TABLE 13 Summary assessment of ROB for the included exposure studies in immunocompromised patients

Study ID (burden)	Recruitment of subjects [consecutive (yes), arbitrary or unreported (no)]	Blinding of test results from exposure [blinded (yes), not blinded or unreported (no)]	Description of index test and threshold [adequate (yes), inadequate or unreported (no)]	Definition and description of exposure [adequate (yes), inadequate or unreported (no)]	Sample attrition [adequate (yes),[a] inadequate or unreported (no)]	Overall quality score of satisfactory features[b]
Ahmadinejad 2013[120] (intermediate)	Yes	No	No	No	No	Low
Al Jahdali 2013[121] (low)	Yes	No	Yes	No	Yes	Moderate
Ates 2009[122] (intermediate)	No	No	No	No	No	Low
Casas 2011[123] (low)	No	No	No	No	Yes	Low
Casas 2011[124] (low)	Yes	No	Yes	No	No	Low
Chkhartishvili 2013[125] (high)	No	No	Yes	No	Yes	Low
Chung 2010[126] (high)	No	No	No	Yes	Yes	Low
Costantino 2013[127] (low)	Yes	No	Yes	No	Yes	Moderate
Hadaya 2013[128] (low)	No	No	No	No	Yes	Low
Hsia 2012[129] (low)	No	No	No	No	Yes	Low
Kim 2010[130] (high)	Yes	No	No	No	Yes	Low
Kim 2013[131] (high)	No	No	Yes	No	Yes	Low
Kim 2013[132] (high)	No	No	Yes	No	No	Low
Kleinert 2012[133] (low)	No	No	No	No	Yes	Low
Laffitte 2009[134] (low)	Yes	No	No	No	Yes	Low
Maritsi 2011[135] (low)	Yes	No	No	No	No	Low

Study ID (burden)	Recruitment of subjects [consecutive (yes), arbitrary or unreported (no)]	Blinding of test results from exposure [blinded (yes), not blinded or unreported (no)]	Description of index test and threshold [adequate (yes), inadequate or unreported (no)]	Definition and description of exposure [adequate (yes), inadequate or unreported (no)]	Sample attrition [adequate (yes),[a] inadequate or unreported (no)]	Overall quality score of satisfactory features[b]
Mutsvangwa 2010[136] (high)	No	No	No	No	Yes	Low
Papay 2011[137] (low)	Yes	No	Yes	No	Yes	Moderate
Ramos, 2013[138] (low)	Yes	No	Yes	No	Yes	Moderate
Seyhan 2010[139] (intermediate)	No	No	Yes	Yes	Yes	Moderate
Shen 2012[140] (high)	No	No	Yes	No	Yes	Low
Souza 2014[153] (intermediate)	Yes	Yes	No	No	No	Low
Takeda 2011[141] (low)	No	No	Yes	No	Yes	Low
Vassilopoulos 2011[142] (low)	Yes	No	No	No	Yes	Low

ID, identification.
a ≥ 90% of participants were included in the follow-up analysis (yes response) and < 90% were classified as 'no response'.
b Studies with one or two 'yes' ratings = low quality; studies with three 'yes' ratings = moderate quality; studies with four or five 'yes' ratings = high quality.
Source: adapted from Dinnes *et al.*[44] The item 'study design' was removed from the original checklist as all studies were considered to be retrospective; furthermore, the item 'sample attrition' was added.

Comparative performance of tests (diagnostic accuracy indices for identifying latent tuberculosis infection)

Incidence of active tuberculosis

Ratios of cumulative incidence ratios

This section included eight newly identified studies (*Table 14*).[114–119,149,155] Of these, R-CIRs were not available for four studies[114,116,117,119] because of missing incidence data for one or both compared tests. Of the remaining four studies, R-CIRs in three studies comparing IGRAs (QFT-G/GIT or T-SPOT.*TB*) with the TST in haematopoietic stem cell transplant candidates[115] and haemodialysis ESRD patients[118,155] were not statistically significant, rendering these results inconclusive (wide 95% CIs). Only one study,[149] which was conducted in haematopoietic stem cell transplant recipients, showed that QFT-GIT performed significantly better than the TST (at ≥ 5 mm or ≥ 10 mm) in identifying people with LTBI (TST at ≥ 5 mm: R-CIR 9.71, 95% CI 1.71 to 55.15; TST at ≥ 10 mm: R-CIR 5.85, 95% CI 1.05 to 32.70). A meta-analysis of R-CIRs could not be performed because of differences in the study populations and tests used.

Sensitivity and specificity

This section included eight newly identified studies.[114–119,149,155] The study by Anibarro *et al.*[117] did not report test performance parameters of sensitivity and specificity. Across the remaining seven studies there was wide variability and the absence of a clear pattern in the estimates of sensitivity (IGRA/TST range 0–100%) (*Figures 25* and *26*) and specificity (IGRAs range 50–88%; TST range 37–93%) (*Figures 27* and *28*). Some or all of this variation was the result of zero count events (unstable estimates) and underlying differences in study populations/conditions and TST thresholds. No meta-analysis was performed given the observed heterogeneity.

Exposure levels

Ratios of diagnostic odds ratios

This section included 26 studies: two studies[174,180] from CG117[10] and 24 more recent studies[120–142,153] (*Table 15*). The association between the screening test results and the risk of LTBI/exposure measured using the R-DOR (IGRA vs. TST) in individual studies ranged from 0.07[131] to 8.45.[140] R-DORs for three studies[120,132,135] could not be estimated because of missing data.

The forest plot analysis of R-DORs from the remaining 21 studies is stratified according to specific conditions/procedures (HIV infection, solid organ transplantation candidates, post-kidney transplantation, haemodialysis – ESRD, immune-mediated inflammatory diseases before antiTNF-α therapy, hepatitis C and lupus erythematosus) (*Figure 29*). There was a significant amount of heterogeneity across all subgroups of participants except for those with haemodialysis in whom IGRA (QFT-GIT) was more strongly associated with exposure groups than TST 10 mm (pooled R-DOR 2.53, 95% CI 1.48 to 4.34; $I^2 = 40\%$). Similarly, in participants with hepatitis C, IGRA (T-SPOT.*TB*) outperformed TST 5 mm in detecting LTBI (R-DOR 8.45, 95% CI 3.71 to 19.24).

TABLE 14 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – incidence studies

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Anibarro 2012,[117] Spain (low)	Number of test results: QFT-GIT 52; TST 52 Test (+/–): QFT-GIT 18/34; TST ≥ 5 mm 11/41 Number of indeterminate results: QFT-GIT 0; TST 0 Number lost to follow-up: 4	QFT-GIT: SN NR; SP NR; PPV NR; NPV 100 (89.28 to 100)	TST ≥ 5 mm: SN NR; SP NR; PPV NR; NPV 100 (89.28 to 100)	QFT-GIT: CI (+) NR; CI (–) 0/32 (0.00); CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 5 mm: CI (+) NR; CI (–) 0/32 (0.00); CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 5 mm) NR; R-IDRR (QFT-GIT vs. TST ≥ 5 mm) NR
Chang 2011,[119] South Korea (high)	Number of test results: QFT-GIT 100; TST 107 Test (+/–): QFT-GIT 36/64; TST ≥ 10 mm 36/71 Number of indeterminate results: QFT-GIT 7; TST 0 Number lost to follow-up: 0	QFT-GIT: SN NR; SP 100 (94.8 to 100); PPV NR; NPV 100 (94.8 to 100)	TST ≥ 10 mm: SN NR; SP 77.14 (66.05 to 85.41); PPV 0/16 (CI 0.0); NPV 100 (93.4 to 100)	QFT-GIT: CI (+) NR; CI (–) 0/64 (0.00); CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 10 mm: CI (+) 0/16 (0.00); CI (–) 0/54 (0.00); CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 10 mm) NR; R-IDRR (QFT-GIT vs. TST ≥ 10 mm) NR
Elzi 2011,[114] Switzerland (low)	Number of test results: T-SPOT.*TB* 43; TST 44 Test (+/–): T-SPOT.*TB* 25/18; TST ≥ 5 mm 22/22 Number of indeterminate results: T-SPOT.*TB* 21; TST 0 Number lost to follow-up: NR	T-SPOT.*TB*: SN 58.14 (43.33 to 71.62); SP NR; PPV NR; NPV NR T-SPOT.*TB* and TST ≥ 5 mm: SN 65.91 (51.14 to 78.12); SP NR; PPV NR; NPV NR	TST ≥ 5 mm: SN 50.00 (35.83 to 64.17); SP NR; PPV NR; NPV NR	T-SPOT.*TB*: CI (+) NR; CI (–) NR; CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR T-SPOT.*TB* and TST ≥ 5 mm: CI (+) NR; CI (–) NR; CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 5 mm: CI (+) NR; CI (–) NR; CIR NR; IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR (T-SPOT.*TB* vs. TST ≥ 5 mm) NR; R-IDRR (T-SPOT.*TB* vs. TST ≥ 5 mm) NR; R-CIR (T-SPOT.*TB* and TST ≥ 5 mm vs. TST ≥ 5 mm) NR; R-IDRR (T-SPOT.*TB* and TST ≥ 5 mm vs. TST ≥ 5 mm) NR

continued

TABLE 14 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – incidence studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
Kim 2011,[116] South Korea (high)	Number of test results: T-SPOT.*TB* 242; TST 272 Test (+/–): T-SPOT.*TB* 71/171; TST ≥ 10 mm 0/272 Number of indeterminate results: T-SPOT.*TB* 30; TST 0 Number lost to follow-up: 2	T-SPOT.*TB*: SN 100 (51.01 to 100.00); SP 71.84 (65.82 to 77.18); PPV 5.63 (2.21 to 13.61); NPV 100 (97.80 to 100)	TST ≥ 10 mm: SN NR; SP NR; PPV NR; NPV 98.53 (96.28 to 99.43)	T-SPOT.*TB*: CI (+) 5.63 (2.21 to 13.61); CI (–) 0/171 (0.0); CIR NR; IDR (+) 3.28 per 100 person-years (0.89 to 8.39 per 100 person-years); IDR (–) 0.00 per 100 person-years (NR); IDR difference: 3.3 per 100 person-years (1.3 to 5.3 per 100 person-years)	TST ≥ 10 mm: CI (+) NR; CI (–) 1.47 (0.43 to 3.85); CIR NR; IDR (+) NR; IDR (–) 0.83 per 100 person-years (0.23 to 2.12 per 100 person-years); IDRR NR	R-CIR (T-SPOT.*TB* vs. TST ≥ 10 mm) NR; R-IDRR (T-SPOT.*TB* vs. TST ≥ 10 mm) NR
Lee 2009,[118] Taiwan (high)	Number of test results: QFT-G 30; T-SPOT.*TB* 32; TST 32 Test (+/–): QFT-G 12/18; T-SPOT.*TB* 15/17; TST ≥ 10 mm 20/12 Number of indeterminate results: QFT-G 2; T-SPOT.*TB* 0; TST 0 Number lost to follow-up: 0	QFT-G: SN 100 (20.65 to 100); SP 60.00 (44.00 to 77.31); PPV 8.33 (1.49 to 35.39); NPV 100 (82.41 to 100) T-SPOT.*TB*: SN 0.00 (0.00 to 65.76); SP 50.00 (33.15 to 66.85); PPV 0.00 (0.00 to 20.39); NPV 88.24 (65.66 to 96.71)	TST ≥ 10 mm (two step): SN 50.00 (9.45 to 90.55); SP 36.67 (21.87 to 54.49); PPV 5.00 (0.89 to 23.61); NPV 100 (74.12 to 100)	QFT-G: CI (+) 8.33 (1.49 to 35.39); CI (–) 5.56 (5.40 to 27.29); CIR 1.55 (0.02 to 124.2); IDR (+) 3.40 per 100 person-years (NR); IDR (–) NR; IDRR NR T-SPOT.*TB*: CI (+) 6.67 (0.17 to 31.9); CI (–) 11.76 (2.03 to 35.59); CIR 0.57 (0.01 to 12.1); IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 10 mm (two step): CI (+) 5.00 (0.89 to 23.61); CI (–) 9.09 (0.23 to 41.3); CIR 0.55 (0.01 to 47.06); IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR [QFT-G vs. TST ≥ 10 mm (two step)] 2.82 (0.13 to 62.64); R-IDRR [QFT-G vs. TST ≥ 10 mm (two step)] NR; R-CIR [T-SPOT.*TB* vs. TST ≥ 10 mm (two step)] 1.04 (0.06 to 17.34); R-IDRR [T-SPOT.*TB* vs. TST ≥ 10 mm (two step)] NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Lee 2014,[149] South Korea (high)	Number of test results: QFT-GIT 159; TST 169 Test (+/–): QFT-GIT 26/133; TST ≥ 5 mm 19/150 TST ≥ 10 mm (12/157) Number of indeterminate results: QFT-GIT 10; TST 0 Number lost to follow-up: 0	QFT-GIT: SN 60.00 (23.07 to 88.24); SP 85.06 (78.59 to 89.84); PPV 11.54 (4.00 to 28.98); NPV 98.5 (94.68 to 99.59)	TST ≥ 5 mm: SN 0.0 (0.0 to 43.45); SP 88.41 (82.61 to 92.46); PPV 0.0 (0.0 to 16.82); NPV 96.67 (92.43 to 98.57) TST ≥ 10 mm: SN 0.0 (0.0 to 43.45); SP 92.68 (87.65 to 95.77); PPV 0.0 (0.0 to 24.25); NPV 96.82 (92.76 to 98.63)	QFT-GIT: CI (+) 11.54 (3.17 to 29.80); CI (–) 1.50 (0.07 to 5.66); CIR 7.67 (1.34 to 43.67); IDR (+) 5.43 per 100 person-years (1.12 to 15.88 per 100 person-years); IDR (–) 0.80 per 100 person-years (0.10 to 2.88 per 100 person-years); IDRR 6.78 per 100 person-years (NR)	TST ≥ 5 mm: CI (+) 2.63 (0.0 to 23.22); CI (–) 3.33 (1.22 to 7.77); CIR 0.79 (0.04 to 13.89); IDR (+) 0 per 100 person-years (0.00 to 8.41 per 100 person-years); IDR (–) 1.79 per 100 person-years (0.58 to 4.18 per 100 person-years); IDRR 0 per 100 person-years (NR) TST ≥ 10 mm: CI (+) 4.16 (0.0 to 33.00); CI (–) 3.18 (1.16 to 7.43); CIR 1.31 (0.07 to 22.55); IDR (+) 0.0 per 100 person-years (0.0 to 14.93 per 100 person-years); IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 5 mm) 9.71 (1.71 to 55.15); R-IDRR (QFT-GIT vs. TST ≥ 5 mm) NR; R-CIR (QFT-GIT vs. TST ≥ 10 mm) 5.85 (1.05 to 32.70); R-IDRR (QFT-GIT vs. TST ≥ 10 mm) NR
Moon 2013,[115] South Korea (high)	Number of test results: QFT-GIT 210; TST 244 Test (+/–): QFT-GIT 40/170; TST ≥ 5 mm 39/205 Number of indeterminate results: QFT-GIT 34; TST 0 Number lost to follow-up: 2	QFT-GIT: SN 50.00 (9.45 to 90.55); SP 81.25 (75.4 to 85.97); PPV 2.50 (0.44 to 12.88); NPV 99.41 (96.74 to 99.9)	TST ≥ 5 mm: SN 0.00 (0.00 to 65.76); SP 83.88 (78.73 to 87.98); PPV 0.00 (0.00 to 8.96); NPV 99.02 (96.51 to 99.73)	QFT-GIT: CI (+) 2.50 (0.44 to 12.88); CI (–) 0.58 (0.00 to 3.59); CIR 4.25 (0.27 to 66.49); IDR (+) 2.80 per 100 person-years (0.07 to 15.81 per 100 person-years); IDR (–) NR; IDRR NR	TST ≥ 5 mm: CI (+) 2.56 (0.06 to 13.5); CI (–) 0.97 (0.03 to 3.71); CIR 2.63 (0.04 to 51.4); IDR (+) 0 per 100 person-years (0.00 to 8.00 per 100 person-years); IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 5 mm) 1.62 (0.16 to 16.18); R-IDRR (QFT-GIT vs. TST ≥ 5 mm) 1.62 (0.16 to 16.18)

continued

TABLE 14 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – incidence studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Sherkat 2014,[155] Iran (intermediate)	Number of test results: T-SPOT.*TB* 44; TST 44 Test (+/–): T-SPOT.*TB* 6/38; TST ≥ 10 mm 8/36 Number of indeterminate results: T-SPOT.*TB* NR; TST NR Number lost to follow-up: 1	T-SPOT.*TB*: SN 100 (20.65 to 100); SP 88.37 (75.52 to 94.93); PPV 16.67 (3.00 to 56.35); NPV 100 (90.82 to 100)	TST ≥ 10 mm: SN 100 (20.65 to 100); SP 83.72 (70.03 to 91.88); PPV 12.5 (2.24 to 47.09); NPV 100 (90.36 to 100)	T-SPOT.*TB*: CI (+) 16.67 (3.00 to 56.35); CI (–) 1.31 (0.00 to 12.86); CIR 12.67 (0.47 to 337.8)	TST ≥ 10 mm: CI (+) 12.5 (0.11 to 47.09); CI (–) 1.39 (0.00 to 13.49); CIR 9.00 (0.33 to 245.7)	R-CIR (T-SPOT.*TB* vs. TST ≥ 10 mm) 1.41 (0.13 to 15.20)

CI (–), cumulative incidence in those who tested negative; CI (+), cumulative incidence in those who tested positive; ID, identification; IDR, incidence density rate; NR, not reported; SN, sensitivity; SP, specificity.

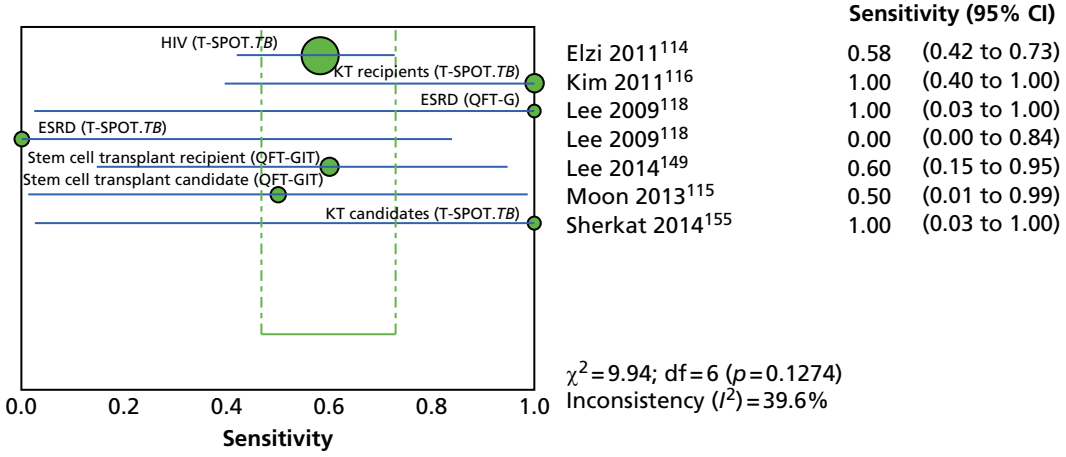


FIGURE 25 Forest plot of sensitivity based on incidence of active TB (IGRA) in immunocompromised patients. df, degrees of freedom; KT, kidney transplant.

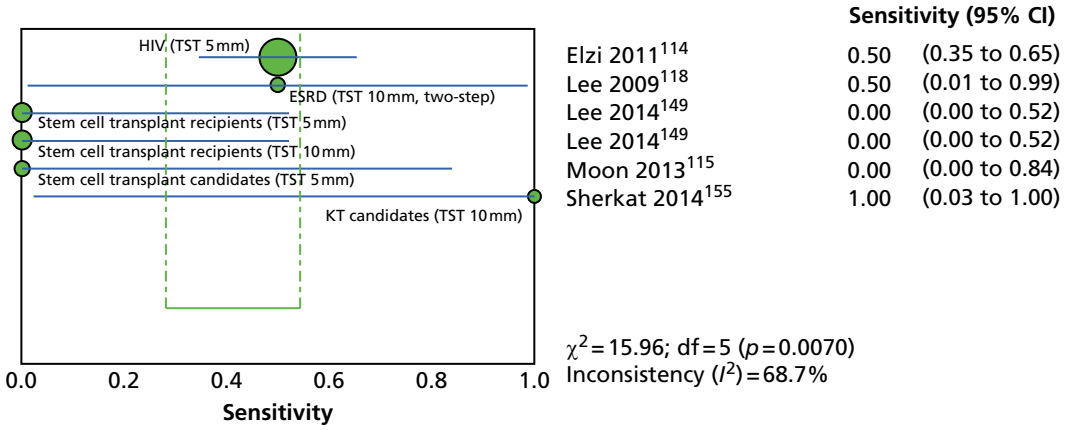
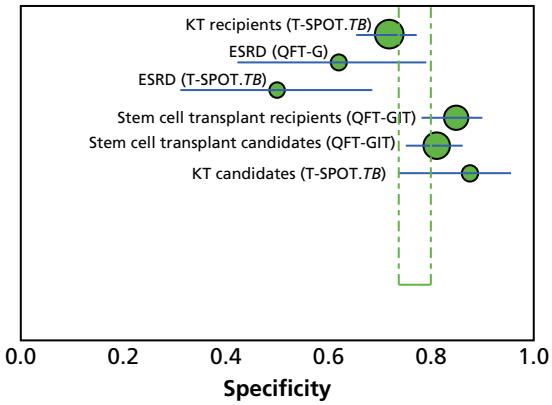


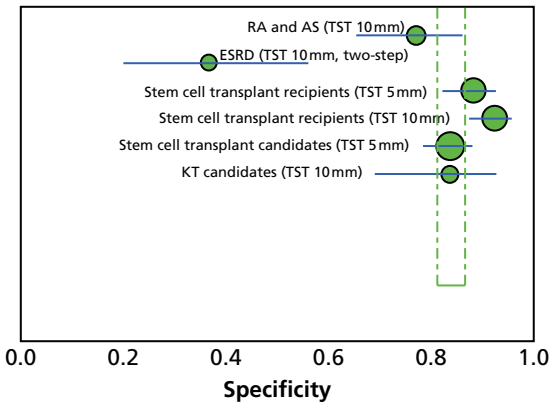
FIGURE 26 Forest plot of sensitivity based on incidence of active TB (TST) in immunocompromised patients. df, degrees of freedom; KT, kidney transplant.



	Specificity (95% CI)	
Kim 2011[116]	0.72	(0.66 to 0.77)
Lee 2009[118]	0.62	(0.42 to 0.79)
Lee 2009[118]	0.50	(0.31 to 0.69)
Lee 2014[149]	0.85	(0.78 to 0.90)
Moon 2013[115]	0.81	(0.75 to 0.86)
Sherkat 2014[155]	0.88	(0.74 to 0.96)

$\chi^2 = 28.55$; df = 5 ($p = 0.0000$)
Inconsistency (I^2) = 82.5%

FIGURE 27 Forest plot of specificity based on incidence of active TB (IGRA) in immunocompromised patients. df, degrees of freedom; KT, kidney transplant.



	Specificity (95% CI)	
Chang 2011[119]	0.77	(0.66 to 0.86)
Lee 2009[118]	0.37	(0.20 to 0.56)
Lee 2014[149]	0.88	(0.83 to 0.93)
Lee 2014[149]	0.93	(0.88 to 0.96)
Moon 2013[115]	0.84	(0.79 to 0.88)
Sherkat 2014[155]	0.84	(0.69 to 0.93)

$\chi^2 = 49.93$; df = 5 ($p = 0.0000$)
Inconsistency (I^2) = 90.0%

FIGURE 28 Forest plot of specificity based on incidence of active TB (TST) in immunocompromised patients. AS, ankylosing spondylitis; df, degrees of freedom; KT, kidney transplant; RA, rheumatoid arthritis.

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Ahmadinejad 2013,[120] Iran (intermediate)	Number of test results: QFT-GIT 159; TST 164 Test (+/–): QFT-GIT 33/126; TST ≥ 10 mm 26/138 Number of indeterminate results: QFT-GIT 5; TST 0	QFT-GIT: Exposure history to active TB vs. no such history: SN 0.00; SP 78.57 (71.44 to 84.32); PPV 0.00; NPV 96.03 (91.05 to 98.29)	TST ≥ 10 mm: Exposure history to active TB vs. no such history: SN 0.00; SP: 83.65 (77.12 to 88.59); PPV 0.00; NPV 96.38 (91.8 to 98.44)	QFT-GIT: Exposure history to active TB vs. no such history: DOR 0.00; DORa NR	TST ≥ 10 mm: Exposure history to active TB vs. no such history: DOR 0.00; DORa NR	QFT-GIT vs. TST ≥ 10 mm: Exposure history to active TB vs. no such history: R-DOR NR; R-DORa NR
Al Jahdali 2013,[121] Saudi Arabia (low)	Number of test results: QFT-GIT 200; TST 200 Test (+/–): QFT-GIT 65/135; TST ≥ 10 mm 26/174 Number of indeterminate results: QFT-GIT NR; TST NR	QFT-GIT: High likelihood of LTBI vs. no high likelihood of LTBI: SN 33.12 (26.00 to 41.00); SP 69.57 (55.19 to 80.92); PPV 78.46 (67.03 to 86.71); NPV 23.70 (17.32 to 31.54)	TST ≥ 10 mm (two step): High likelihood of LTBI vs. no high likelihood of LTBI: SN 12.34 (8.04 to 18.47); SP 84.78 (71.78 to 92.43); PPV 73.08 (53.92 to 86.3); NPV 22.41 (16.85 to 29.17)	QFT-GIT: High likelihood of LTBI vs. no high likelihood of LTBI: DOR 1.13 (0.55 to 2.31); DORa NR	TST ≥ 10 mm (two step): High likelihood of LTBI vs. no high likelihood of LTBI: DOR 0.78 (0.31 to 2.00); DORa NR	QFT-GIT vs. TST ≥ 10 mm (two step): High likelihood of LTBI vs. no high likelihood of LTBI: R-DOR 1.45 (0.79 to 2.64); R-DORa NR
Ates 2009,[122] Turkey (intermediate)	Number of test results: QFT-GIT 246; TST 259 Test (+/–): QFT-GIT 115/131; TST ≥ 10 mm 92/167 Number of indeterminate results: QFT-GIT 29; TST 16	QFT-GIT: TB exposure vs. no TB exposure: SN 58.82 (36.01 to 78.39); SP 54.15 (47.68 to 60.48); PPV 8.69 (4.79 to 15.27); NPV 94.66 (89.38 to 97.39)	TST ≥ 10 mm: TB exposure vs. no TB exposure: SN 29.41 (13.28 to 53.13); SP 64.05 (57.83 to 69.83); PPV 5.43 (2.34 to 12.10); NPV 92.81 (87.86 to 95.84)	QFT-GIT: TB exposure vs. no TB exposure: DOR 1.68 (0.62 to 4.58); DORa 1.30 (0.43 to 3.91)	TST ≥ 10 mm: TB exposure vs. no TB exposure: DOR 0.74 (0.25 to 2.17); DORa 0.49 (0.17 to 1.45)	QFT-GIT vs. TST ≥ 10 mm: TB exposure vs. no TB exposure: R-DOR 2.27 (1.07 to 4.81); R-DORa 2.65 (1.21 to 5.82)

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Casas 2011,[123] Spain (low)	Number of test results: QFT-GIT 214; TST 214 Test (+/–): QFT-GIT 45/157; TST ≥ 5 mm 52/162 Number of indeterminate results: QFT-GIT 12; TST 0	QFT-GIT: Risk factors for TB infection vs. no risk factors for TB infection: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 5 mm: Risk factors for TB infection vs. no risk factors for TB infection: SN: NR; SP NR; PPV NR; NPV NR	QFT-GIT: Risk factors for TB infection vs. no risk factors for TB infection: DOR 2.50 (1.20 to 5.10); DORa 2.90 (1.30 to 6.30)	TST ≥ 5 mm: Risk factors for TB infection vs. no risk factors for TB infection: DOR 2.80 (1.40 to 5.50); DORa 2.90 (1.40 to 6.00)	QFT-GIT vs. TST ≥ 5 mm: Risk factors for TB infection vs. no risk factors for TB infection: R-OR 0.89 (0.54 to 1.48); R-ORa 1.00 (0.58 to 1.73)
Casas 2011,[124] Spain (low)	Number of test results: QFT-GIT 95; TST 95 Test (+/–): QFT-GIT 42/51; TST ≥ 5 mm 44/51 Number of indeterminate results: QFT-GIT 2; TST 0	QFT-GIT: Risk factors for TB infection vs. no risk factors for TB infection: SN 45.00 (33.09 to 57.51); SP 57.14 (40.86 to 72.02); PPV 64.29 (49.17 to 77.01); NPV 37.74 (25.94 to 51.19)	TST ≥ 5 mm (two step): Risk factors for TB infection vs. no risk factors for TB infection: SN 50.00 (37.73 to 62.27); SP 60.00 (43.57 to 74.45); PPV 68.18 (53.44 to 80.00); NPV 41.18 (28.75 to 54.83)	QFT-GIT: Risk factors for TB infection vs. no risk factors for TB infection: DOR 1.66 (0.66 to 3.33); DORa 1.50 (0.50 to 4.10)	TST ≥ 5 mm (two step): Risk factors for TB infection vs. no risk factors for TB infection: DOR 1.25 (0.50 to 2.50); DORa 1.80 (0.60 to 5.10)	QFT-GIT vs. TST ≥ 5 mm (two step): Risk factors for TB infection vs. no risk factors for TB infection: R-DOR 1.33 (0.74 to 2.38); R-DORa 0.83 (0.39 to 1.79)
Chkhartishvili 2013,[125] Georgia (high)	Number of test results: QFT-GIT 237; T-SPOT.*TB* 218; TST 236 Test (+/–): QFT-GIT 70/167; T-SPOT.*TB* 56/162; TST ≥ 5 mm 41/195	QFT-GIT: Household member treated for TB vs. no household member treated for TB: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 5 mm: Household member treated for TB vs. no household member treated for TB: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Household member treated for TB vs. no household member treated for TB DOR 0.43 (0.09 to 1.97); DORa NR	TST ≥ 5 mm: Household member treated for TB vs. no household member treated for TB: DOR 1.48 (0.39 to 5.62); DORa NR	QFT-GIT vs. TST ≥ 5 mm: Household member treated for TB vs. no household member treated for TB: R-DOR 0.29 (0.10 to 0.82); R-DORa NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
	Number of indeterminate results: QFT-GIT 3; T-SPOT.*TB* 22; TST 4	T-SPOT.*TB*: Household member treated for TB vs. no household member treated for TB: SN NR; SP NR; PPV NR; NPV NR		T-SPOT.*TB*: Household member treated for TB vs. no household member treated for TB: DOR 1.48 (0.44 to 5.00); DORa NR		T-SPOT.*TB* vs. TST ≥ 5 mm Household member treated for TB vs. no household member treated for TB: R-DOR 1.00 (0.40 to 2.51); R-DORa NR
Chung 2010,[126] South Korea (high)	Number of test results: QFT-G 146; T-SPOT.*TB* 146; TST 146 Test (+/–): QFT-G 56/90; T-SPOT.*TB* 83/63; TST ≥ 10 mm 32/114 Number of indeterminate results: QFT-G NR; T-SPOT.*TB* NR; TST NR	QFT-GIT: High risk for LTBI vs. low risk for LTBI: SN 52.94 (30.96 to 73.84); SP 63.57 (54.98 to 71.37); PPV 16.07 (8.69 to 27.81); NPV 91.11 (83.43 to 95.43) T-SPOT.*TB*: High risk for LTBI vs. low risk for LTBI: SN 47.06 (26.16 to 69.04); SP 41.86 (33.70 to 50.49); PPV 9.64 (4.96 to 17.88); NPV 85.71 (75.03 to 92.30)	TST ≥ 10 mm: High risk for LTBI vs. low risk for LTBI: SN 11.76 (3.28 to 34.34); SP 76.74 (68.75 to 83.20); PPV 6.25 (1.73 to 20.15); NPV 86.84 (79.42 to 91.86)	QFT-GIT: High risk for LTBI vs. low risk for LTBI: DOR 1.96 (0.71 to 5.43); DORa NR T-SPOT.*TB*: High risk for LTBI vs. low risk for LTBI: DOR 0.64 (0.23 to 1.76); DORa NR	TST ≥ 10 mm: High risk for LTBI vs. low risk for LTBI: DOR 0.44 (0.09 to 2.03); DORa NR	QFT-G vs. TST ≥ 10 mm: High risk for LTBI vs. low risk for LTBI: R-DOR 4.45 (1.72 to 11.51); R-DORa NR T-SPOT.*TB* vs. TST ≥ 10 mm High risk for LTBI vs. low risk for LTBI: R-DOR 1.45 (0.56 to 3.76); R-DORa NR

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Costantino 2013,[127] France (low)	Number of test results: T-SPOT.*TB* 475; TST 514 Test (+/–): T-SPOT.*TB* 122/353; TST ≥ 5 mm 196/318 Number of indeterminate results: T-SPOT.*TB* 88; TST 49	T-SPOT.*TB*: Conventional risk factors for LTBI vs. no risk factors for LTBI: SN 47.92 (34.47 to 61.67); SP 76.81 (72.58 to 80.57); PPV 18.85 (12.9 to 26.70); NPV 92.92 (89.75 to 95.16)	TST ≥ 5 mm: Conventional risk factors for LTBI vs. no risk factors for LTBI: SN 63.27 (49.27 to 75.34); SP 64.52 (60.06 to 68.73); PPV 15.82 (11.37 to 21.58); NPV 94.34 (91.23 to 96.39)	T-SPOT.*TB*: Conventional risk factors for LTBI vs. no risk factors for LTBI: DOR 3.05 (1.65 to 5.60); DORa 2.70 (1.49 to 4.89)	TST ≥ 5 mm: Conventional risk factors for LTBI vs. no risk factors for LTBI: DOR 3.13 (1.70 to 5.77); DORa 1.95 (1.13 to 3.36)	T-SPOT.*TB* vs. TST ≥ 5 mm: Conventional risk factors for LTBI vs. no risk factors for LTBI: R-DOR 0.97 (0.63 to 1.51); R-DORa 1.38 (0.92 to 2.09)
Hadaya 2013,[128] Switzerland (low)	Number of test results: QFT-GIT 202; T-SPOT.*TB* 203; TST 200 Test (+/–): QFT-GIT 47/155; T-SPOT.*TB* 41/162; TST ≥ 5 mm 9/191 Number of indeterminate results: QFT-GIT 3; T-SPOT.*TB* 2; TST 0	QFT-GIT: Risk for LTBI vs. no risk for LTBI: SN 33.30 (19.60 to 49.50); SP 80.10 (72.90 to 86.20); PPV NR; NPV 81.10 (73.80 to 87.00) T-SPOT.*TB*: Risk for LTBI vs. no risk for LTBI: SN 33.30 (19.60 to 49.50); SP 85.50 (78.90 to 90.70); PPV NR; NPV 81.90 (75.00 to 87.60)	TST ≥ 5 mm: Risk for LTBI vs. no risk for LTBI: SN 7.10 (1.50 to 19.50); SP 95.50 (90.80 to 98.20); PPV NR; NPV 78.40 (71.70 to 84.20)	QFT-GIT: Risk for LTBI vs. no risk for LTBI: DOR 2.01 (1.25 to 2.76); DORa NR T-SPOT.*TB*: Risk for LTBI vs. no risk for LTBI: DOR 3.02 (1.36 to 6.71); DORa NR	TST ≥ 5 mm: Risk for LTBI vs. no risk for LTBI: DOR 1.73 (0.41 to 7.24); DORa NR	QFT-GIT vs. TST ≥ 5 mm: Risk for LTBI vs. no risk for LTBI: R-DOR 1.16 (0.51 to 2.66); R-DORa NR T-SPOT.*TB* vs. TST ≥ 5 mm: Risk for LTBI vs. no risk for LTBI: R-DOR 1.75 (0.76 to 4.04); R-DORa NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Hsia 2012,[129] USA (low)	Number of test results: QFT-GIT 2241; TST 2282 Test (+/–): QFT-GIT 160/2081; TST ≥ 5 mm 215/2067 Number of indeterminate results: QFT-GIT 41; TST 0	QFT-GIT: Geographical study location: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 5 mm: Geographical study location: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Western Europe vs. North America: DOR NR; DORa 3.41 (1.99 to 5.83) Latin America vs. North America: DOR NR; DORa 3.43 (1.64 to 7.19) Eastern Europe vs. North America: DOR NR; DORa 3.58 (1.93 to 6.63) Asia vs. North America: DOR NR; DORa 8.48 (4.78 to 15.03)	TST ≥ 5 mm: Western Europe vs. North America: DOR NR; DORa 2.10 (1.30 to 3.38) Latin America vs. North America: DOR NR; DORa 1.56 (0.80 to 3.05) Eastern Europe vs. North America: DOR NR; DORa 0.95 (0.53 to 1.70) Asia vs. North America: DOR NR; DORa 7.47 (4.61 to 12.08)	QFT-GIT vs. TST ≥ 5 mm: Western Europe vs. North America: R-DOR NR; R-DORa 1.62 (1.13 to 2.34) Latin America vs. North America: R-DOR NR; R-DORa 2.20 (1.32 to 3.66) Eastern Europe vs. North America: R-DOR NR; R-DORa 3.77 (2.44 to 5.81) Asia vs. North America: R-DOR NR; R-DORa 1.14 (0.77 to 1.66)
Kim 2010,[130] South Korea (low)	Number of test results: T-SPOT.*TB* 184; TST ≥ 5 mm 209; TST ≥ 10 mm 209 Test (+/–): T-SPOT.*TB* 65/119; TST ≥ 5 mm 47/162; TST ≥ 10 mm 21/188 Number of indeterminate results: T-SPOT.*TB* 25; TST ≥ 5 mm 0; TST ≥ 10 mm 0	T-SPOT.*TB*: Risk group for LTBI vs. no risk group for LTBI: SN 52.63 (31.71 to 72.67); SP 66.67 (59.17 to 73.41); PPV 15.38 (8.57 to 26.06); NPV 92.44 (86.25 to 95.97)	TST ≥ 5 mm: Risk group for LTBI vs. no risk group for LTBI: SN 36.36 (19.73 to 57.05); SP 79.14 (72.76 to 84.35); PPV 17.02 (8.88 to 30.14); NPV 91.36 (86.02 to 94.78)	T-SPOT.*TB*: Risk group for LTBI vs. no risk group for LTBI: DOR 2.35 (0.90 to 6.12); DORa 2.38 (0.87 to 6.52)	TST ≥ 5 mm: Risk group for LTBI vs. no risk group for LTBI: DOR 2.17 (0.85 to 5.54); DORa 2.11 (0.82 to 5.46)	T-SPOT.*TB* vs. TST ≥ 5 mm: Risk group for LTBI vs. no risk group for LTBI: R-DOR 1.02 (0.52 to 2.03); R-DORa 1.08 (0.55 to 2.15)

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
			TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: SN 18.18 (7.31 to 38.52); SP 90.91 (85.92 to 94.25); PPV 19.05 (7.66 to 40.00); NPV 90.43 (85.37 to 93.86)		TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: DOR 2.22 (0.67 to 7.32); DORa 2.12 (0.60 to 7.49)	T-SPOT.*TB* vs. TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: R-DOR 1.00 (0.46 to 2.19); R-DORa 1.06 (0.48 to 2.31)
Kim 2013,[131] South Korea (high)	Number of test results: QFT-GIT 120; TST 119 Test (+/–): QFT-GIT 53/67; TST ≥ 10 mm 35/91 Number of indeterminate results: QFT-GIT 6; TST 7	QFT-GIT: Risk group for LTBI vs. no risk group for LTBI: SN 73.33 (48.05 to 89.1); SP 60.00 (50.44 to 68.86); PPV 20.75 (12.00 to 33.46); NPV 94.03 (85.63 to 97.65)	TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: SN 86.67 (62.12 to 96.26); SP 90.38 (83.2 to 94.69); PPV 56.52 (36.81 to 74.37); NPV 97.92 (92.72 to 99.43)	QFT-GIT: Risk group for LTBI vs. no risk group for LTBI: DOR 4.13 (1.23 to 13.82); DORa 4.62 (1.15 to 18.64)	TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: DOR 61.1 (12.03 to 310.4); DORa NR	QFT-GIT vs. TST ≥ 10 mm: Risk group for LTBI vs. no risk group for LTBI: R-DOR 0.07 (0.02 to 0.19); R-DORa NR
Kim 2013,[132] South Korea (high)	Number of test results: QFT-GIT 102; TST 93 Test (+/–): QFT-GIT 21/81; TST ≥ 10 mm 12/81 Number of indeterminate results: QFT-GIT 4; TST 0	QFT-GIT: History of treated TB vs. no such history: SN 100 (34.24 to 100); SP 81.32 (72.10 to 88.00); PPV 10.53 (2.93 to 31.39); NPV 100 (95.06 to 100) Abnormal chest radiograph vs. no abnormal chest radiograph: SN 75.00 (30.06 to 95.44); SP 82.02 (72.77 to 88.62); PPV 15.79 (5.52 to 37.57); NPV 98.65 (92.73 to 99.76)	TST ≥ 10 mm: History of treated TB vs. no such history: SN NR; SP NR; PPV NR; NPV NR Abnormal chest radiograph vs. no abnormal chest radiograph: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: History of treated TB vs. no such history: DOR NR; DORa 9.21 (NR) Abnormal chest radiograph vs. no abnormal chest radiograph: DOR 13.69 (1.33 to 140.30); DORa 27.95 (1.22 to 636.62)	TST ≥ 10 mm: History of treated TB vs. no such history: DOR NR; DORa NR (NS) Abnormal chest radiograph vs. no abnormal chest radiograph: DOR NR; DORa NR (NS)	QFT-GIT vs. TST ≥ 10 mm: History of treated TB vs. no such history: R-DOR NR; R-DORa NR Abnormal chest radiograph vs. no abnormal chest radiograph: R-DOR NR; R-DORa NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Kleinert 2012,[133] Germany (low)	Number of test results: QFT-G 685; T-SPOT.*TB* 844; TST 1529 Test (+/–): QFT-G 50/635; T-SPOT.*TB* 70/774; TST ≥ 5 mm 173/1356 Number of indeterminate results: QFT-G + T-SPOT.*TB* 80; TST NR	QFT-G: Presence of CRF vs. absence of CRF: SN 16.67 (9.02 to 28.74); SP 93.5 (91.3 to 95.17); PPV 18.00 (9.77 to 30.8); NPV 92.91 (90.65 to 94.66) T-SPOT.*TB*: Presence of CRF vs. absence of CRF: SN 35.29 (25.00 to 47.16); SP 94.07 (92.18 to 95.53); PPV 34.29 (24.25 to 45.96); NPV 94.32 (92.45 to 95.74)	TST ≥ 5 mm: Presence of CRF vs. absence of CRF: SN 39.34 (31.13 to 48.21); SP 91.12 (89.52 to 92.49); PPV 27.75 (21.61 to 34.85); NPV 94.54 (93.2 to 95.63)	QFT-G: Presence of CRF vs. absence of CRF: DOR 2.88 (1.31 to 6.29); DORa 2.63 (1.15 to 5.98) T-SPOT.*TB*: Presence of CRF vs. absence of CRF: DOR 8.65 (4.84 to 15.46); DORa 8.74 (4.83 to 15.82)	TST ≥ 5 mm: Presence of CRF vs. absence of CRF: DOR 6.65 (4.42 to 9.99); DORa 6.20 (4.08 to 9.44)	QFT-G vs. TST ≥ 10 mm: Presence of CRF vs. absence of CRF: R-DOR 0.43 (0.28 to 0.68); R-DORa 0.42 (0.26 to 0.68) T-SPOT.*TB* vs. TST ≥ 10 mm: Presence of CRF vs. absence of CRF: R-DOR 1.30 (0.91 to 1.87); R-DORa 1.41 (0.97 to 2.04)
Laffitte 2009,[134] Switzerland (low)	Number of test results: T-SPOT.*TB* 50; TST ≥ 5 mm 50; TST ≥ 10 mm 50 Test (+/–): T-SPOT.*TB* 10/40; TST ≥ 5 mm 20/30; TST ≥ 10 mm 18/32 Number of indeterminate results: T-SPOT.*TB* NR; TST ≥ 5 mm NR; TST ≥ 10 mm NR	T-SPOT.*TB*: Probable LTBI vs. no probable LTBI: SN 36.36 (19.73 to 57.05); SP 92.86 (77.35 to 98.02); PPV 80.00 (49.02 to 94.33); NPV 65.00 (49.51 to 77.87)	TST ≥ 5 mm: Probable LTBI vs. no probable LTBI: SN 50.00 (30.72 to 69.28); SP 67.86 (49.34 to 82.07); PPV 55.00 (34.21 to 74.18); NPV 63.33 (45.51 to 78.13)	T-SPOT.*TB*: Probable LTBI vs. no probable LTBI: DOR 7.43 (1.38 to 39.90); DORa NR	TST ≥ 5 mm: Probable LTBI vs. no probable LTBI: DOR 3.00 (0.93 to 9.70); DORa NR TST ≥ 10 mm: Probable LTBI vs. no probable LTBI: DOR 2.08 (0.64 to 6.73); DORa NR	T-SPOT.*TB* vs. TST ≥ 5 mm: Probable LTBI vs. no probable LTBI: R-DOR 3.52 (1.25 to 9.96); R-DORa NR T-SPOT.*TB* vs. TST ≥ 10 mm: Probable LTBI vs. no probable LTBI: R-DOR 1.69 (0.58 to 4.89); R-DORa NR

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
			TST ≥ 10 mm: Probable LTBI vs. no probable LTBI: SN 54.55 (34.66 to 73.08); SP 78.57 (60.46 to 89.79); PPV 66.67 (43.75 to 83.72); NPV 68.75 (51.43 to 82.05)			
Maritsi 2011,[135] UK (low)	Number of test results: QFT-GIT 23; TST 14 Test (+/–): QFT-GIT 1/20; TST ≥ NR mm 0/14 Number of indeterminate results: QFT-GIT 2; TST 0	QFT-GIT: High-risk group vs. low-risk group: SN 33.33 (6.15 to 79.23); SP 100 (82.41 to 100); PPV 100 (20.65 to 100); NPV 90.00 (69.9 to 97.21)	TST ≥ NR mm: High-risk group vs. low-risk group: SN 0.00 (0.00 to 56.15); SP 100 (74.12 to 100); PPV NR; NPV 78.57 (52.41 to 92.43)	QFT-GIT: High-risk group vs. low-risk group: DOR NR; DORa NR	TST ≥ NR mm: High-risk group vs. low-risk group: DOR NR; DORa NR	QFT-GIT vs. TST ≥ NR mm: High-risk group vs. low-risk group: R-DOR NR; R-DORa NR
Mutsvangwa 2010,[136] Zimbabwe (high)	Number of test results: T-SPOT.*TB* 73; TST 73 Test (+/–): T-SPOT.*TB* 22/51; TST ≥ 10 mm 33/40 Number of indeterminate results: T-SPOT.*TB* NR; TST NR	T-SPOT.*TB*: Contact of index TB case vs. contact of index control: SN 34.55 (23.36 to 47.75); SP 83.33 (60.78 to 94.16); PPV 86.36 (66.66 to 95.25); NPV 29.41 (18.71 to 43.0) Smear status of index case (smear –ve, culture +ve vs. smear –ve, culture –ve): SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm (two step): Contact of index TB case vs. contact of index control: SN 49.09 (36.38 to 61.92); SP 66.67 (43.75 to 83.72); PPV 81.82 (65.61 to 91.39); NPV 30.00 (18.07 to 45.43) Smear status of index case (smear –ve, culture +ve vs. smear –ve, culture –ve): SN NR; SP NR; PPV NR; NPV NR	T-SPOT.*TB*: Contact of index TB case vs. contact of index control: DOR 2.64 (0.67 to 10.27); DORa NR Smear status of index case (smear –ve, culture +ve vs. smear –ve, culture –ve): DOR 1.60 (0.20 to 12.69); DORa 1.87 (0.22 to 16.16)	TST ≥ 10 mm (two step): Contact of index TB case vs. contact of index control: DOR 1.93 (0.63 to 5.87); DORa NR Smear status of index case (smear –ve, culture +ve vs. smear –ve, culture –ve): DOR 1.50 (0.24 to 9.46); DORa 1.09 (0.13 to 9.42)	T-SPOT.*TB* vs. TST ≥ 10 mm (two step): Contact of index TB case vs. contact of index: R-DOR 1.37 (0.56 to 3.36); R-DORa NR Smear status of index case (smear –ve, culture +ve vs. smear –ve, culture –ve): R-DOR 1.07 (0.26 to 4.39); R-DORa 1.72 (0.36 to 8.06)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
		Smear status of index case (smear +ve, culture +ve vs. smear –ve, culture –ve): SN NR; SP NR; PPV NR; NPV NR	Smear status of index case (smear +ve, culture +ve vs. smear –ve, culture –ve): SN NR; SP NR; PPV NR; NPV NR	Smear status of index case (smear +ve, culture +ve vs. smear –ve, culture –ve): DOR 4.80 (1.05 to 21.91); DORa 5.36 (1.11 to 25.93)	Smear status of index case (smear +ve, culture +ve vs. smear –ve, culture –ve): DOR 3.50 (0.88 to 13.93); DORa 3.43 (0.76 to 15.52)	Smear status of index case (smear +ve, culture +ve vs. smear –ve, culture –ve): R-DOR 1.37 (0.48 to 3.91); R-DORa 1.56 (0.51 to 4.76)
Papay 2011,[137] Austria (low)	Number of test results: QFT-GIT 192; TST 192 Test (+/–): QFT-GIT 15/177; TST ≥ 5 mm 26/166 Number of indeterminate results: QFT-GIT 0; TST 0	QFT-GIT: Presence of risk factors vs. absence of risk factors: SN 13.85 (7.45 to 24.27); SP 95.28 (90.08 to 97.82); PPV 60.00 (35.75 to 80.18); NPV 68.36 (61.18 to 74.76) Origin from a high-incidence country vs. origin from a low-incidence country: SN 14.29 (5.69 to 31.49); SP 93.29 (88.39 to 96.21); PPV 26.67 (10.9 to 51.95); NPV 86.44 (80.62 to 90.72) History of contact with index case vs. no history of contact: SN 20.00 (5.668 to 50.98); SP 92.86 (88.16 to 95.78); PPV 13.33 (3.736 to 37.88); NPV 95.48 (91.34 to 97.69)	TST ≥ 5 mm: Presence of risk factors vs. absence of risk factors: SN 21.74 (13.64 to 32.82); SP 92.09 (86.38 to 95.52); PPV 57.69 (38.95 to 74.46); NPV 70.33 (63.33 to 76.49) Origin from a high-incidence country vs. origin from a low-incidence country: SN 37.93 (22.69 to 56); SP 91.62 (86.64 to 94.86); PPV 42.31 (25.54 to 61.05); NPV 90.11 (84.91 to 93.65) History of contact with index case vs. no history of contact: SN 36.36 (15.17 to 64.62); SP 88.83 (83.67 to 92.51); PPV: 15.38 (6.15 to 33.53); NPV: 96.15 (92.27 to 98.12)	QFT-GIT: Presence of risk factors vs. absence of risk factors: DOR 3.24 (1.10 to 9.54); DORa NR Origin from a high-incidence country vs. origin from a low-incidence country: DOR 2.32 (0.68 to 7.87); DORa NR History of contact with index case vs. no history of contact: DOR 3.25 (0.62 to 16.91); DORa NR	TST ≥ 5 mm: Presence of risk factors vs. absence of risk factors: DOR 3.23 (1.39 to 7.49); DORa NR Origin from a high-incidence country vs. origin from a low-incidence country: DOR 6.68 (2.67 to 16.73); DORa NR History of contact with index case vs. no history of contact: DOR 4.54 (1.23 to 16.78); DORa NR	QFT-GIT vs. TST ≥ 5 mm: Presence of risk factors vs. absence of risk factors: R-DOR 1.00 (0.50 to 2.02); R-DORa NR Origin from a high-incidence country vs. origin from a low-incidence country: R-DOR 0.35 (0.16 to 0.76); R-DORa NR History of contact with index case vs. no history of contact: R-DOR 0.72 (0.24 to 2.10); R-DORa NR

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Ramos 2013,[138] Spain (low)	Number of test results: QFT-GIT 153; TST 153 Test (+/–): QFT-GIT 15/137; TST ≥ 5 mm 43/110 Number of indeterminate results: QFT-GIT 1; T-SPOT.*TB* 0; TST 0	QFT-GIT: Contact of index TB case vs. contact of index control: SN 42.86 (15.82 to 74.95); SP 91.72 (86.09 to 95.20); PPV 20.00 (7.04 to 45.19); NPV 97.08 (92.73 to 98.86) Born in an endemic country vs. not born in an endemic country: SN 50.00 (21.52 to 78.48); SP 92.36 (86.84 to 95.68); PPV 26.67 (10.90 to 51.95); NPV 97.08 (92.73 to 98.86)	TST ≥ 5 mm: Contact of index TB case vs. contact of index control: SN 57.14 (25.05 to 84.18); SP 73.29 (65.58 to 79.8); PPV 9.30 (3.67 to 21.6); NPV 97.27 (92.29 to 99.07) Born in an endemic country vs. not born in an endemic country: SN 50.00 (21.52 to 78.48); SP 73.1 (65.36 to 79.66); PPV 9.30 (3.67 to 21.60); NPV 96.36 (91.02 to 98.58)	QFT-GIT: Contact of index TB case vs. contact of index control: DOR 8.31 (1.66 to 41.56); DORa NR Born in an endemic country vs. not born in an endemic country: DOR 12.09 (2.65 to 55.07); DORa NR	TST ≥ 5 mm: Contact of index TB case vs. contact of index control: DOR 3.66 (0.78 to 17.08); DORa NR Born in an endemic country vs. not born in an endemic country: DOR 2.72 (0.65 to 11.40); DORa NR	QFT-GIT vs. TST ≥ 5 mm: Contact of index TB case vs. contact of index control: R-DOR 2.27 (0.73 to 7.08); R-DORa NR Born in an endemic country vs. not born in an endemic country: R-DOR 4.44 (1.53 to 12.89); R-DORa NR
Seyhan 2010,[139] Turkey (intermediate)	Number of test results: QFT-GIT 100; TST 100 Test (+/–): QFT-GIT 43/57; TST ≥ 10 mm 34/66 Number of indeterminate results: QFT-GIT NR; TST 0	QFT-GIT: Previous contact with an index case vs. no contact: SN 76.92 (49.74 to 91.82); SP 62.07 (51.57 to 71.55); PPV 23.26 (13.15 to 37.74); NPV 94.74 CI (85.63 to 98.19)	TST ≥ 10 mm: Previous contact with an index case vs. no contact: SN 46.15 (23.21 to 70.86); SP 67.82 (57.43 to 76.7); PPV 17.65 (8.349 to 33.51); NPV 89.39 (79.69 to 94.77)	QFT-GIT: Previous contact with an index case vs. no contact: DOR 5.45 (1.40 to 21.27); DORa NR Previous TB disease vs. no previous disease: DOR 4.46 (0.85 to 23.31); DORa NR	TST ≥ 10 mm: Previous contact with an index case vs. no contact: DOR 1.81 (0.55 to 5.87); DORa NR Previous TB disease vs. no previous disease: DOR 1.18 (0.26 to 5.26); DORa NR	QFT-GIT vs. TST ≥ 10 mm: Previous contact with an index case vs. no contact: R-DOR 3.01 (1.20 to 7.56); R-DORa NR Previous TB disease vs. no previous disease: R-DOR 3.78 (1.21 to 11.83); R-DORa NR

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
		Previous TB disease vs. no previous disease: SN 75.0 (40.93 to 92.85); SP 59.78 (49.57 to 69.22); PPV 13.95 (6.556 to 27.26); NPV 96.49 (88.08 to 99.03)	Previous TB disease vs. no previous disease: SN 37.5 (13.68 to 69.43); SP 66.3 (56.17 to 75.14); PPV 8.824 (3.047 to 22.96); NPV 92.42 (83.46 to 96.72)			
Shen 2012,[140] China (high)	Number of test results: T-SPOT.*TB* 70; TST 70 Test (+/–): T-SPOT.*TB* 26/44; TST ≥ 5 mm 34/36 Number of indeterminate results: T-SPOT.*TB* 0; TST 0	T-SPOT.*TB*: Suspected TB disease vs. no suspected TB: SN 70.97 (53.41 to 83.90); SP 89.74 (76.42 to 95.94); PPV 84.62 (66.47 to 93.85); NPV 79.55 (65.5 to 88.85)	TST ≥ 5 mm: Suspected TB disease vs. no suspected TB: SN 61.29 (43.82 to 76.27); SP 61.54 (45.9 to 75.11); PPV 55.88 (39.45 to 71.12); NPV 66.67 (50.33 to 79.79)	T-SPOT.*TB*: Suspected TB disease vs. no suspected TB: DOR 21.39 (5.87 to 77.93); DORa NR	TST ≥ 5 mm: Suspected TB disease vs. no suspected TB: DOR 2.53 (0.96 to 6.67); DORa NR	T-SPOT.*TB* vs. TST ≥ 5 mm: Suspected TB disease vs. no suspected TB: R-DOR 8.45 (3.71 to 19.28); R-DORa NR
Souza 2014,[153] Brazil (intermediate)	Number of test results: QFT-GIT 299; TST 300 Test (+/–): QFT-GIT 14/285; TST ≥ 5 mm 10/290 Number of indeterminate results: QFT-GIT 1; TST 0	QFT-GIT: History of contact with index case vs. no history of contact with index case: SN 0.0 (0.00 to 9.89); SP 94.96 (91.57 to 97.03); PPV 0.0 (0.00 to 22.81); NPV 87.5 (83.11 to 90.87)	TST ≥ 5 mm: History of contact with index case vs. no history of contact with index case: SN 2.86 (0.50 to 14.53); SP 96.91 (94.02 to 98.43); PPV 11.11 (1.99 to 43.5); NPV 88.07 (83.79 to 91.34)	QFT-GIT: History of contact with index case vs. no history of contact with index case: DOR 0.50 (0.06 to 4.24); DORa NR	TST ≥ 5 mm: History of contact with index case vs. no history of contact with index case: DOR 0.93 (0.11 to 7.61); DORa 1.21 (0.13 to 11.16)	QFT-GIT vs. TST ≥ 5 mm: History of contact with index case vs. no history of contact with index case: R-DOR 0.54 (0.12 to 2.49); R-DORa NR
Takeda 2011,[141] Japan (low)	Number of test results: QFT-GIT 71; TST 43 Test (+/–): QFT-GIT 2/46; TST ≥ 10 mm 3/40 Number of indeterminate results: QFT-GIT 23; T-SPOT.*TB* NR; TST 0	QFT-GIT: Risk of LTBI vs. no risk of LTBI: SN 11.11 (10 to 32.80); SP 100.00 (88.65 to 100.00); PPV 100.00 (34.24 to 100.00); NPV 65.22 (53.45 to 75.38)	TST ≥ 10 mm: Risk of LTBI vs. no risk of LTBI: SN 7.14 (1.27 to 31.47); SP 93.10 (78.04 to 98.09); PPV 33.33 (6.15 to 79.23); NPV 67.50; (52.02 to 79.92)	QFT-GIT: Risk of LTBI vs. no risk of LTBI: DOR 3.75 (0.31 to 44.6); DORa NR	TST ≥ 10 mm: Risk of LTBI vs. no risk of LTBI: DOR 1.04 (0.08 to 12.53); DORa NR	QFT-GIT vs. TST ≥ 10 mm: Risk of LTBI vs. no risk of LTBI: R-DOR 3.61 (0.59 to 21.99); R-DORa NR

continued

TABLE 15 Comparison of test performance in immunocompromised patients: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy) DOR (95% CI) (vs. non-exposed; reference group)		
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	R-DOR (95% CI), IGRA vs. TST (by threshold)
Vassilopoulos 2011,[142] Greece (low)	Number of test results: QFT-GIT 157; T-SPOT.*TB* 157; TST 157 Test (+/–): QFT-GIT 32/123; T-SPOT.*TB* 39/116; TST ≥ 5 mm 58/97 Number of indeterminate results: QFT-GIT 2; T-SPOT.*TB* 2; TST 2	T-SPOT.*TB*: TB exposure vs. no exposure: SN 25.00 (11.19 to 46.87); SP 74.81 (66.88 to 81.38); PPV 12.82 (5.60 to 26.71); NPV 87.07 (79.76 to 92.00) QFT-GIT: TB exposure vs. no exposure: SN 15.00 (5.23 to 36.04); SP 78.52 (70.85 to 84.61); PPV 9.37 (3.24 to 24.22); NPV 86.18 (78.98 to 91.19)	TST ≥ 5 mm: TB exposure vs. no exposure: SN 50.00 (29.93 to 70.07); SP 64.44, (56.07 to 72.02); PPV 17.24 (9.64 to 28.91); NPV 89.69 (82.05 to 94.3)	T-SPOT.*TB*: TB exposure vs. no exposure: DOR 0.99 (0.33 to 2.92); DORa NR QFT-GIT: TB exposure vs. no exposure: DOR 0.64 (0.17 to 2.35); DORa NR	TST ≥ 5 mm: TB exposure vs. no exposure: DOR 1.81 (0.70 to 4.66); DORa NR	T-SPOT.*TB* vs. TST ≥ 5 mm: TB exposure vs. no exposure: R-DOR 0.55 (0.26 to 1.14); R-DORa NR QFT-GIT vs. TST ≥ 5 mm: TB exposure vs. no exposure: R-DOR 0.35 (0.15 to 0.81); R-DORa NR

–ve, negative; +ve, positive; CRF, compound risk factor; DORa, adjusted diagnostic odds ratio; ID, identification; NR, not reported; R-DORa, adjusted ratio of diagnostic odds ratios; SN, sensitivity; SP, specificity.

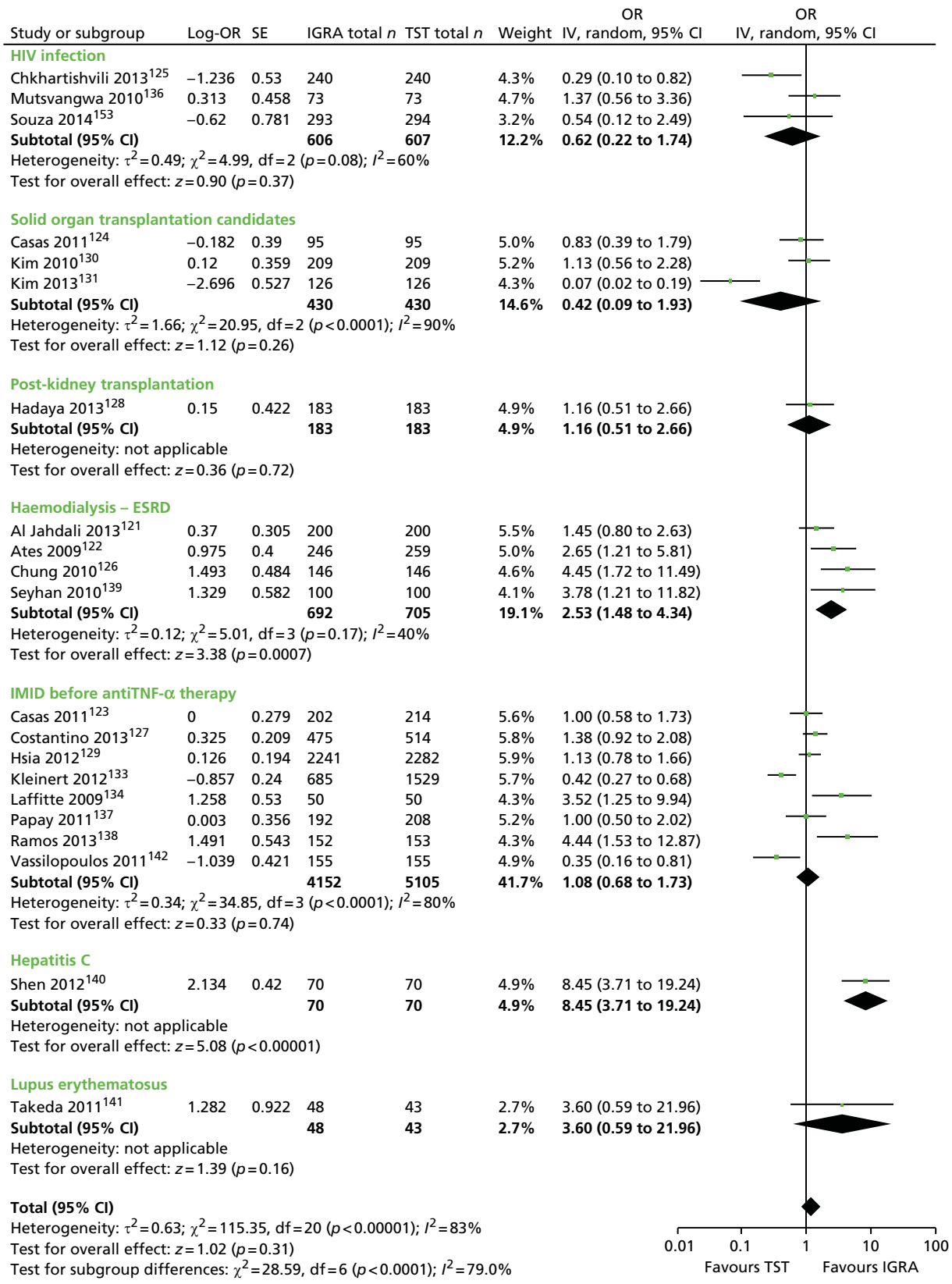


FIGURE 29 Pooled R-DOR of IGRAs vs. TST in all studies based on high- and low-risk exposure in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; IV, inverse variance; SE, standard error.

Within-subgroup heterogeneity by IGRA type (QFT-GIT, T-SPOT.*TB*) and TST threshold (5 mm, 10 mm, 15 mm) could not be examined for most subgroups because of sparse data. The underlying differences in the definition/measurement of exposure and differential performance of tests across the disease spectrum may have additionally contributed to the non-uniformity observed in the R-DOR estimates (*Figures 30–33*). For example, for participants with immune-mediated inflammatory diseases before antiTNF-α therapy, the non-uniformity persisted even after accounting for the type of IGRA (QFT-GIT) and TST threshold (5 mm) (pooled R-DOR 0.90, 95% CI 0.52 to 1.54; $I^2 = 80\%$; see *Figure 30*). However, the stratification by IGRA type and TST threshold revealed that the TST 5 mm was better than the IGRA (QFT-GIT) at detecting LTBI in participants with HIV infection (pooled R-DOR 0.35, 95% CI 0.15 to 0.83; $I^2 = 0\%$; see *Figure 30*). Based on the results from two studies of solid organ transplantation candidates, there was no significant difference between the performance of IGRAs (T-SPOT.*TB*[130] and QFT-GIT[124]) and the TST 5 mm in relation to the identification of LTBI (see *Figures 30*, *32* and *33*). In contrast, in another study of solid organ transplantation candidates,[131] the TST 10 mm outperformed QFT-GIT (R-DOR 0.07, 95% CI 0.02 to 0.19; see *Figure 31*). In two studies, the performance of QFT-GIT did not significantly differ from that of the TST among participants with lupus erythematosus (QFT-GIT vs. TST 10 mm: R-DOR 3.60, 95% CI 0.59 to 21.96; see *Figure 31*)[141] and kidney transplant recipients (QFT-GIT vs. TST 5 mm: R-DOR 1.16, 95% CI 0.51 to 2.66; see *Figure 30*).[128]

Sensitivity and specificity

This section incorporates 24 newly identified studies[120–142,153] (see *Table 15*). Three studies[123,125,129] did not report sensitivity and specificity parameters for both IGRA and TST and one study[132] reported them only for TST. The forest plots for the remaining 21 studies displayed a wide variability in sensitivity (IGRA range 0–75%; TST 5 mm range 0–61%; TST 10 mm range 0–87%) and specificity (IGRA range 57–100%; TST 5 mm range 62–96%; TST 10 mm range 64–93%). The heterogeneity persisted even after stratifying the estimates by type of IGRA (QFT-GIT, T-SPOT.*TB*) and TST threshold (5 mm, 10 mm). Of the two IGRAs, QFT-GIT/G demonstrated markedly wider variation in the estimates of specificity and sensitivity than T-SPOT.*TB*. In general, for both the IGRAs and the TST, specificity tended to be greater than sensitivity (*Figures 34–41*). The absence of any clear pattern in the distribution of sensitivity and specificity values reflects the underlying between-study differences in study populations/conditions and settings and variation in exposure definitions and measurement. In light of the observed heterogeneity, no meta-analysis was undertaken.

Influence of bacillus Calmette–Guérin vaccination status on test positivity

Of the 24 newly identified studies included in this section,[120–142,153] only 14[120,122–125,127,129–131,133,134,138,139,142] reported on the association between test positivity and BCG vaccination status. Overall, there was no evidence indicating a differential effect of BCG vaccination status on IGRA and TST positivity.[120,122–125,130,131,133,134,137–142] In other words, the odds of test positivity for the IGRA and TST were not significantly different between the BCG vaccinated and the non-vaccinated groups (*Table 16*). Only one study[139] demonstrated a significantly increased OR for TST 10 mm positivity (OR 4.28, 95% CI 1.35 to 13.64) as opposed to a non-significant OR for the IGRA (OR 1.89, 95% CI 0.75 to 4.73) in relation to BCG vaccination status.

Between-test concordance, discordance and agreement

This section included 16 studies[167–182] reviewed in CG117[10] (see *Appendix 5*) and 32 more recent studies[114–142,149,153,155] reviewed in this update (see *Appendix 9*). Overall, nine studies[114,125,136,153,167,170–172,181] were conducted in people with HIV infection, three studies[115,149,175] in people with haematological disorders, four studies[120,124,130,131] in solid organ transplantation candidates, three studies[116,128,132] in people who had undergone kidney transplantation, seven studies[117,118,121,122,126,139,155] in people with ESRD/haemodialysis, one study[140] in those with hepatitis C, one study[141] in those with lupus erythematosus and 18 studies[119,123,127,129,133–135,137,138,142,168,169,174,176,178–180,182] in patients with immune-mediated inflammatory diseases before antiTNF-α therapy (rheumatoid arthritis, rheumatic or inflammatory diseases). The remaining two studies looked at patients with chronic liver[173] and mixed (HIV infection with liver transplantation)[177] conditions.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
HIV infection						
Chkhartishvili 2013[125]	–1.236	0.53	240	240	7.8%	0.29 (0.10 to 0.82)
Souza 2014[153]	–0.62	0.781	293	294	4.9%	0.54 (0.12 to 2.49)
Subtotal (95% CI)			**533**	**534**	**12.7%**	**0.35 (0.15 to 0.83)**
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.43$, df = 1 ($p=0.51$); $I^2=0\%$						
Test for overall effect: $z=2.38$ ($p=0.02$)						
Solid organ transplantation candidates						
Casas 2011[124]	–0.182	0.39	95	95	10.2%	0.83 (0.39 to 1.79)
Subtotal (95% CI)			**95**	**95**	**10.2%**	**0.83 (0.39 to 1.79)**
Heterogeneity: not applicable						
Test for overall effect: $z=0.47$ ($p=0.64$)						
Post-kidney transplantation						
Hadaya 2013[128]	0.15	0.422	183	183	9.6%	1.16 (0.51 to 2.66)
Subtotal (95% CI)			**183**	**183**	**9.6%**	**1.16 (0.51 to 2.66)**
Heterogeneity: not applicable						
Test for overall effect: $z=0.36$ ($p=0.72$)						
IMID before antiTNF-α therapy						
Casas 2011[123]	0	0.279	202	214	12.4%	1.00 (0.58 to 1.73)
Hsia 2012[129]	0.126	0.194	2241	2282	14.0%	1.13 (0.78 to 1.66)
Kleinert 2012[133]	–0.857	0.24	685	1529	13.1%	0.42 (0.27 to 0.68)
Papay 2011[137]	0.003	0.356	195	208	10.8%	1.00 (0.50 to 2.02)
Ramos 2013[138]	1.491	0.543	152	153	7.6%	4.44 (1.53 to 12.87)
Vassilopoulos 2011[142]	–1.039	0.421	155	155	9.6%	0.35 (0.16 to 0.81)
Subtotal (95% CI)			**3627**	**4541**	**67.5%**	**0.90 (0.52 to 1.54)**
Heterogeneity: $\tau^2=0.35$; $\chi^2=24.75$, df = 5 ($p=0.0002$); $I^2=80\%$						
Test for overall effect: $z=0.40$ ($p=0.69$)						
Total (95% CI)			**4438**	**5353**	**100.0%**	**0.81 (0.54 to 1.22)**
Heterogeneity: $\tau^2=0.27$; $\chi^2=29.63$, df = 9 ($p=0.0005$); $I^2=70\%$						
Test for overall effect: $z=1.02$ ($p=0.31$)						
Test for subgroup differences: $\chi^2=4.43$, df = 3 ($p=0.22$); $I^2=32.3\%$						

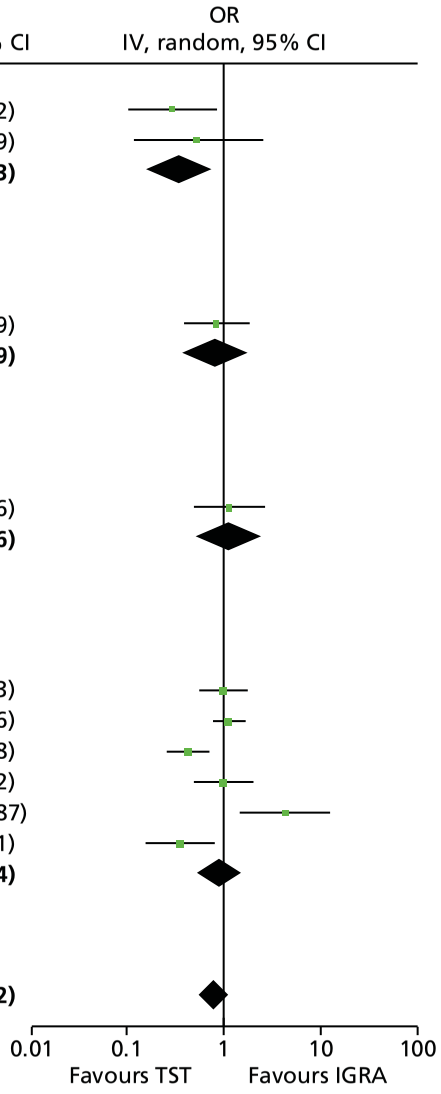


FIGURE 30 Pooled R-DOR of QFT-GIT/G vs. TST 5 mm based on high- and low-risk exposure in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Solid organ transplantation candidates						
Kim 2013[131]	−2.696	0.527	126	126	16.9%	0.07 (0.02 to 0.19)
Subtotal (95% CI)			**126**	**126**	**16.9%**	**0.07 (0.02 to 0.19)**
Heterogeneity: not applicable						
Test for overall effect: $z = 5.12$ ($p < 0.00001$)						
Haemodialysis – ESRD						
Al Jahdali 2013[121]	0.37	0.305	200	200	18.5%	1.45 (0.80 to 2.63)
Ates 2009[122]	0.975	0.4	246	259	17.9%	2.65 (1.21 to 5.81)
Chung 2010[126]	1.493	0.484	146	146	17.2%	4.45 (1.72 to 11.49)
Seyhan 2010[139]	1.329	0.582	100	100	16.4%	3.78 (1.21 to 11.82)
Subtotal (95% CI)			**692**	**705**	**69.9%**	**2.53 (1.48 to 4.34)**
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 5.01$, df = 3 ($p = 0.17$); $I^2 = 40\%$						
Test for overall effect: $z = 3.38$ ($p = 0.0007$)						
Lupus erythematosus						
Takeda 2011[141]	1.282	0.922	48	43	13.2%	3.60 (0.59 to 21.96)
Subtotal (95% CI)			**48**	**43**	**13.2%**	**3.60 (0.59 to 21.96)**
Heterogeneity: not applicable						
Test for overall effect: $z = 1.39$ ($p = 0.16$)						
Total (95% CI)			**866**	**874**	**100.0%**	**1.54 (0.48 to 4.92)**
Heterogeneity: $\tau^2 = 1.80$; $\chi^2 = 45.14$, df = 5 ($p < 0.00001$); $I^2 = 89\%$						
Test for overall effect: $z = 0.73$ ($p = 0.47$)						
Test for subgroup differences: $\chi^2 = 38.61$, df = 2 ($p < 0.00001$); $I^2 = 94.8\%$						

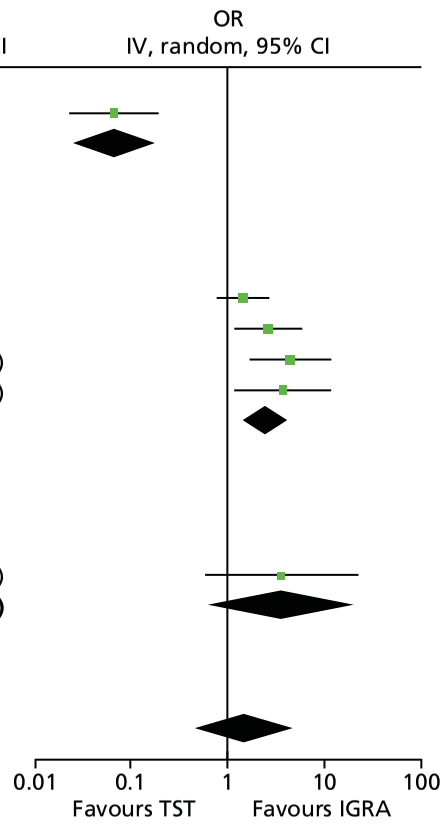


FIGURE 31 Pooled R-DOR of QFT-GIT/G vs. TST 10 mm based on high- and low-risk exposure in immunocompromised patients. df, degrees of freedom; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
HIV infection						
Chkhartishvili 2013[125]	0	0.469	218	236	10.6%	1.00 (0.40 to 2.51)
Subtotal (95% CI)			**218**	**236**	**10.6%**	**1.00 (0.40 to 2.51)**
Heterogeneity: not applicable						
Test for overall effect: $z = 0.00$ ($p = 1.00$)						
Solid organ transplantation candidates						
Kim 2010[130]	0.12	0.359	184	209	12.7%	1.13 (0.56 to 2.28)
Subtotal (95% CI)			**184**	**209**	**12.7%**	**1.13 (0.56 to 2.28)**
Heterogeneity: not applicable						
Test for overall effect: $z = 0.33$ ($p = 0.74$)						
Post-kidney transplantation						
Hadaya 2013[128]	0.557	0.427	183	183	11.4%	1.75 (0.76 to 4.03)
Subtotal (95% CI)			**183**	**183**	**11.4%**	**1.75 (0.76 to 4.03)**
Heterogeneity: not applicable						
Test for overall effect: $z = 1.30$ ($p = 0.19$)						
IMID before antiTNF-α therapy						
Costantino 2013[127]	0.325	0.209	475	514	15.7%	1.38 (0.92 to 2.08)
Kleinert 2012[133]	0.343	0.188	844	1529	16.1%	1.41 (0.97 to 2.04)
Laffitte 2009[134]	1.258	0.53	50	50	9.5%	3.52 (1.25 to 9.94)
Vassilopoulos 2011[142]	−0.603	0.375	155	155	12.4%	0.55 (0.26 to 1.14)
Subtotal (95% CI)			**1524**	**2248**	**53.8%**	**1.31 (0.80 to 2.14)**
Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 9.11$, df = 3 ($p = 0.03$); $I^2 = 67\%$						
Test for overall effect: $z = 1.07$ ($p = 0.28$)						
Hepatitis C						
Shen 2012[140]	2.134	0.42	70	70	11.5%	8.45 (3.71 to 19.24)
Subtotal (95% CI)			**70**	**70**	**11.5%**	**8.45 (3.71 to 19.24)**
Heterogeneity: not applicable						
Test for overall effect: $z = 5.08$ ($p < 0.00001$)						
Total (95% CI)			**2179**	**2946**	**100.0%**	**1.61 (1.01 to 2.57)**
Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 28.51$, df = 7 ($p = 0.0002$); $I^2 = 75\%$						
Test for overall effect: $z = 1.99$ ($p = 0.05$)						
Test for subgroup differences: $\chi^2 = 18.26$, df = 4 ($p = 0.001$); $I^2 = 78.1\%$						

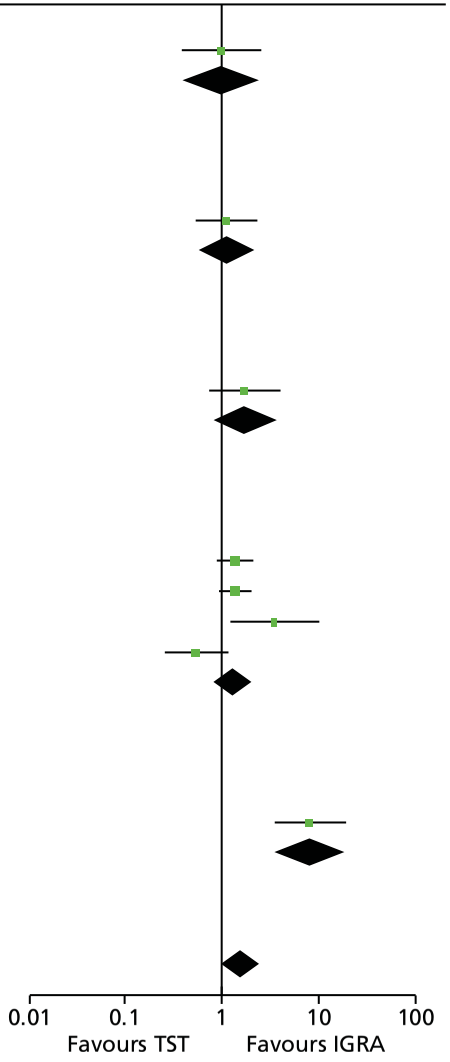


FIGURE 32 Pooled R-DOR of T-SPOT.*TB* vs. TST 5 mm based on high- and low-risk exposure in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; IV, inverse variance; SE, standard error.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
HIV infection						
Mutsvangwa 2010[136]	0.313	0.458	73	73	20.1%	1.37 (0.56 to 3.36)
Subtotal (95% CI)			**73**	**73**	**20.1%**	**1.37 (0.56 to 3.36)**
Heterogeneity: not applicable						
Test for overall effect: $z = 0.68$ ($p = 0.49$)						
Solid organ transplantation candidates						
Kim 2010[130]	0.115	0.42	184	209	21.0%	1.12 (0.49 to 2.56)
Subtotal (95% CI)			**184**	**209**	**21.0%**	**1.12 (0.49 to 2.56)**
Heterogeneity: not applicable						
Test for overall effect: $z = 0.27$ ($p = 0.78$)						
Haemodialysis – ESRD						
Chung 2010[126]	0.374	0.484	146	146	19.5%	1.45 (0.56 to 3.75)
Subtotal (95% CI)			**146**	**146**	**19.5%**	**1.45 (0.56 to 3.75)**
Heterogeneity: not applicable						
Test for overall effect: $z = 0.77$ ($p = 0.44$)						
IMID before antiTNF-α therapy						
Laffitte 2009[134]	1.273	0.534	50	50	18.4%	3.57 (1.25 to 10.17)
Subtotal (95% CI)			**50**	**50**	**18.4%**	**3.57 (1.25 to 10.17)**
Heterogeneity: not applicable						
Test for overall effect: $z = 2.38$ ($p = 0.02$)						
Hepatitis C						
Shen 2012[140]	2.134	0.42	70	70	21.0%	8.45 (3.71 to 19.24)
Subtotal (95% CI)			**70**	**70**	**21.0%**	**8.45 (3.71 to 19.24)**
Heterogeneity: not applicable						
Test for overall effect: $z = 5.08$ ($p < 0.00001$)						
Total (95% CI)			**523**	**548**	**100.0%**	**2.32 (1.05 to 5.12)**
Heterogeneity: $\tau^2 = 0.60$; $\chi^2 = 15.38$, df = 4 ($p = 0.004$); $I^2 = 74\%$						
Test for overall effect: $z = 2.09$ ($p = 0.04$)						
Test for subgroup differences: $\chi^2 = 15.38$, df = 4 ($p = 0.004$); $I^2 = 74.0\%$						

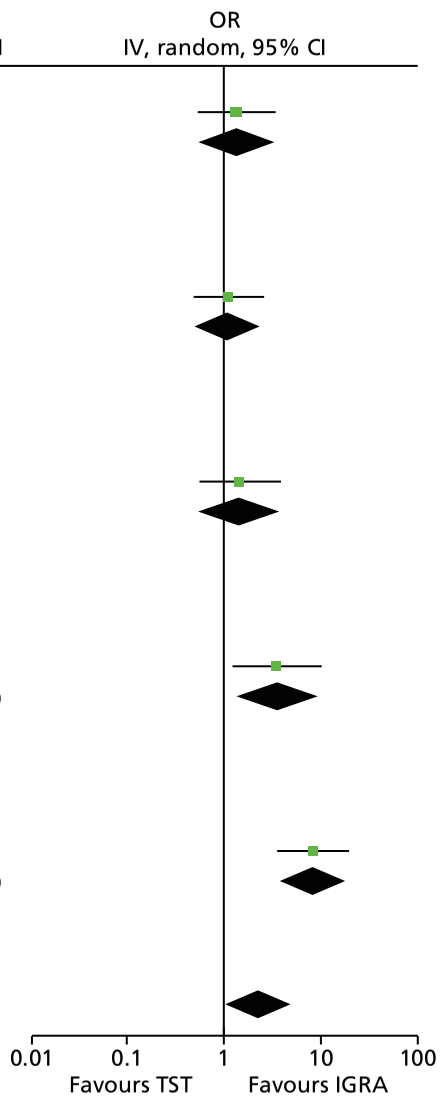
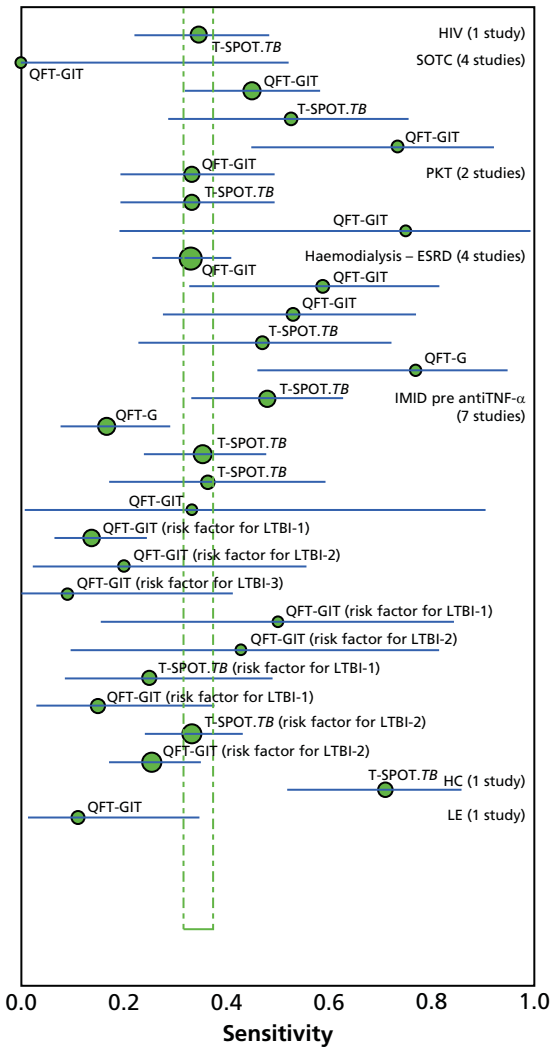


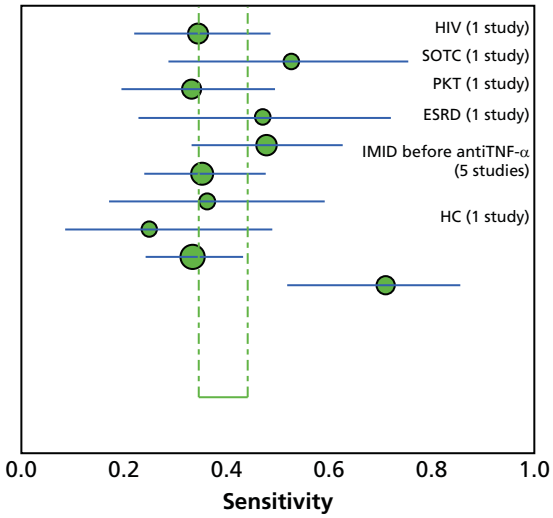
FIGURE 33 Pooled R-DOR of T-SPOT.*TB* vs. TST 10 mm based on high- and low-risk exposure in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; IV, inverse variance; SE, standard error.



	Sensitivity	(95% CI)
Mutsvangwa 2010[136]	0.35	(0.22 to 0.49)
Ahmadinejad 2013[120]	0.00	(0.00 to 0.52)
Casas 2011[124]	0.45	(0.32 to 0.58)
Kim 2010[130]	0.53	(0.29 to 0.76)
Kim 2013[131]	0.73	(0.45 to 0.92)
Hadaya 2013[128]	0.33	(0.20 to 0.50)
Hadaya 2013[128]	0.33	(0.20 to 0.50)
Kim 2013[132]	0.75	(0.19 to 0.99)
Al Jahdali 2013[121]	0.33	(0.26 to 0.41)
Ates 2009[122]	0.59	(0.33 to 0.82)
Chung 2010[126]	0.53	(0.28 to 0.77)
Chung 2010[126]	0.47	(0.23 to 0.72)
Seyhan 2010[139]	0.77	(0.46 to 0.95)
Costantino 2013[127]	0.48	(0.33 to 0.63)
Kleinert 2012[133]	0.17	(0.08 to 0.29)
Kleinert 2012[133]	0.35	(0.24 to 0.48)
Laffitte 2009[134]	0.36	(0.17 to 0.59)
Maritsi 2011[135]	0.33	(0.01 to 0.91)
Papay 2011[137]	0.14	(0.07 to 0.25)
Papay 2011[137]	0.20	(0.03 to 0.56)
Papay 2011[137]	0.09	(0.00 to 0.41)
Ramos 2013[138]	0.50	(0.16 to 0.84)
Ramos 2013[138]	0.43	(0.10 to 0.82)
Vassilopoulos 2011[142]	0.25	(0.09 to 0.49)
Vassilopoulos 2011[142]	0.15	(0.03 to 0.38)
Vassilopoulos 2011[142]	0.33	(0.24 to 0.43)
Vassilopoulos 2011[142]	0.25	(0.17 to 0.35)
Shen 2012[140]	0.71	(0.52 to 0.86)
Takeda 2011[141]	0.11	(0.01 to 0.35)

$\chi^2 = 102.90$; df = 28 ($p = 0.0000$)
Inconsistency (I^2) = 72.8%

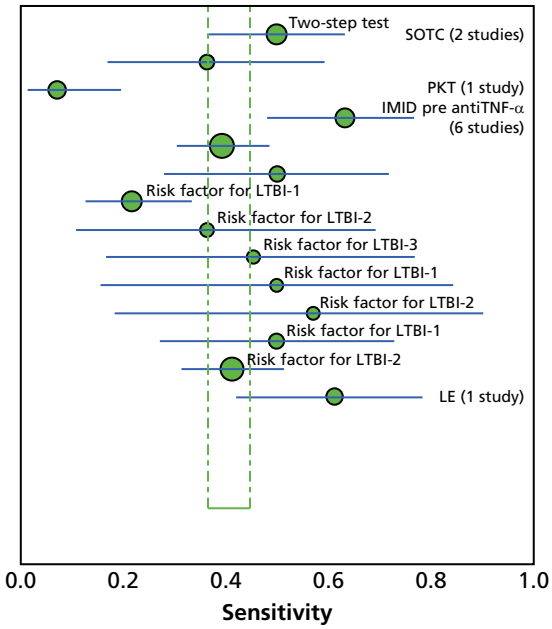
FIGURE 34 Forest plot of sensitivity based on exposure groups (QFT-GIT/G) in immunocompromised patients. df, degrees of freedom; HC, hepatitis C; IMID, immune-mediated inflammatory disease; LE, lupus erythematosus; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.



	Sensitivity	(95% CI)
Mutsvangwa 2010[136]	0.35	(0.22 to 0.49)
Kim 2010[130]	0.53	(0.29 to 0.76)
Hadaya 2013[128]	0.33	(0.20 to 0.50)
Chung 2010[126]	0.47	(0.23 to 0.72)
Costantino 2013[127]	0.48	(0.33 to 0.63)
Kleinert 2012[133]	0.35	(0.24 to 0.48)
Laffitte 2009[134]	0.36	(0.17 to 0.59)
Vassilopoulos 2011[142]	0.25	(0.09 to 0.49)
Vassilopoulos 2011[142]	0.33	(0.24 to 0.43)
Shen 2012[140]	0.71	(0.52 to 0.86)

$\chi^2 = 21.08$; df = 9 ($p = 0.0123$)
Inconsistency (I^2) = 57.3%

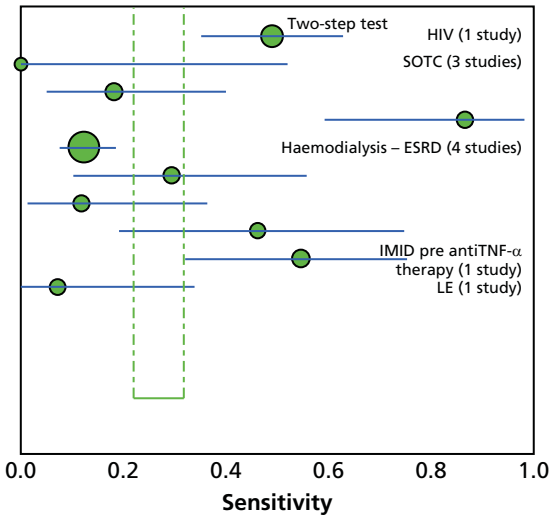
FIGURE 35 Forest plot of sensitivity based on exposure groups (T-SPOT.*TB*) in immunocompromised patients. df, degrees of freedom; HC, hepatitis C; IMID, immune-mediated inflammatory disease; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.



	Sensitivity (95% CI)	
Casas 2011[124]	0.50	(0.37 to 0.63)
Kim 2010[130]	0.36	(0.17 to 0.59)
Hadaya 2013[128]	0.07	(0.01 to 0.19)
Costantino 2013[127]	0.63	(0.48 to 0.77)
Kleinert 2012[133]	0.39	(0.31 to 0.49)
Laffitte 2009[134]	0.50	(0.28 to 0.72)
Papay 2011[137]	0.22	(0.13 to 0.33)
Papay 2011[137]	0.36	(0.11 to 0.69)
Papay 2011[137]	0.45	(0.17 to 0.77)
Ramos 2013[138]	0.50	(0.16 to 0.84)
Ramos 2013[138]	0.57	(0.18 to 0.90)
Vassilopoulos 2011[142]	0.50	(0.27 to 0.73)
Vassilopoulos 2011[142]	0.41	(0.32 to 0.51)
Shen 2012[140]	0.61	(0.42 to 0.78)

$\chi^2 = 56.22$; df = 13 ($p = 0.0000$)
Inconsistency (I^2) = 76.9%

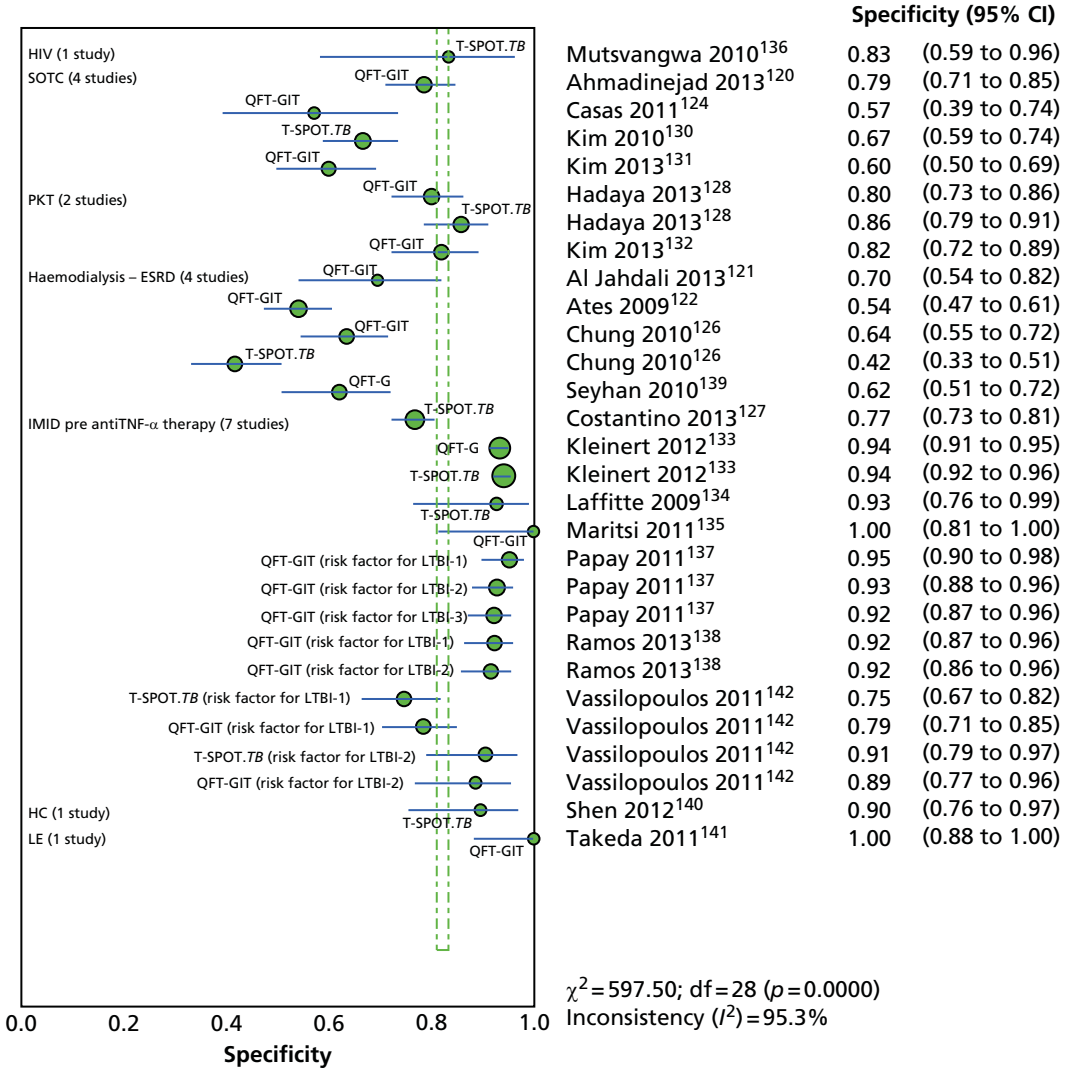
FIGURE 36 Forest plot of sensitivity based on exposure groups (TST 5 mm) in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; LE, lupus erythematosus; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.



	Sensitivity (95% CI)	
Mutsvangwa 2010[136]	0.49	(0.35 to 0.63)
Ahmadinejad 2013[120]	0.00	(0.00 to 0.52)
Kim 2010[130]	0.18	(0.05 to 0.40)
Kim 2013[131]	0.87	(0.60 to 0.98)
Al Jahdali 2013[121]	0.12	(0.08 to 0.19)
Ates 2009[122]	0.29	(0.10 to 0.56)
Chung 2010[126]	0.12	(0.01 to 0.36)
Seyhan 2010[139]	0.46	(0.19 to 0.75)
Laffitte 2009[134]	0.55	(0.32 to 0.76)
Takeda 2011[141]	0.07	(0.00 to 0.34)

$\chi^2 = 74.93$; df = 9 ($p = 0.0000$)
Inconsistency (I^2) = 88.0%

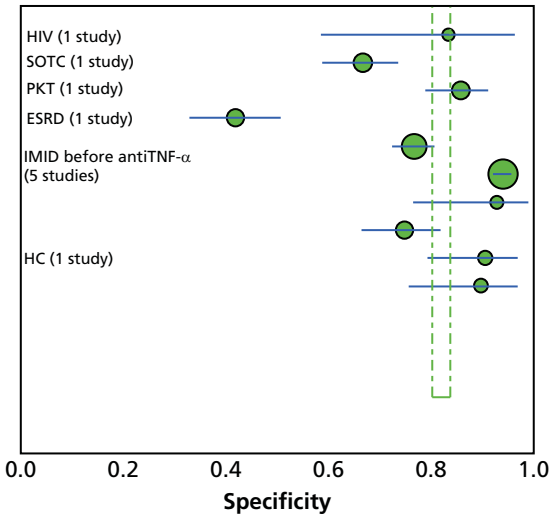
FIGURE 37 Forest plot of sensitivity based on exposure groups (TST 10 mm) in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; LE, lupus erythematosus; SOTC, solid organ transplantation candidate.



	Specificity	(95% CI)
Mutsvangwa 2010[136]	0.83	(0.59 to 0.96)
Ahmadinejad 2013[120]	0.79	(0.71 to 0.85)
Casas 2011[124]	0.57	(0.39 to 0.74)
Kim 2010[130]	0.67	(0.59 to 0.74)
Kim 2013[131]	0.60	(0.50 to 0.69)
Hadaya 2013[128]	0.80	(0.73 to 0.86)
Hadaya 2013[128]	0.86	(0.79 to 0.91)
Kim 2013[132]	0.82	(0.72 to 0.89)
Al Jahdali 2013[121]	0.70	(0.54 to 0.82)
Ates 2009[122]	0.54	(0.47 to 0.61)
Chung 2010[126]	0.64	(0.55 to 0.72)
Chung 2010[126]	0.42	(0.33 to 0.51)
Seyhan 2010[139]	0.62	(0.51 to 0.72)
Costantino 2013[127]	0.77	(0.73 to 0.81)
Kleinert 2012[133]	0.94	(0.91 to 0.95)
Kleinert 2012[133]	0.94	(0.92 to 0.96)
Laffitte 2009[134]	0.93	(0.76 to 0.99)
Maritsi 2011[135]	1.00	(0.81 to 1.00)
Papay 2011[137]	0.95	(0.90 to 0.98)
Papay 2011[137]	0.93	(0.88 to 0.96)
Papay 2011[137]	0.92	(0.87 to 0.96)
Ramos 2013[138]	0.92	(0.87 to 0.96)
Ramos 2013[138]	0.92	(0.86 to 0.96)
Vassilopoulos 2011[142]	0.75	(0.67 to 0.82)
Vassilopoulos 2011[142]	0.79	(0.71 to 0.85)
Vassilopoulos 2011[142]	0.91	(0.79 to 0.97)
Vassilopoulos 2011[142]	0.89	(0.77 to 0.96)
Shen 2012[140]	0.90	(0.76 to 0.97)
Takeda 2011[141]	1.00	(0.88 to 1.00)

$\chi^2 = 597.50$; df = 28 ($p = 0.0000$)
Inconsistency (I^2) = 95.3%

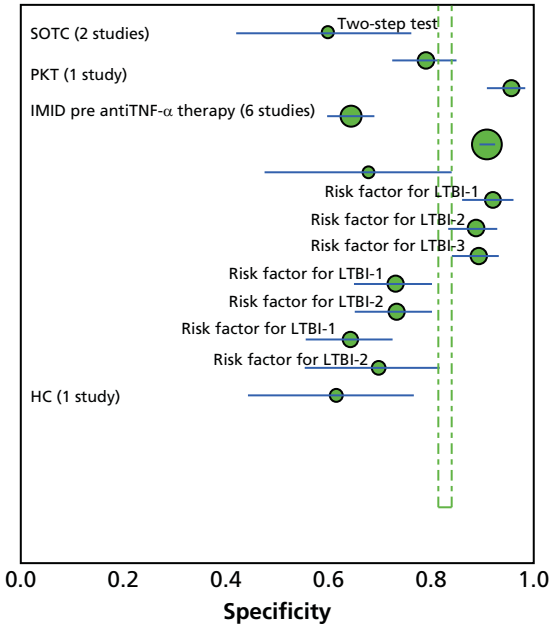
FIGURE 38 Forest plot of specificity based on exposure groups (QFT-GIT/G) in immunocompromised patients. df, degrees of freedom; HC, hepatitis C; IMID, immune-mediated inflammatory disease; LE, lupus erythematosus; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.



	Specificity	(95% CI)
Mutsvangwa 2010[136]	0.83	(0.59 to 0.96)
Kim 2010[130]	0.67	(0.59 to 0.74)
Hadaya 2013[128]	0.86	(0.79 to 0.91)
Chung 2010[126]	0.42	(0.33 to 0.51)
Costantino 2013[127]	0.77	(0.73 to 0.81)
Kleinert 2012[133]	0.94	(0.92 to 0.96)
Laffitte 2009[134]	0.93	(0.76 to 0.99)
Vassilopoulos 2011[142]	0.75	(0.67 to 0.82)
Vassilopoulos 2011[142]	0.91	(0.79 to 0.97)
Shen 2012[140]	0.90	(0.76 to 0.97)

$\chi^2 = 244.57$; df = 9 ($p = 0.0000$)
Inconsistency (I^2) = 96.3%

FIGURE 39 Forest plot of specificity based on exposure groups (T-SPOT.*TB*) in immunocompromised patients. df, degrees of freedom; HC, hepatitis C; IMID, immune-mediated inflammatory disease; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.



	Specificity	(95% CI)
Casas 2011[124]	0.60	(0.42 to 0.76)
Kim 2010[130]	0.79	(0.73 to 0.85)
Hadaya 2013[128]	0.96	(0.91 to 0.98)
Costantino 2013[127]	0.65	(0.60 to 0.69)
Kleinert 2012[133]	0.91	(0.90 to 0.93)
Laffitte 2009[134]	0.68	(0.48 to 0.84)
Papay 2011[137]	0.92	(0.86 to 0.96)
Papay 2011[137]	0.89	(0.84 to 0.93)
Papay 2011[137]	0.89	(0.84 to 0.93)
Ramos 2013[138]	0.73	(0.65 to 0.80)
Ramos 2013[138]	0.73	(0.65 to 0.80)
Vassilopoulos 2011[142]	0.64	(0.56 to 0.72)
Vassilopoulos 2011[142]	0.70	(0.56 to 0.82)
Shen 2012[140]	0.62	(0.45 to 0.77)

$\chi^2 = 287.89$; df = 13 ($p = 0.0000$)
Inconsistency (I^2) = 95.5%

FIGURE 40 Forest plot of specificity based on exposure groups (TST 5 mm) in immunocompromised patients. df, degrees of freedom; HC, hepatitis C; IMID, immune-mediated inflammatory disease; PKT, post-kidney transplantation; SOTC, solid organ transplantation candidate.

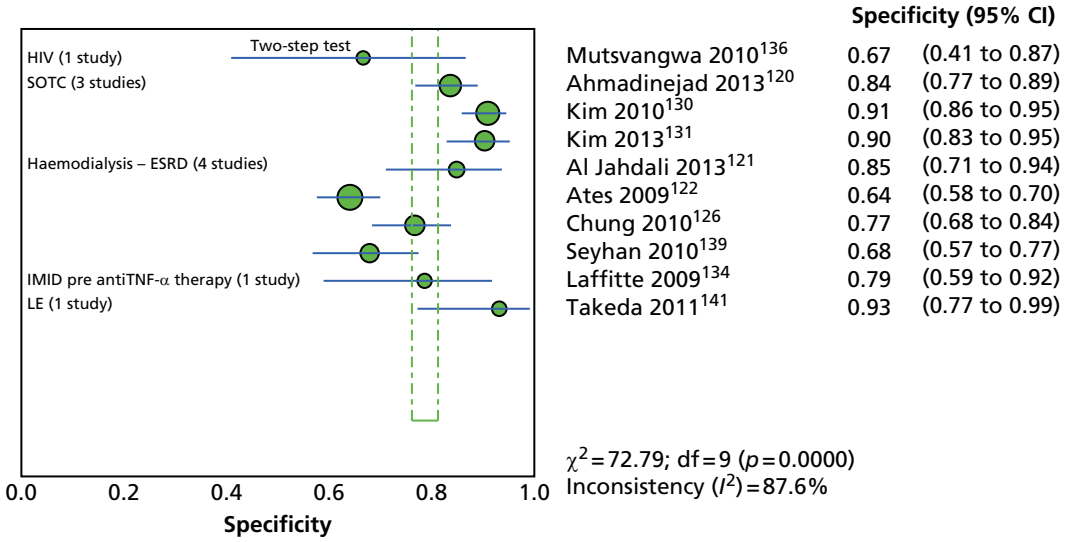


FIGURE 41 Forest plot of specificity based on exposure groups (TST 10 mm) in immunocompromised patients. df, degrees of freedom; IMID, immune-mediated inflammatory disease; LE, lupus erythematosus; SOTC, solid organ transplantation candidate.

TABLE 16 Association between test positivity and BCG vaccination status in immunocompromised patients: exposure studies

Study ID, country (burden)	Sample size, *n*	Type of IGRA/TST induration threshold	Association between test positivity and BCG vaccination status: OR (95% CI)	
			Crude/unadjusted	Adjusted
Ahmadinejad 2013,[120] Iran (intermediate)	159	QFT-GIT	0.38 (0.11 to 1.24)	NR
	164	TST 10 mm	0.60 (0.15 to 2.34)	NR
Al Jahdali 2013,[121] Saudi Arabia (low)	NA	QFT-GIT	NR	NR
	NA	TST 10 mm (two step)	NR	NR
Ates 2009,[122] Turkey (intermediate)	246	QFT-GIT	1.13 (0.68 to 1.86)	1.14 (0.68 to 1.92)
	259	TST 10 mm	0.85 (0.51 to 1.43)	0.87 (0.50 to 1.51)
Casas 2011,[123] Spain (low)	214	QFT-GIT	1.20 (0.50 to 3.20)	NR
	214	TST 5 mm	1.70 (0.90 to 3.40)	1.50 (0.70 to 3.40)
Casas 2011,[124] Spain (low)	95	QFT-GIT	0.62 (0.26 to 1.42)	NR
	95	TST 5 mm (two step)	0.83 (0.35 to 2.00)	NR
Chkhartishvili 2013,[125] Georgia (high)	240	QFT-GIT	1.41 (0.38 to 5.29)	NR
	240	T-SPOT.*TB*	1.78 (0.38 to 8.28)	NR
	240	TST 5 mm	2.55 (0.32 to 20.18)	NR
Chung 2010,[126] South Korea (high)	146	QFT-GIT	NR	NR
	146	T-SPOT.*TB*	NR	NR
	146	TST 10 mm	NR	NR

continued

TABLE 16 Association between test positivity and BCG vaccination status in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Sample size, *n*	Type of IGRA/TST induration threshold	Association between test positivity and BCG vaccination status: OR (95% CI)	
			Crude/unadjusted	Adjusted
Costantino 2013,[127] France (low)	563	T-SPOT.*TB*	NR	0.39 (0.24 to 0.62)
	563	TST 5 mm	NR	NR ($p = 0.11$, NS)
Hadaya 2013,[128] Switzerland (low)	183	QFT-GIT	NR	NR
	183	T-SPOT.*TB*	NR	NR
	183	TST 5 mm	NR	NR
Hsia 2012,[129] USA (low)	2029	QFT-GIT	NR	1.00 (0.66 to 1.51)
	2029	TST 5 mm	NR	2.47 (1.71 to 3.55)
Kim 2010,[130] South Korea (high)	184	T-SPOT.*TB*	0.69 (0.36 to 1.34)	NR
	209	TST 5 mm	1.25 (0.55 to 2.82)	NR
	209	TST 10 mm	0.89 (0.31 to 2.58)	NR
Kim 2013,[131] South Korea (high)	120	QFT-GIT	1.94 (0.48 to 7.91)	2.32 (0.50 to 10.66)
	119	TST 10 mm	2.56 (0.31 to 21.06)	3.32 (0.38 to 28.97)
Kim 2013,[132] South Korea (high)	93	QFT-GIT	NR	NR
	93	TST 10 mm	NR	NR
Kleinert 2012,[133] Germany (low)	685	QFT-G	NR	0.43 (0.17 to 1.10)
	844	T-SPOT.*TB*	NR	1.07 (0.47 to 2.43)
	1529	TST 5 mm	3.17 (2.19 to 4.58)	2.95 (2.00 to 4.35)
Laffitte 2009,[134] Switzerland (low)	50	T-SPOT.*TB*	1.00 (0.01 to 10.07)	NR
	50	TST 5 mm	2.92 (0.30 to 28.29)	NR
	50	TST 10 mm	2.43 (0.25 to 23.57)	NR
Maritsi 2011[135] UK (low)	NR	QFT-GIT	NR	NR
	NR	TST NR mm	NR	NR
Mutsvangwa 2010,[136] Zimbabwe (high)	NR	T-SPOT.*TB*	NR	NR
	NR	TST 10 mm (two step)	NR	NR
Papay 2011,[137] Austria (low)	192	QFT-GIT	NR	NR
	192	TST 5 mm	NR	NR
Ramos 2013,[138] Spain (low)	153	QFT-GIT	NR	5.10 (1.50 to 17.50)
	153	TST 5 mm	NR	2.40 (1.01 to 5.80)
Seyhan 2010,[139] Turkey (intermediate)	100	QFT-G	NR	NR
	100	TST 10 mm	NR	4.10 (1.30 to 13.90)
Shen 2012,[140] China (high)	70	T-SPOT.*TB*	NR	NR
	70	TST 5 mm	NR	NR

TABLE 16 Association between test positivity and BCG vaccination status in immunocompromised patients: exposure studies (*continued*)

Study ID, country (burden)	Sample size, *n*	Type of IGRA/TST induration threshold	Association between test positivity and BCG vaccination status: OR (95% CI)	
			Crude/unadjusted	Adjusted
Souza 2014,[153] Brazil (intermediate)	299	QFT-GIT	NR	NR
	300	TST 5 mm	NR	NR
Takeda 2011,[141] Japan (low)	71	QFT-2G (QFT-G)	NR	NR
	43	TST 10 mm	NR	NR
Vassilopoulos 2011,[142] Greece (low)	157	T-SPOT.*TB*	0.75 (NR; $p = 0.45$)	0.51 (NR; $p = 0.17$)
	157	TST	1.36 (NR; $p = 0.39$)	1.43 (NR; $p = 0.34$)
	157	QFT-GIT	1.14 (NR; $p = 0.76$)	1.05 (NR; $p = 0.90$)

ID, identification; NA, not applicable; NR, not reported; NS, not significant.

The data on between-test concordance, discordance and agreement from the 32 more recent studies are presented in *Table 17*. Six[116,126,133,135,140,141] of the 32 studies did not report these data (see *Table 17*). Overall, the per cent concordance and kappa ranges between QFT-GIT and TST according to each condition were as follows: HIV infection – concordance 75–96%, kappa 0.29–0.48; haematological disorders – concordance 70.6–80%, kappa 0.09–0.16; solid organ transplantation candidates – concordance 65–80%, kappa 0.19–0.57; post-kidney transplantation – concordance 80%, kappa 0.09–0.27; ESRD/haemodialysis – concordance 60–86.4%, kappa 0.21–0.49; and immune-mediated inflammatory diseases before antiTNF-α therapy – concordance 60–93%, kappa 0.08–0.56 (see *Table 17*).

Four studies[115,127,129,130] reported between-test agreement parameters by BCG vaccination status, three[127,129,130] of which showed a lower per cent concordance and kappa values for BCG-vaccinated participants than for non-vaccinated participants (see *Table 17*).

Indeterminate test results

This section included three studies[170,171,181] reviewed in CG117[10] (see *Appendix 5*) and 32 more recent studies (see previous section) (see *Appendix 9*). Of the recent studies, six[121,126,133,134,136,155] did not report this outcome.

The proportions of indeterminate results according to each condition and type of IGRA test were follows: HIV infection – QFT-GIT 0.30–17.87%, T-SPOT.*TB* 32.80%;[114,125,153,170,171,181] haematological disorders – QFT-GIT 6.00–13.93%;[115,149] solid organ transplantation candidates – QFT-GIT 2.11–4.76%, T-SPOT.*TB* 11.96%;[120,124,130,131] post-kidney transplantation – QFT-GIT 1.64–4.30%, T-SPOT.*TB* 11%;[116,128,132] ESRD/haemodialysis – QFT-GIT 0–10.55%, T-SPOT.*TB* 0%;[117,118,122,139] immune-mediated inflammatory diseases before antiTNF-α therapy – QFT-GIT 0–7.69%, T-SPOT.*TB* 0–15.63%;[119,123,127,129,137,138,142] hepatitis C – T-SPOT.*TB* 0%;[140] and lupus erythematosus – QFT-GIT 32.39%.[141]

TABLE 17 Between-test concordance and discordance in immunocompromised patients: exposure and incidence studies

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
HIV infection					
Chkhartishvili 2013,[125] Georgia (high)	233	QFT-GIT vs. TST 5 mm	74.25 (68.27 to 79.44)	25.75 (20.56 to 31.73)	0.29 (0.16 to 0.42)
	217	T-SPOT.*TB* vs. TST 5 mm	75.12 (68.96 to 80.4)	24.88 (19.6 to 31.04)	0.22 (0.07 to 0.29)
Elzi 2011,[114] Switzerland (low)	32	T-SPOT.*TB* vs. TST 5 mm	56.25 (39.33 to 71.83)	43.75 (28.17 to 60.67)	0.12 (–0.22 to 0.46)
Mutsvangwa 2010,[136] Zimbabwe (high)	Total	T-SPOT.*TB* vs. TST 10 mm (two step)	NR	NR	NR
	55 TB index case contacts	T-SPOT.*TB* vs. TST 10 mm (two step)	70.91 (57.86 to 81.23)	29.09 (18.77 to 42.14)	0.41 (0.16 to 0.66)
	18 control index contacts	T-SPOT.*TB* vs. TST 10 mm (two step)	72.22 (49.13 to 87.5)	27.78 (12.5 to 50.87)	0.28 (–0.13 to 0.70)
Souza 2014,[153] Brazil (intermediate)	299	QFT-GIT vs. TST 5 mm	96.00 (93.12 to 97.69)	4.01 (2.31 to 6.88)	0.48 (0.37 to 0.59)
Haematopoietic stem cell transplantation candidates					
Lee 2014,[149] South Korea (high)	159	QFT-GIT vs. TST 5 mm	79.87 (72.97 to 85.37)	20.13 (14.63 to 27.03)	0.16 (0.01 to 0.31)
	159	QFT-GIT vs. TST 10 mm	NR	NR	NR
Moon 2013,[115] South Korea (high)	210	QFT-GIT vs. TST 5 mm	73.81 (67.47 to 79.29)	26.19 (20.71 to 32.53)	0.09 (–0.04 to 0.22)
	210	QFT-GIT vs. TST 10 mm	78.57 (72.53 to 83.58)	21.43 (16.42 to 27.47)	0.15 (0.02 to 0.27)
	176 with BCG history	QFT-GIT vs. TST 5 mm	74.43 (67.51 to 80.31)	25.57 (19.69 to 32.49)	0.13 (–0.02 to 0.27)
	34 with no BCG history	QFT-GIT vs. TST 5 mm	70.59 (53.83 to 83.17)	29.41 (16.83 to 46.17)	–0.10 (–0.35 to 0.14)
Solid organ transplantation candidates					
Ahmadinejad 2013,[120] Iran (intermediate)	159	QFT-GIT vs. TST 10 mm	79.87 (72.97 to 85.37)	20.13 (14.63 to 27.03)	0.32 (0.17 to 0.47)
Casas 2011,[124] Spain (low)	95	QFT-GIT vs. TST 5 mm (two step)	78.95 (69.71 to 85.94)	36.36 (24.93 to 49.58)	0.57 (0.37 to 0.77)
Kim 2010,[130] South Korea (high)	184 total	T-SPOT.*TB* vs. TST 10 mm	71.2 (64.27 to 77.25)	28.8 (22.75 to 35.73)	0.23 (0.12 to 0.34)
	145 BCG vaccinated	T-SPOT.*TB* vs. TST 10 mm	70.34 (62.46 to 77.18)	29.66 (22.82 to 37.54)	0.19 (0.06 to 0.31)

TABLE 17 Between-test concordance and discordance in immunocompromised patients: exposure and incidence studies (*continued*)

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Kim 2013,[131] South Korea (high)	119	QFT-G vs. TST 10 mm	65.49 (56.34 to 73.61)	34.51 (26.39 to 43.66)	0.26 (0.10 to 0.41)
Post-kidney transplantation					
Hadaya 2013,[128] Switzerland (low)	200	QFT-GIT vs. TST 5 mm	NR	NR	0.11 ($p = 0.010$)
	200	T-SPOT.*TB* vs. TST 5 mm	NR	NR	0.09 ($p = 0.034$)
Kim 2011,[116] South Korea (high)	NR	NR	NR	NR	NR
Kim 2013,[132] South Korea (high)	93	QFT-G vs. TST 10 mm	79.57 (70.28 to 86.51)	20.43 (13.49 to 29.72)	0.27 (0.07 to 0.46)
Haemodialysis – ESRD					
Al Jahdali 2013,[121] Saudi Arabia (low)	200	QFT-GIT vs. TST 10 mm (two step)	75.50 (69.10 to 80.94)	24.50 (19.06 to 30.90)	0.34 (0.22 to 0.45)
Anibarro 2012,[117] Spain (low)	52	QFT-GIT vs. TST 5 mm	71.15 (57.73 to 81.67)	28.85 (18.33 to 42.27)	0.21 (0.04 to 0.37)
	52	QFT-GIT vs. TST 5 mm (two step)	78.85 (65.97 to 87.76)	21.15 (12.24 to 34.03)	0.49 (0.22 to 0.74)
Ates 2009,[122] Turkey (intermediate)	230	QFT-GIT vs. TST 10 mm	67.83 (61.54 to 73.53)	32.17 (26.47 to 38.46)	0.34 (0.21 to 0.47)
Chung 2010,[126] South Korea (high)	146	QFT-G vs. TST 10 mm	NR	NR	NR
	146	T-SPOT.*TB* vs. TST 10 mm	NR	NR	NR
Lee 2009,[118] Taiwan (high)	32	QFT-G vs. TST 10 mm (two step)	60.00 (NR)	40.00 (NR)	0.25 (–0.06 to 0.56)
	32	T-SPOT.*TB* vs. TST 10 mm (two step)	65.60 (NR)	34.40 (NR)	0.32 (–0.01 to 0.65)
Seyhan 2010,[139] Turkey (intermediate)	100	QFT-GIT vs.TST 10 mm	65.00 (55.25 to 73.64)	35.00 (26.36 to 44.75)	0.27 (0.07 to 0.46)
Sherkat 2014,[155] Iran (intermediate)	44	T-SPOT.*TB* vs. TST 10 mm	86.36 (73.29 to 93.6)	13.64 (6.40 to 26.71)	0.49 (0.20 to 0.78)

continued

TABLE 17 Between-test concordance and discordance in immunocompromised patients: exposure and incidence studies (*continued*)

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Immune-mediated inflammatory diseases before antiTNF-α therapy					
Casas 2011,[123] Spain (low)	202	QFT-GIT vs.TST 5 mm	84.16 (78.49 to 88.55)	15.84 (11.45 to 21.51)	0.56 (0.42 to 0.70)
Chang 2011,[119] South Korea (high)	100	QFT-GIT vs. TST 10 mm	67.0 (57.31 to 75.44)	33.0 (24.56 to 42.69)	0.26 (0.07 to 0.45)
	42 RA sample	QFT-GIT vs. TST 10 mm	76.20 (61.47 to 86.52)	23.80 (13.48 to 38.53)	0.46 (0.21 to 0.72)
	58 AS sample	QFT-GIT vs. TST 10 mm	60.34 (47.49 to 71.91)	39.66 (28.09 to 52.51)	0.14 (–0.10 to 0.39)
Costantino 2013,[127] France (low)	444 total	T-SPOT.*TB* vs. TST 5 mm	62.84 (58.25 to 67.2)	37.16 (32.8 to 41.75)	0.16 (0.07 to 0.25)
	NR BCG vaccinated	T-SPOT.*TB* vs. TST 5 mm	NR	NR	0.15 (NR)
	NR BCG non-vaccinated	T-SPOT.*TB* vs. TST 5 mm	NR	NR	0.22 (NR)
Hsia 2012,[129] USA (low)	2282 total	QFT-GIT vs. TST 5 mm	NR	NR	0.22 (0.15 to 0.27)
	781 BCG vaccinated	QFT-GIT vs. TST 5 mm	82.84 (80.04 to 85.32)	17.16 (14.68 to 19.96)	0.20 (0.13 to 0.27)
	1248 BCG non-vaccinated	QFT-GIT vs. TST 5 mm	93.11 (91.57 to 94.39)	6.89 (5.61 to 8.43)	0.32 (0.26 to 0.37)
Kleinert 2012,[133] Germany (low)	685	QFT-G vs. TST 5 mm	NR	NR	NR
	844	T-SPOT.*TB* vs. TST 5 mm	NR	NR	NR
Laffitte 2009,[134] Switzerland (low)	50	T-SPOT.*TB* vs. TST 5 mm	72.00 (58.33 to 82.53)	28.00 (17.47 to 41.67)	0.36 (0.12 to 0.61)
Maritsi 2011,[135] South Africa (high)	NR	QFT-G vs. TST NR mm	NR	NR	NR
Papay 2011,[137] Austria (low)	192	QFT-GIT vs. TST 5 mm	84.90 (79.15 to 89.27)	15.10 (10.73 to 20.85)	0.21 (0.07 to 0.34)
Ramos 2013,[138] Spain (low)	90	QFT-GIT vs. TST 5 mm	75.56 (65.75 to 83.27)	24.44 (16.73 to 34.25)	0.08 (–0.05 to 0.22)
Vassilopolous 2011,[142] Greece (low)	155	QFT-GIT vs. TST 5 mm	63.87 (56.06 to 71.01)	36.13 (28.99 to 43.94)	0.15 (0.01 to 0.29)
	155	T-SPOT.*TB* vs. TST 5 mm	71.0 (63.38 to 77.54)	29.03 (22.46 to 36.62)	0.34 (0.17 to 0.50)

TABLE 17 Between-test concordance and discordance in immunocompromised patients: exposure and incidence studies (*continued*)

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Hepatitis C					
Shen 2012,[140] China (high)	70	T-SPOT.*TB* vs. TST 5 mm	NR	NR	NR
Lupus erythematosus					
Takeda 2011,[141] Japan (low)	NR	QFT-GIT vs. TST 10 mm	NR	NR	NR

AS, ankylosing spondylitis; ID, identification; NR, not reported; RA, rheumatoid arthritis.

Summary of studies in immunocompromised patients

This section included 48 studies: 16 studies reviewed in CG117[10] (see *Appendix 5*) and 32 more recent studies published from 2009 onwards (see *Appendix 9*). The studies were stratified and analysed according to the following subgroups: HIV infection, solid organ transplantation candidates, post-kidney transplantation, haemodialysis (ESRD), immune-mediated inflammatory diseases before antiTNF-α therapy, hepatitis C and lupus erythematosus. The majority of the more recent studies were rated as being at moderate/high ROB (incidence studies) or of moderate/low methodological quality (exposure studies).

Only two of eight studies reported sufficient data to calculate R-CIRs to compare the performance of IGRAs and the TST in predicting the incidence of active TB. The R-CIR estimates in both studies were non-significant with very wide CIs, thereby rendering their interpretation inconclusive. These studies were not combined because the TST was used with different thresholds and one study used a two-step TST.

Across the 32 newly identified studies there was wide variability and the absence of a clear pattern in the estimates of sensitivity and specificity. In general, for both the IGRAs and TST, specificity tended to be greater than sensitivity. Some or all of the observed variation was the result of zero count events (unstable estimates), underlying differences in study populations/conditions and settings, and variation in exposure definitions and measurement and TST thresholds. The heterogeneity persisted even after stratifying the estimates by type of IGRA (QFT-GIT, T-SPOT.*TB*) and TST threshold (5 mm, 10 mm). In light of the observed heterogeneity, no meta-analysis was undertaken.

The association between the screening test results and the risk of LTBI/exposure level was measured using the R-DOR (IGRA vs. TST) in individual studies and ranged from 0.07 to 8.45. The forest plot analysis of R-DORs included 21 studies and revealed a significant amount of heterogeneity across all subgroups of participants except for those undergoing haemodialysis, in whom the IGRA (QFT-GIT) was more strongly associated with exposure groups than the TST 10 mm (pooled R-DOR 2.53, 95% CI 1.48 to 4.34). Similarly, in participants with hepatitis C, the IGRA (T-SPOT.*TB*) outperformed the TST 5 mm in detecting LTBI (R-DOR 8.45, 95% CI 3.71 to 19.24). In people with HIV/AIDS, the TST 10 mm performed significantly better than QFT-GIT (pooled R-DOR 0.35, 95% CI 0.15 to 0.83). For the remaining subgroups (lupus erythematosus, solid organ transplantation candidates, kidney transplant recipients), the performance of QFT-GIT did not significantly differ from that of the TST (wide 95% CIs and inconclusive results). For most subgroups the within-subgroup heterogeneity by IGRA type (QFT-GIT, T-SPOT.*TB*) and TST threshold (5 mm, 10 mm, 15 mm) could not be examined because of sparse data.

Overall, there was no evidence indicating a differential effect of BCG vaccination status on IGRA and TST positivity in the 14 newly identified studies reporting the association between test positivity and BCG vaccination status. Only one study demonstrated a significantly increased OR for TST 10 mm positivity (OR 4.28, 95% CI 1.35 to 13.64) as opposed to the non-significant OR for IGRA (OR 1.89, 95% CI 0.75 to 4.73) in relation to BCG vaccination status.

Overall, the per cent concordance and kappa ranges between QFT-GIT and TST according to each condition were as follows: HIV – concordance 75–96%, kappa 0.29–0.48; haematological disorders – concordance 70.6–80%, kappa 0.09–0.16; solid organ transplantation candidates – concordance 65–80%, kappa 0.19–0.57; post-kidney transplantation – concordance 80%; kappa 0.09–0.27); ESRD/ haemodialysis – concordance 60–86.4%, kappa 0.21–0.49; and immune-mediated inflammatory diseases before antiTNF-α therapy – concordance 60–93%, kappa 0.08–0.56. Three studies reported between-test agreement parameters by BCG vaccination status, which showed a lower per cent concordance and kappa values for BCG-vaccinated participants than for non-vaccinated participants.

Recent arrivals from countries with a high incidence of tuberculosis

Description of baseline characteristics

This section included 15 studies in total.[143–147,166,183–191] Our searches identified five studies[143–147] in individuals who had recently arrived from mainly high TB incidence countries: two[143,144] investigated the incidence of active TB following testing for LTBI (incidence studies) and three[145–147] investigated levels of exposure in relationship to LTBI test outcomes (exposure studies). An additional 10 studies[166,183–191] in recently arrived immigrants were identified in CG117.[10] Details of the additional studies included from CG117[10] can be found in *Appendix 5*.

Incidence studies

Two studies[143,144] investigated the agreement of a QFT test with the TST in individuals recently arrived from high TB incidence countries, one[143] from Norway and the other[144] from the Netherlands. Both studies used a prospective cohort design and were community based. Follow-up ranged from 23 to 32 months in the study by Harstad *et al.*[143] whereas Kik *et al.*[144] followed up participants for 24 months.

Harstad *et al.*[143] compared the QFT-GIT and TST with cut-off values of ≥ 6 mm and ≥ 15mm, whereas Kik *et al.*[144] compared the QFT-GIT, T-SPOT.*TB* and TST with cut-off values of ≥ 10 mm and ≥ 15 mm. Around 25%[143] and 43%[144] of patients in the studies were female. Kik *et al.*[144] included people who were aged 16–45 years and Harstad *et al.*[143] included people aged > 18 years. In the study by Kik *et al.*[144] approximately 8% of the study population originated from Europe/North America, 8% from South America, 36% from Asia, 29% from African countries other than sub-Saharan countries and 17% from sub-Saharan Africa, with 1.5% of participants being of unknown geographical origin. In this study the proportion of patients who had received a BCG vaccination was high at 81%.[144] In the study by Harstad *et al.*,[143] 13% of participants were from Europe, 42% from Africa, a further 42% from Asia and 3% from other countries. BCG vaccination was not reported in this study. *Table 18* provides further details on these studies.

TABLE 18 Baseline characteristics of studies in recent arrivals from countries with a high incidence of TB: incidence studies

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Numbers of recruited and excluded study participants	Comments
Harstad 2010,[143] Norway (low)	Aim: to compare PPV and NPV between QFT-GIT and the TST in asylum seekers in Norway Setting: community based Design: prospective cohort study Follow-up: 23–32 months Funding source: Norwegian Health Association; regional Health Authorities	NR	Inclusion criteria: asylum seekers aged ≥ 18 years Exclusion criteria: active TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA: NR; TST: induration of ≥ 6 mm and ≥ 15 mm	Age range: 18–34 years $n = 587$, 35–49 years $n = 201$ and ≥ 50 years $n = 35$ Female, *n* (%): 206 (25.0) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): Europe 103 (12.5), Africa 347 (42.0), Asia 346 (42.0), other 27 (3.3) BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n/N* (%): 9/823 (1.1) Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): NA Comorbidity, *n* (%): NA	Total number of recruited patients: NR; total number of excluded patients: NR	

continued

TABLE 18 Baseline characteristics of studies in recent arrivals from countries with a high incidence of TB: incidence studies (*continued*)

Study ID, country (burden)	Study aim, setting, design, follow-up duration and funding source	Method(s) of diagnosis of active TB	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Numbers of recruited and excluded study participants	Comments
Kik 2010,[144] Netherlands (low)	Aim: to assess PPV and NPV, sensitivity and specificity for TB disease of QFT-GIT, T-SPOT.*TB* and TST in immigrant individuals in the Netherlands who were recently exposed to infectious pulmonary TB patients Setting: community based Design: prospective cohort study Follow-up: 24 months Funding source: unrestricted grants from the Netherlands Organisation for Health Research and Development	Contacts diagnosed with TB ≥ 3 months after the diagnosis of the index patient were considered to be incident cases whereas TB cases diagnosed < 3 months after the diagnosis of the index patient were considered to be coprevalent and were excluded from the analysis. The diagnosis of TB disease was based on chest radiography, symptoms, smear and/or culture results	Inclusion criteria: close contacts (aged ≥ 16 years and born in a TB-endemic country) of sputum smear-positive pulmonary TB patients who tested positive on the TST (≥ 5 mm) Exclusion criteria: contacts with known conditions associated with an increased risk of progression to disease (including diabetes and HIV infection) and individuals who were given preventative treatment	Type of tests: IGRA (QFT-GIT), IGRA (T-SPOT.*TB*), TST Cut-off values/ thresholds: IGRA (QFT-GIT): two-tube format positive test was defined as ≥ 0.35 IU/ml; IGRA (T-SPOT.*TB*): according to the manufacturer; TST: induration of ≥ 10 mm and ≥ 15 mm	Age range: 16–24 years *n* = 53 (15.6%), 25–34 years *n* = 80 (23.6%), 35–44 years *n* = 115 (33.9%) and ≥ 45 years *n* = 91 (26.8%) Female, *n* (%): 147 (43.4) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): Europe/North America 27 (8.0), South America 27 (8.0), Asia 123 (36.3), other Africa 98 (28.9), sub-Saharan Africa 59 (17.4), unknown 5 (1.5) BCG vaccination, *n* (%): 274 (80.8) History of antiTB treatment, *n* (%): 0 Total incidence of active TB, *n/N* (%): 9/339 (2.65) Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR	Total number of recruited patients: 433; total number of excluded patients: 91 (furthermore, five contacts were excluded in the secondary analysis as their follow-up started 12 months before 1 August 2008)	

ID, identification; NA, not applicable; NR, not reported.

Exposure studies

Three studies[145–147] compared an IGRA test with the TST test in recent arrivals from countries with a high incidence of TB, relating test outcome to previous level of exposure. All studies within this group were therefore classed as having either a retrospective cohort or a cross-sectional design. The tests compared were the QFT-GIT and TST (≥ 10 mm),[145–147] with Lucas *et al.*[145] also testing the T-SPOT.*TB*. The studies were undertaken in community settings in Australia[145] and Italy.[146,147] Lucas *et al.*[145] studied children with a mean age of 7.5 years from Africa (78%) and Asia (22%), with the exposed group having definite or suspected household TB contact and the unexposed group having no contact. BCG vaccination in this cohort was 69%. Participants in the Italian studies were young adults of whom 56% were female in the study by Orlando *et al.*[146] but only 4% were female in the study by Saracino *et al.*[147] Immigrants arrived from Latin America (50%), Eastern Europe (27%), Africa (16%) and Asia (7%) in the study by Orlando *et al.*[146] and from Africa (48%), Eastern Mediterranean countries (47%), Europe (3%) and South-East Asia (2%) in the study by Saracino *et al.*[147] Orlando *et al.*[146] reported an overall very low rate of BCG vaccination (6%), whereas the study by Saracino *et al.*[147] did not report BCG vaccination of participants.[147] Both studies defined exposure groups by geographical area of origin and the level of TB burden[147] or TB prevalence[146] in the country of origin. In addition, Orlando *et al.*[146] specified a third exposed group as contacts of TB cases and compared this with an unexposed group without TB contact. *Table 19* provides further details on these studies.

Study quality

Incidence of active tuberculosis

Only one[144] of the studies provided an adequate description about study design, study participants, study attrition, statistical analysis and reporting; this study was judged to have a low ROB. The other study[143] was judged as being at high ROB because of selection bias, confounding and selective reporting of results. *Table 20* provides further details.

Exposure levels

All three[145–147] of the exposure studies identified since the publication of CG117[10] concerning recent arrivals from countries with a high incidence of TB were rated as being of low quality. There was a lack of blinding of test results from exposure, inadequate descriptions of exposure and inadequate reporting of sample attrition. *Table 21* provides further details.

TABLE 19 Baseline characteristics of studies in recent arrivals from countries with a high incidence of TB: exposure studies

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Numbers of recruited and excluded study participants	Comments
Lucas 2010,[145] Australia (low)	Aim: to compare IGRAs and the TST for the diagnosis of LTBI in recently resettled refugee children Setting: community based Design: retrospective cohort/cross-sectional study Funding source: Oxford Immunotec	Household TB contact: non-exposed: none; exposed 1: definite/suspected; exposed 2: NA	Inclusion criteria: children aged from 5 months to 16 years from refugee families attending the Migrant Health Unit Exclusion criteria: NR	Type of tests: IGRA (T-SPOT.*TB*), IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (T-SPOT.*TB*): NR; IGRA (QFT-GIT): NR; TST: induration of ≥ 10 mm given that all children originated from high-prevalence countries or ≥ 15 mm if children were aged < 5 years and had received a BCG vaccination [5 mm was subtracted from these cut-off values for children at increased risk for TB infection (such as household contacts) and for those aged > 1 year]	Mean (range) age: 7.5 (2.8–11.9) years Female, *n* (%): 260 (49.6) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): African 411 (78.4), Asian 113 (21.56) BCG vaccination, *n* (%): 361 (69.0) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NR Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): malaria 486 (92.7), hepatitis B 356 (68.0), hepatitis C 492 (94.0), schistosomiasis 431 (82.2) Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: 524; total number of excluded patients: NR	NA

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Numbers of recruited and excluded study participants	Comments
Orlando 2010,[146] Italy (low)	Aim: to compare the efficiency and efficacy of the TST and QFT-GIT for the detection of LTBI in recent immigrants from highly endemic countries Setting: community based (outpatient ward) Design: retrospective cohort/cross-sectional study Funding source: Provincia di Milano, Assessorato alle Politiche Sociali	(1) Continent: non-exposed: Africa (reference group); exposed 1: Asia; exposed 2: East Europe; exposed 3: Latin America (2) TB prevalence in country of origin: non-exposed: < 50 per 100,000 population (reference group); exposed 1: 50–200 per 100,000 population; exposed 2: > 200 per 100,000 population (3) Contact with TB patient: non-exposed: no (reference group); exposed 1: yes	Inclusion criteria: NR Exclusion criteria: active TB	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): positive if the IFN-γ value after stimulation with TB antigen minus the value in the nil control was ≥ 0.35 UI/ml; TST: induration of ≥ 10 mm	Median (IQR) age: 35.3 (27.7–44.5) years Female, *n* (%): 630 (55.7) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): Latin America 562 (49.73), Eastern Europe 308 (27.26), Africa 181 (16.02), Asia 79 (6.99) BCG vaccination, *n* (%): 72 (6.37), unknown 46 (4.07) History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): yes Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): treatment for LTBI was offered to 57 of the 79 eligible patients according to standard guidelines	Total number of recruited patients: NR; total number of excluded patients: NR	NA

continued

TABLE 19 Baseline characteristics of studies in recent arrivals from countries with a high incidence of TB: exposure studies (*continued*)

Study ID, country (burden)	Study aim, setting, design and funding source	Definition of construct validity (i.e. LTBI exposure-based proxy)	Inclusion/exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	Numbers of recruited and excluded study participants	Comments
Saracino 2009,[147] Italy (low)	Aim: to evaluate the agreement between the QFT-GIT and the TST for LTBI screening in a population of recent immigrants to Italy from high-incidence countries Setting: community based Design: retrospective cohort/cross-sectional study Funding source: NR	(1) Born in a country with a TB burden (*n* cases per 100,000): non-exposed: NR; exposed 1: 30–100; exposed 2: 101–200; exposed 3: > 301 (2) Region of origin: non-exposed: NR; exposed 1: African; exposed 2: Eastern Mediterranean; exposed 3: European; exposed 4: South-East Asian	Inclusion criteria: recent (< 2 months) immigrants to Italy Exclusion criteria: active TB, HIV infection	Type of tests: IGRA (QFT-GIT), TST Cut-off values/ thresholds: IGRA (QFT-GIT): positive if the IFN-γ level was above the cut-off test value (≥ 0.35 IU/ml); TST: induration of ≥ 10 mm after 72 hours (≥ 5 mm and ≥ 15 mm were used for comparison)	Mean (SD) age: 27.1 (6.2) years Female, *n* (%): 11 (4) Race/ethnicity, *n* (%): NR Geographical origin, *n* (%): African 135 (48.4), Eastern Mediterranean 131 (46.95), European 7 (2.5), South-East Asian 6 (2.2) BCG vaccination, *n* (%): NR History of antiTB treatment, *n* (%): NR Total incidence of active TB, *n* (%): NA Chest radiography (yes/no): yes Clinical examination (yes/no): NR Morbidity, *n* (%): NR Comorbidity, *n* (%): NR Type of during-study treatment, *n* (%): NR	Total number of recruited patients: NR; total number of excluded patients: NR	NA

ID, identification; NA, not applicable; NR, not reported; SD, standard deviation.

TABLE 20 Summary assessment of ROB for the included incidence studies in recent arrivals from countries with a high incidence of TB

Study ID (burden)	Study design	Study participation (risk of selection bias)	Study attrition (risk of selection bias)	Prognostic factor measurement (risk of exposure measurement bias)	Outcome/construct measurement (ROB in misclassification of individuals in relation to construct validity groups)	Study confounding (ROB from confounding)	Statistical analysis and reporting (ROB from analysis and selective reporting)	Total ROB (high, moderate, low)
Harstad 2010[143] (low)	Low	High	Low	High	Moderate	High	High	High
Kik 2010[144] (low)	Low	Low	Low	Low	Low	Low	Low	Low

ID, identification.
Source: adapted from Hayden *et al.*[90]

TABLE 21 Summary assessment of ROB for the included exposure studies in recent arrivals from countries with a high incidence of TB

Study ID (burden)	Recruitment of subjects [consecutive (yes), arbitrary or unreported (no)]	Blinding of test results from exposure [blinded (yes), not blinded or unreported (no)]	Description of index test and threshold [adequate (yes), inadequate or unreported (no)]	Definition and description of exposure [adequate (yes), inadequate or unreported (no)]	Sample attrition [adequate (yes),[a] inadequate or unreported (no)]	Overall quality score of satisfactory features[b]
Lucas 2010[145] (low)	Yes	No	No	No	No	Low quality
Orlando 2010[146] (low)	Yes	No	Yes	No	No	Low quality
Saracino 2009[147] (low)	No	No	Yes	No	No	Low quality

ID, identification.
a ≥ 90% of participants were included in the follow-up analysis (yes response) and < 90% were classified as 'no response'.
b Studies with one or two 'yes' ratings = low quality; studies with three 'yes' ratings = moderate quality; studies with four or five 'yes' ratings = high quality.
Source: adapted from Dinnes *et al.*[44] The item 'study design' was removed from the original checklist as all studies were considered to be retrospective; furthermore, the item 'sample attrition' was added.

Comparative performance of tests (diagnostic accuracy indices for identifying latent tuberculosis infection)

Incidence of active tuberculosis

Ratios of cumulative incidence ratios

This section included two studies[143,144] that followed up participants for the development of active TB. Both studies correlated IGRA (QFT-GIT;[143] QFT-GIT and T-SPOT.*TB*[144]) and TST results with the cumulative incidence of active TB. The resulting CIRs for QFT-GIT were not significantly different from those for TST 5 mm (R-CIR 2.55, 95% CI 0.57 to 11.40)[143] and TST 10 mm (R-CIR 0.87, 95% CI 0.17 to 4.56)[144] (*Table 22*). Similarly, in the study by Kik *et al.*,[144] the R-CIR for T-SPOT.*TB* vs. TST 15 mm was not significant (R-CIR 0.37, 95% CI 0.10 to 1.41).

The pooled estimate of the R-CIR across the two studies indicated no significant difference between QFT-GIT and TST (5 mm or 10 mm) (pooled R-CIR 1.57, 95% CI 0.52 to 4.76) (*Figure 42*).

Sensitivity and specificity

This section included two newly identified studies.[143,144] There was homogeneity in the sensitivity of both QFT-GIT (pooled sensitivity 76%, 95% CI 50% to 93%; $I^2 = 40.7\%$) and TST 5 mm/10 mm (pooled sensitivity 94%, 95% CI 73% to 100%; $I^2 = 30.8\%$). In contrast, specificity estimates for QFT-GIT (71% and 46%; $I^2 = 98.4\%$) and TST (49% and 15%; $I^2 = 99.2\%$) were heterogeneous and these estimates could not be pooled (*Figures 43–46*). In summary, QFT-GIT demonstrated greater specificity values (range 46–71%) than TST (range 15–49%) but lower sensitivity (pooled estimate 76%) than TST (pooled estimate 94%). One study[144] showed that TST 15 mm performed better than T-SPOT.*TB* in terms of both sensitivity (87% vs. 75%) and specificity (44% vs. 40%).

TABLE 22 Comparison of test performance in recent arrivals from countries with a high incidence of TB: diagnostic accuracy indices for identifying LTBI – incidence studies

Study ID, country (burden)	Test results	Test diagnostic accuracy in % (95% CI)		Development of active TB		
				Cumulative incidence (%), CIR, IDR, IDRR (95% CI)		R-CIR, R-IDRR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Harstad 2010,[143] Norway (low)	Number of test results: QFT-GIT 823; TST 823 Test (+/–): QFT-GIT 246/577; TST ≥ 6 mm 426/395; TST ≥ 15 mm 128/693 Number of indeterminate results: QFT-GIT NR; TST NR Number lost to follow-up: NR	QFT-GIT/G: SN 88.89 (56.5 to 98.01); SP 71.46 (68.25 to 74.47); PPV 3.36 (1.71 to 6.49); NPV 99.83 (99.02 to 99.97)	TST ≥ 6 mm: SN 88.89 (56.5 to 98.01); SP 49.19 (45.74 to 52.65); PPV 1.92 (0.98 to 3.75); NPV 99.75 (98.58 to 99.96) TST ≥ 15 mm: SN 33.33 (12.06 to 64.58); SP 85.32 (82.71 to 87.60); PPV 2.48 (0.84 to 7.03); NPV 99.13 (98.12 to 99.6)	QFT-GIT: CI (+) 3.36 (1.71 to 6.49); CI (–) 0.17 (0.00 to 1.08); CIR 19.39 (2.43 to 154.2); IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 6 mm: CI (+) 1.92 (0.98 to 3.75); CI (–) 0.25 (0.00 to 1.57); CIR 7.61 (0.95 to 60.59); IDR (+) NR; IDR (–) NR; IDRR NR TST ≥ 15 mm: CI (+) 2.48 (0.84 to 7.03); CI (–) 0.86 (0.35 to 1.92); CIR: 2.86 (0.725 to 11.28); IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 6 mm) 2.55 (0.57 to 11.40); R-IDRR (QFT-GIT vs. TST ≥ 6 mm) NR R-CIR (QFT-GIT vs. TST ≥ 15 mm) 0.38 (0.11 to 1.34); (QFT-GIT vs. TST ≥ 15 mm) NR
Kik 2010,[144] the Netherlands (low)	Number of test results: QFT-GIT 339; T-SPOT.*TB* 339; TST: 339 Test (+/–): QFT-GIT 178/149; T-SPOT.*TB* 181/118; TST ≥ 10 mm 288/51; TST ≥ 15 mm 184/138 Number of indeterminate results: QFT-GIT 12; T-SPOT.*TB* 40; TST ≥ 10 mm 0; TST ≥ 15 mm 0 Number lost to follow-up: NR	QFT-GIT: SN 62.50 (30.57 to 86.32); SP 45.77 (40.38 to 51.25); PPV 2.80 (1.20 to 6.40); NPV 98.0 (94.20 to 99.31) T-SPOT.*TB*: SN 5.00 (40.93 to 92.85); SP 39.86 (34.4 to 45.58); PPV 3.31 (1.52 to 7.04); NPV 98.31 (94.03 to 99.53)	TST ≥ 10 mm: SN 100.00 (70.08 to 100.00); SP 15.45 (11.95 to 19.75); PPV 3.12 (1.65 to 5.83); NPV 100.00 (93.00 to 100.00) TST ≥ 15 mm: SN 87.5 (52.91 to 97.76); SP 43.63 (38.25 to 49.16); PPV 3.80 (1.85 to 7.64); NPV 99.28 (96.01 to 99.87)	QFT-GIT: CI (+) 2.80 (1.20 to 6.40); CI (–) 2.00 (0.42 to 6.02); CIR 1.39 (0.34 to 5.74); IDR (+) NR; IDR (–) NR; IDRR NR T-SPOT.*TB*: CI (+) 3.31 (1.52 to 7.04); CI (–) 1.69 (0.08 to 6.35); CIR 1.95 (0.40 to 9.52); IDR (+) NR; IDR (–) NR; IDRR NR	TST ≥ 10 mm: CI (+) 3.12 (1.65 to 5.83); CI (–) 1.96 (0.05 to 10.4); CIR 1.59 (0.21 to 71.2); IDR (+) NR; IDR (–) NR; IDRR NR TST ≥ 15 mm: CI (+) 3.80 (1.85 to 7.64); CI (–) 0.72 (0.00 to 4.39); CIR 5.25 (0.65 to 42.17); IDR (+) NR; IDR (–) NR; IDRR NR	R-CIR (QFT-GIT vs. TST ≥ 10 mm) 0.87 (0.17 to 4.56); R-IDRR (QFT-GIT vs. TST ≥ 10 mm) NR R-CIR (T-SPOT.*TB* vs. TST ≥ 15 mm) 0.37 (0.10 to 1.41); R-IDRR (T-SPOT.*TB* vs. TST ≥ 15 mm) NR

CI (–), cumulative incidence in those who tested negative; CI (+), cumulative incidence in those who tested positive; IDR, incidence density rate; NR, not reported; SN, sensitivity; SP, specificity.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST 5/10 mm total *n*	Weight	Risk ratio IV, random, 95% CI
Harstad 2010[143]	0.935	0.764	815	810	54.8%	2.55 (0.57 to 11.39)
Kik 2010[144]	–0.134	0.842	327	339	45.2%	0.87 (0.17 to 4.56)
Total (95% CI)			**1142**	**1149**	**100.0%**	**1.57 (0.52 to 4.76)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.88$, df = 1 ($p = 0.35$); $I^2 = 0\%$
Test for overall effect: $z = 0.80$ ($p = 0.42$)

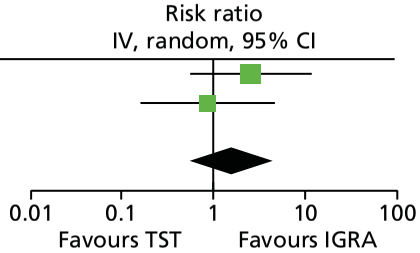


FIGURE 42 Pooled R-CIR of QFT-GIT vs. TST (5 mm or 10 mm) based on high- and low-risk exposure in recent arrivals from countries with a high incidence of TB. df, degrees of freedom; IV, inverse variance; SE, standard error.

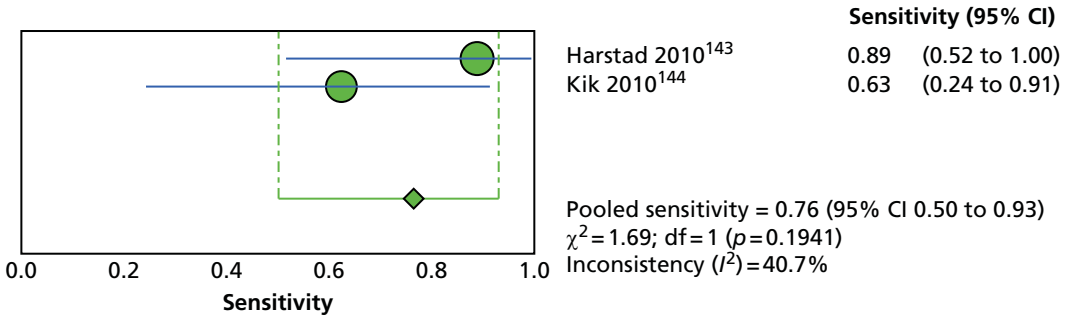


FIGURE 43 Forest plot of sensitivity based on incidence of active TB (QFT-GIT) in recent arrivals from countries with a high incidence of TB. df, degrees of freedom.

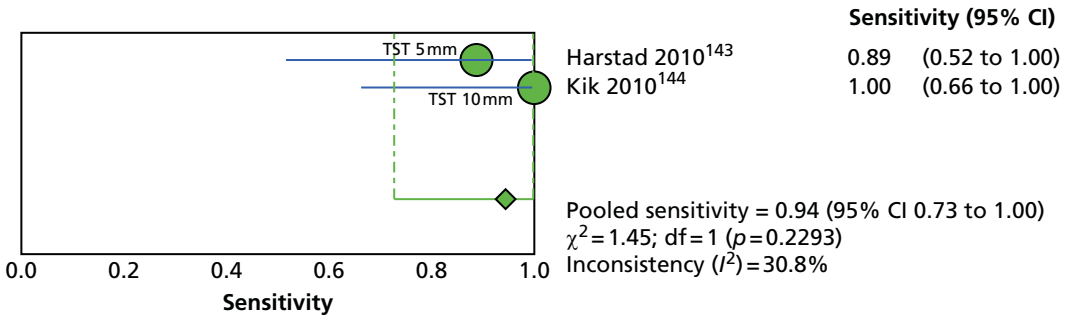


FIGURE 44 Forest plot of sensitivity based on incidence of active TB (TST) in recent arrivals from countries with a high incidence of TB. df, degrees of freedom.

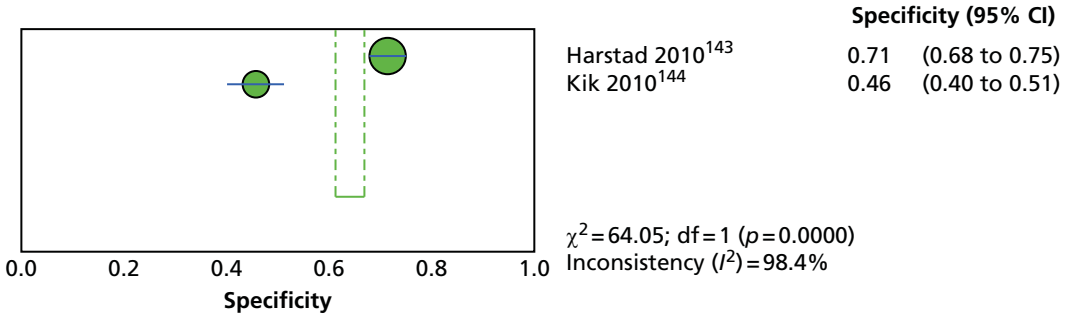


FIGURE 45 Forest plot of specificity based on incidence of active TB (QFT-GIT) in recent arrivals from countries with a high incidence of TB. df, degrees of freedom.

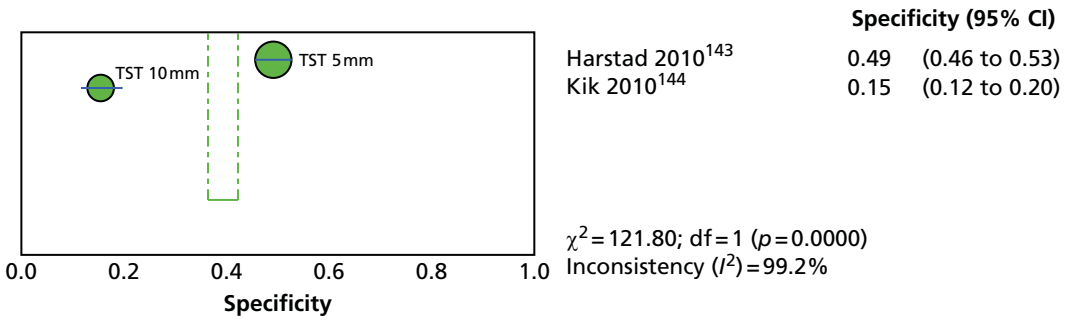


FIGURE 46 Forest plot of specificity based on incidence of active TB (TST) in recent arrivals from countries with a high incidence of TB. df, degrees of freedom.

Exposure levels

Ratios of diagnostic odds ratios

Seven[166,185,186,188–191] of the 10 studies reviewed in CG117[10] (see *Appendix 5*) found significant strong associations between exposure and positive test results, presented as DORs for both IGRA and TST (5 mm, 10 mm, 15 mm) across exposure gradient groups defined as place of birth, racial group and country prevalence. The estimates of R-DORs comparing IGRA with TST across these studies ranged from 0.14[191] to 0.98.[188] As CG117[10] did not provide the 95% CIs around these estimates, it is not clear what the predictive performance of IGRA relative to TST is in terms of identifying LTBI. With regard to the studies identified in the present review, one study[146] showed that IGRA compared with TST was more strongly correlated with the exposure groups of geographical origin (Latin America/East Europe vs. Africa; R-DOR 1.42) and TB prevalence (> 200/50–200 per 100,000 vs. < 50 per 100,000; R-DOR range 1.88–1.91), but this correlation across the two tests was similar for contact with TB case (R-DOR 1.13, 95% CI 0.85 to 1.49). In two other studies[145,147] the comparisons of IGRA and TST in relation to exposure to TB (R-DOR 0.60, 95% CI 0.32 to 1.12) and birth in TB burden country (R-DOR 1.00, 95% CI 0.60 to 1.66) were not statistically significant (*Table 23*).

Based on the meta-analysis of the three studies,[145–147] the pooled R-DOR for the IGRA (QFT-GIT) compared with TST 10 mm (contact with TB case, exposure to TB, birth in TB burden country) (R-DOR 0.96, 95% CI 0.69 to 1.33) was not statistically significant, suggesting that there is no evidence that IGRA performs better than TST in identifying LTBI in this population (*Figure 47*).

Sensitivity, specificity, positive predictive value and negative predictive value

None of the three studies reported these parameters and there was not sufficient information to derive 2 × 2 table cell counts to calculate sensitivity and specificity values.

Influence of bacillus Calmette–Guérin vaccination status on test positivity

Of the three newly identified studies,[145–147] only one[145] reported the association between test positivity and BCG vaccination status. Given the study results, there was no evidence indicating a differential effect of BCG vaccination status on IGRA (QFT, T-SPOT.*TB*) and TST positivity. Namely, the odds of test positivity for QFT-GIT (OR 1.70, 95% CI 0.80 to 3.60), T-SPOT.*TB* (OR 1.80, 95% CI 0.80 to 4.00) and TST (OR 1.70, 95% CI 0.80 to 3.50) were not significantly different between the BCG-vaccinated group and the non-vaccinated group (*Table 24*).

Between-test concordance, discordance and agreement

This relevant evidence was reported for nine CG117[10] studies[166,183–188,190,191] (see *Appendix 5*) and three newly identified studies[145–147] (see *Appendix 9*). In overall samples, the per cent concordance between the IGRA and the TST 10 mm ranged from 63.6%[188] to 84.2%.[190] The corresponding concordance between the IGRA and the TST 5 mm was similar and ranged from 60.7%[188] to 90%.[191] The kappa values between the IGRA and the TST (regardless of TST threshold and BCG vaccination status) ranged from 0.08 to 0.68,[188] with most values being < 0.45. Both concordance and kappa were greater among BCG-unvaccinated (or total sample) than among vaccinated-only groups[146,166,183–186,188,190] (*Table 25*; see *Appendix 5* for CG117[10] studies).

Summary of studies on recent arrivals from countries with a high incidence of tuberculosis

Two studies that correlated IGRA (QFT-GIT and T-SPOT.*TB*) and TST results with cumulative incidence of active TB showed no significant difference in CIRs for QFT-GIT compared with TST 5 mm (R-CIR 2.55, 95% CI 0.57 to 11.40) and QFT-GIT compared with TST 10 mm (R-CIR 0.87, 95% CI 0.17 to 4.56). The pooled estimate of R-CIRs across the two studies was not significant (pooled R-CIR 1.57, 95% CI 0.52 to 4.76). Based on two studies, the QFT-GIT demonstrated greater specificity values (range 46–71%) than the TST (range 15–49%) but lower sensitivity (pooled estimate 76%) than the TST (pooled estimate 94%). One study showed TST 15 mm to have performed better than T-SPOT.*TB* in terms of both sensitivity (87% vs. 75%) and specificity (44% vs. 40%).

TABLE 23 Comparison of test performance in recent arrivals from countries with a high incidence of TB: diagnostic accuracy indices for identifying LTBI – exposure studies

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		R-DOR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
Lucas 2010,[145] Australia (low)	Number of test results: QFT-GIT 460; T-SPOT.*TB* 420; TST 304 Test (+/–): QFT-GIT 45/345; T-SPOT.*TB* 38/374; TST ≥ 10 mm 54/250 Number of indeterminate results: QFT-GIT 70; T-SPOT.*TB* 8; TST 0 Number lost to follow-up: 37	QFT-GIT: High exposure level vs. low exposure level: SN NR; SP NR; PPV NR; NPV NR T-SPOT.*TB* High exposure level vs. low exposure level: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm High exposure level vs. low exposure level: SN NR; SP NR; PPV NR; NPV NR T-SPOT.*TB* High exposure level vs. low exposure level: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: High exposure level vs. low exposure level: DOR 2.40 (1.00 to 5.80); DORa NR T-SPOT.*TB*: High exposure level vs. low exposure level: DOR 2.50 (0.90 to 6.50); DORa NR	TST ≥ 10 mm: High exposure level vs. low exposure level: DOR 4.00 (1.70 to 9.50); DORa NR T-SPOT.*TB*: High exposure level vs. low exposure level: DOR 4.00 (1.70 to 9.50); DORa NR	QFT-GIT vs. TST ≥ 10 mm: High exposure level vs. low exposure level: Low: R-DOR 0.60 (0.32 to 1.12); R-DORa NR T-SPOT.*TB* vs. TST ≥ 10 mm: High exposure level vs. low exposure level: Low: R-DOR 0.63 (0.32 to 1.22); R-DORa NR
Orlando 2010,[146] Italy (low)	Number of test results: QFT-GIT 1130; TST 1129 Test (+/–): QFT-GIT 337/778; TST ≥ 10 mm 407/492 Number of indeterminate results: QFT-GIT 15; TST 0 Number lost to follow-up: TST 230 (dropouts)	QFT-GIT: Asian continent vs. African continent: SN NR; SP NR; PPV NR; NPV NR Latin America vs. Africa: SN NR; SP NR; PPV NR; NPV NR TB prevalence (number per 100,000): 50–200 vs. < 50: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm: Asian continent vs. African continent: SN NR; SP NR; PPV NR; NPV NR Latin America vs. Africa: SN NR; SP NR; PPV NR; NPV NR TB prevalence (number per 100,000): 50–200 vs. < 50: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Asian continent vs. African continent: DOR 1.61 (0.90 to 2.88); DORa 1.07 (0.52 to 2.23) Latin America vs. Africa: DOR 1.46 (0.99 to 2.16); DORa 0.81 (0.46 to 1.42) TB prevalence (number per 100,000): 50–200 vs. < 50: DOR 1.76 (1.10 to 2.80); DORa 1.34 (0.72 to 2.49)	TST ≥ 10 mm: Asian continent vs. African continent: DOR 0.91 (0.50 to 1.64); DORa 0.72 (0.34 to 1.53) Latin America vs. Africa: DOR 0.86 (0.59 to 1.26); DORa 0.57 (0.33 to 1.00) TB prevalence (number per 100,000): 50–200 vs. < 50: DOR 0.66 (0.44 to 1.01); DORa 0.70 (0.39 to 1.25)	QFT-GIT vs. TST ≥ 10 mm: Asian continent vs. African continent: R-DOR 1.77 (1.16 to 2.70); R-DORa 1.49 (0.87 to 2.53) Latin America vs. Africa: R-DOR 1.70 (1.29 to 2.24); R-DORa 1.42 (0.95 to 2.24)

continued

TABLE 23 Comparison of test performance in recent arrivals from countries with a high incidence of TB: diagnostic accuracy indices for identifying LTBI – exposure studies (*continued*)

Study ID, country (burden)	Test results	Test diagnostic accuracy (95% CI) (%)		Construct validity (i.e. LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		R-DOR (95% CI), IGRA vs. TST (by threshold)
		IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	IGRA: QFT-GIT/G and/or T-SPOT.*TB*	TST (by threshold)	
		TB prevalence (number per 100,000): ≥ 200 vs. < 50: SN NR; SP NR; PPV NR; NPV NR Contact with TB case vs. no contact: SN NR; SP NR; PPV NR; NPV NR	TB prevalence (number per 100,000): ≥ 200 vs. < 50: SN NR; SP NR; PPV NR; NPV NR Contact with TB case vs. no contact: SN NR; SP NR; PPV NR; NPV NR	TB prevalence (number per 100,000): ≥ 200 vs. < 50: DOR 2.31 (1.48 to 3.61); DORa 2.72 (1.70 to 5.02) Contact with TB case vs. no contact: DOR 2.54 (1.82 to 3.54); DORa 2.11 (1.47 to 3.03)	TB prevalence (number per 100,000): ≥ 200 vs. < 50: DOR 0.99 (0.66 to 1.48); DORa 1.45 (0.80 to 2.62) Contact with TB case vs. no contact: DOR 1.87 (1.30 to 2.69); DORa 1.87 (1.24 to 2.80)	TB prevalence (Number per 100,000): 50–200 vs. < 50: R-DOR 2.67 (1.94 to 3.67); R-DORa 1.91 (1.24 to 2.95) TB prevalence (Number per 100,000): ≥ 200 vs. < 50: R-DOR 2.33 (1.72 to 3.17); DORa 1.88 (1.25 to 2.83) Contact with TB case vs. no contact: R-DOR 1.36 (1.06 to 1.75); R-DORa 1.13 (0.85 to 1.49)
Saracino 2009,[147] Australia (low)	Number of test results: QFT-GIT 452; TST 452 Test (+/–): QFT-GIT 107/172; TST ≥ 10 mm 72/207 Number of indeterminate results: QFT-GIT 173; TST 173 Number lost to follow-up: QFT-GIT 169; TST 169	QFT-GIT: Region of origin vs. region of origin: SN NR; SP NR; PPV NR; NPV NR	TST ≥ 10 mm: Region of origin vs. region of origin: SN NR; SP NR; PPV NR; NPV NR	QFT-GIT: Region of origin vs. region of origin: DOR NR; DORa NR	TST ≥ 10 mm: Region of origin vs. region of origin: DOR NR; DORa NR	QFT-GIT vs. TST ≥ 10 mm: Region of origin vs. region of origin: R-DOR NR; R-DORa NR

DORa, adjusted diagnostic odds ratio; ID, identification; NR, not reported; R-DORa, adjusted ratio of diagnostic odds ratios; SN, sensitivity; SP, specificity.

Study or subgroup	Log-OR	SE	IGRA total *n*	TST total *n*	Weight	OR IV, random, 95% CI
Lucas 2010[145]	–0.51	0.319	390	304	20.6%	0.60 (0.32 to 1.12)
Orlando 2010[146]	0.12	0.141	1115	899	51.8%	1.13 (0.86 to 1.49)
Saracino 2009[147]	0	0.259	279	279	27.6%	1.00 (0.60 to 1.66)
Total (95% CI)			**1784**	**1482**	**100.0%**	**0.96 (0.69 to 1.33)**

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 3.27$, df = 2 ($p = 0.20$); $I^2 = 39\%$
Test for overall effect: $z = 0.26$ ($p = 0.80$)

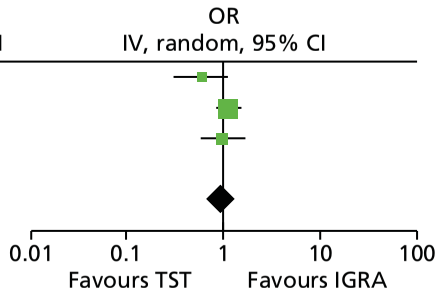


FIGURE 47 Pooled R-DOR for IGRA vs. TST 10 mm based on high- and low-risk exposure in recent arrivals from countries with a high incidence of TB. df, degrees of freedom; IV, inverse variance; SE, standard error.

TABLE 24 Association between test positivity and BCG vaccination status in recent arrivals from countries with a high incidence of TB: exposure studies

Study ID, country (burden)	Sample size, *n*	Type of IGRA/TST induration threshold	Association between test positivity and BCG vaccination status: OR (95% CI)	
			Crude/unadjusted	Adjusted
Lucas 2010,[145] Australia (low)	420	QFT-GIT	1.70 (0.80 to 3.60)	NR
	460	T-SPOT.*TB*	1.80 (0.80 to 4.00)	NR
	304	TST ≥ 10 mm	1.70 (0.80 to 3.50)	NR
Orlando 2010,[146] Italy (low)	1130	QFT-GIT	NR	NR
	1129	TST ≥ 10 mm	NR	NR
Saracino 2009,[147] Australia (low)	452	QFT-GIT	NR	NR
	452	TST ≥ 10 mm	NR	NR

ID, identification; NR, not reported.

TABLE 25 Between-test concordance and discordance in recent arrivals from countries with a high incidence of TB: exposure and incidence studies

Study ID, country (burden)	Sample size, total or by subgroup, *n*	Type of IGRA vs. TST induration threshold	Concordance (95% CI) (%)	Discordance (95% CI) (%)	Agreement kappa (95% CI)
Lucas 2010,[145] Australia (low)	NR	T-SPOT.*TB* vs. TST 10 mm	NR	NR	0.45 (0.38 to 0.53)
	NR	QFT-GIT vs. TST 10 mm	NR	NR	0.46 (0.39 to 0.53)
Orlando 2010,[146] Italy (low)	887	QFT-GIT vs. TST 10 mm	70.46 (67.32 to 73.43)	29.53 (NR)	0.38 (NR)
	56 BCG vaccinated	QFT-GIT vs. TST 10 mm	66.07 (52.09 to 77.84)	33.92 (NR)	0.35 (NR)
	789 unvaccinated	QFT-GIT vs. TST 10 mm	71.36 (68.04 to 74.46)	28.64 (NR)	0.40 (NR)
Saracino 2009,[147] Australia (low)	279 total	QFT-GIT vs. TST 10 mm	70.97 (65.39 to 75.98)	29.03 (24.02 to 34.61)	0.35 (0.23 to 0.46)
Harstad 2010,[143] Norway (low)	823	QFT-GIT vs. TST 10 mm	NR	NR	NR
	823	QFT-GIT vs. TST 15 mm	NR	NR	NR
Kik 2010,[144] the Netherlands (low)	433	QFT-GIT vs. TST 10 mm	NR	NR	NR

ID, identification; NR, not reported.

Seven of the 10 studies reviewed in CG117 found significant strong associations presented as DORs for both the IGRA and the TST (5 mm, 10 mm, 15 mm) across exposure gradient groups defined as place of birth, racial group and country prevalence. However, the R-DORs comparing IGRA with TST across these studies ranged from 0.14 to 0.98. As CG117[10] did not provide the 95% CIs, it is not clear what the predictive performance of IGRA relative to TST was in terms of identifying LTBI. Based on the meta-analysis of the three more recent studies, the pooled R-DOR for IGRA (QFT-GIT) compared with TST 10 mm (contact with TB case, exposure to TB, birth in TB burden country) was not statistically significant, suggesting that the IGRA does not perform better than the TST in identifying LTBI.

Given the results from one study, there was no evidence indicating a differential effect of BCG vaccination on IGRA (QFT-GIT, T.SPOT.*TB*) and TST positivity. The odds of test positivity for the QFT-GIT (OR 1.70, 95% CI 0.80 to 3.60), T.SPOT.*TB* (OR 1.80, 95% CI 0.80 to 4.00) and TST (OR 1.70, 95% CI 0.80 to 3.50) were not significantly different between the BCG-vaccinated group and the non-vaccinated group.

Based on nine CG117[10] and three newly identified studies, the overall per cent concordance between the IGRA and the TST 10 mm ranged from 63.6% to 84.2%. The corresponding concordance between the IGRA and the TST 5 mm was similar (range 60.7–90%). Most kappa values between the IGRA and the TST (regardless of TST threshold and BCG vaccination status) were < 0.45. Both concordance and kappa were greater among BCG-unvaccinated groups.

Overall summary of results

We identified 53 studies published since the previous NICE clinical guidance work in 2011 (CG117).[10] ROB was assessed for 15 studies that evaluated the incidence of active TB and methodological quality was assessed for the remaining 38 studies, which correlated test results with previous TB exposure. Seven of the 15 incidence studies were identified as having a high ROB, six as having a moderate ROB and two as having a low ROB. All had important drawbacks with regard to design, methods and reporting. Of the 38 exposure studies, 29 were generally of lower quality, six were of moderate quality and three were of high quality.

Children and adolescents

Although the limited evidence in children and adolescents showed no significant difference in test accuracy between QFT-GIT and TST 5 mm (pooled R-CIR 1.12, 95% CI 0.72 to 1.75), QFT-GIT performed significantly better than TST 10 mm in predicting risk of active TB (pooled R-CIR 4.33, 95% CI 1.32 to 14.23). The IGRA (QFT-GIT/G) demonstrated a similar sensitivity to (range 48–100%) and a slightly better specificity (range 49–90%) than TST 5 mm (sensitivity range 57–100%; specificity range 45–65%). Although the sensitivities of IGRA and TST 5 mm were higher than those for TST 10 mm (range 30–56%), the corresponding specificities of these tests were lower than those for TST 10 mm (range 63–93%). Evidence from exposure studies suggested the superiority of IGRAs over TST in identifying LTBI in the low TB burden setting (pooled R-DOR 4.74, 95% CI to 2.15 to 10.44) compared with high TB burden settings (pooled R-DOR 1.13, 95% CI to 0.78 to 1.65).

Immunocompromised people

In terms of LTBI diagnosis, IGRAs (QFT-GIT or T.SPOT.*TB*) performed better than TST 5 mm/10 mm in people receiving haemodialysis (pooled R-DOR 2.53, 95% CI 1.48 to 4.34) and people with hepatitis C (R-DOR 8.45, 95% CI 3.71 to 19.24). In contrast, for patients with HIV/AIDS, TST 10 mm performed significantly better than QFT-GIT (pooled R-DOR 0.35, 95% CI 0.15 to 0.83). The comparative evidence on the performance of the IGRAs and TST for the remaining subgroups (e.g. those with lupus erythematosus, solid organ transplantation candidates, kidney transplant recipients) was inconclusive because of the high level of uncertainty around the effect estimates.

Recent arrivals from countries with a high incidence of tuberculosis

Overall, based on studies of incidence, there was no significant difference between the performance of QFT-GIT and TST 5 mm/10 mm in identifying LTBI among newly arrived people from high TB burden countries (pooled R-CIR 1.57, 95% CI 0.52 to 4.76). Similarly, there was no significant difference between T.SPOT.*TB* and TST 10 mm in predicting LTBI (R-CIR 0.37, 95% CI 0.10 to 1.41). Likewise, the pooled result showed no significant difference between QFT-GIT and TST 10 mm for the association with previous TB exposure (pooled R-DOR 0.96, 95% CI 0.69 to 1.33).

The studies identified in this review were highly heterogeneous in terms of types of tests for LTBI, TST cut-off levels, study settings and definitions of constructs for previous TB exposure for defining LTBI. Previous exposure to TB was highly variable and ill-defined, lacking a description of duration and proximity of contact to index TB cases. Overall, although the number of studies identified was substantial, extensive heterogeneity across many potential test performance modifier factors (e.g. study methodology, test administration, study populations and exposure-based construct definitions) precluded a more meaningful subgroup analysis because of the scarcity of evidence for each subgroup.

Chapter 5 Systematic review of economic evaluation studies

Identification and selection of studies

Search methods for cost-effectiveness

A comprehensive search of the health-care literature for published economic evaluations, cost studies and utility studies was performed. The purpose of this search was to identify existing cost-effectiveness models and model designs, and also to identify studies that reported costs and health-related quality-of-life data for use in generating cost per quality-adjusted life-years (QALYs).

The main cost-effectiveness search was developed and conducted as part of the wider systematic review that aimed to compare both the clinical effectiveness and the cost-effectiveness of screening tests (IGRAs and TST) for LTBI in high-risk groups: children, immunocompromised people or those at risk from immunosuppression, and people recently arriving from countries with a high incidence of active TB. The bibliographic database search strategies for the main cost-effectiveness search were the same as those used for the clinical effectiveness review and focused on the diagnosis of LTBI using IGRAs compared with other methods. Searches were limited to articles in English and articles that had been added to the databases since the health economics searches for the equivalent questions in CG117[10] were carried out (5–6 January 2010; see *Appendix 1*). These searches automatically picked up comparisons between IGRAs and TSTs and therefore it was not necessary to search independently for comparator technologies (e.g. TSTs). The searches were not restricted by study type and therefore an economics search filter was not required. The search strategies are provided in *Appendix 2*. Details of the databases and other sources searched are provided in *Chapter 3* (see *Identification and selection of studies*). Additional databases searched for cost-effectiveness studies were:

- Research Papers in Economics
- Cost-Effectiveness Analysis Registry
- Health Economic Evaluations Database (Wiley).

A separate search in MEDLINE was performed to identify existing cost-effectiveness model designs for LTBI. The search strategy is available in *Appendix 2*.

Inclusion and exclusion of relevant studies

To be included in the review, the following inclusion criteria were applied:

- Population:
  - Children (both sexes, aged < 18 years, immunocompetent) (research question 1).
  - People (both sexes, any age) who are immunocompromised or at risk from immunosuppression (e.g. transplant recipients or those with HIV infection, renal disease, diabetes, liver disease, haematological disease, cancer or autoimmune disease or who are on or about to start antiTNF-α treatment, steroids or ciclosporins) (research question 2).
  - People (both sexes, any age, immunocompetent) who have recently arrived from regions with a high incidence/prevalence of TB (countries/territories with an estimated incidence rate of ≥ 40 cases per 100,000, e.g. those in Africa, Central/South America, Eastern Europe and Asia) (research question 3).

- Intervention: IGRAs (QFT-G, QFT-GIT and T-SPOT.*TB*)
- Comparator: TST (Mantoux method)
- Outcome measures:
  - The main outcome measure was the cost per QALY.
  - Other outcomes such as correct diagnosis of LTBI and cost per active TB case prevented were also considered.
- Study design: studies including a formal economic evaluation involving direct comparison between IGRAs (QFT-G, QFT-GIT or T-SPOT.*TB*) and the TST and including a decision-analytic model in identifying people with LTBI
- Type and language of publication:
  - Full-text reports published in English.
  - Abstracts (only if companion publications to full-text included studies).

Two reviewers (PA and AT) reviewed the titles and abstracts of the citations retrieved from the initial database searches. Full texts of potentially relevant articles were read and those that were considered model-based economic evaluations were reviewed.

Data extraction

Data extraction was conducted by one reviewer (PA) and further cross-checked by a second reviewer (AT). Any disagreements were resolved by discussion or by recourse to a third-party reviewer. Data were extracted on study details (title, author and year of study), baseline characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness, current assumptions and analytical methods), results (study parameters, base-case and sensitivity analysis results), discussion (study findings, limitations of the models and generalisability) and 'other' (source of funding and conflicts of interests). The completed data extraction sheets are presented in *Appendix 11*.

Quality assessment

The economic evaluations were appraised against a framework for best practice for reporting economic evaluation studies developed by the Consolidated Health Economic Reporting Standards (CHEERS) task force.[194] The CHEERS assessment tool consists of six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions, a series of questions check whether or not the criteria have been clearly reported (see *Appendix 12*). Additionally, the models were critically appraised against a framework for best practice for reporting decision-analytical models developed by Phillips *et al.*[195] The Phillips *et al.*[195] quality assessment tool includes two main dimensions: structure of the model and data used to parameterise the model. Under these dimensions several questions assess whether or not the criteria have been clearly reported (see *Appendix 13*).

Study quality was assessed by one reviewer (PA) and cross-checked by a second reviewer (AT). Any disagreements were resolved by discussion or by recourse to a third-party reviewer.

Data synthesis

Information extracted from the included studies was summarised and tabulated. The findings from individual studies are compared narratively and recommendations for the future modelling of LTBI are discussed.

Results

The electronic database searches and searches of other sources identified 5959 records (*Figure 48*). After removing duplicates, 3057 records were screened for inclusion. On the basis of title and abstract, 3032 records were excluded and the remaining 25 records were included for full-text screening. A further 15 articles were excluded at the full-text stage, with the reasons for exclusion shown in *Figure 48* (see *Appendix 14* for a list of excluded studies), leaving 10 studies[10,77,196–203] that included a decision-analytical model to estimate the cost-effectiveness of IGRAs compared with the TST in diagnosing people who are at high risk of LTBI.

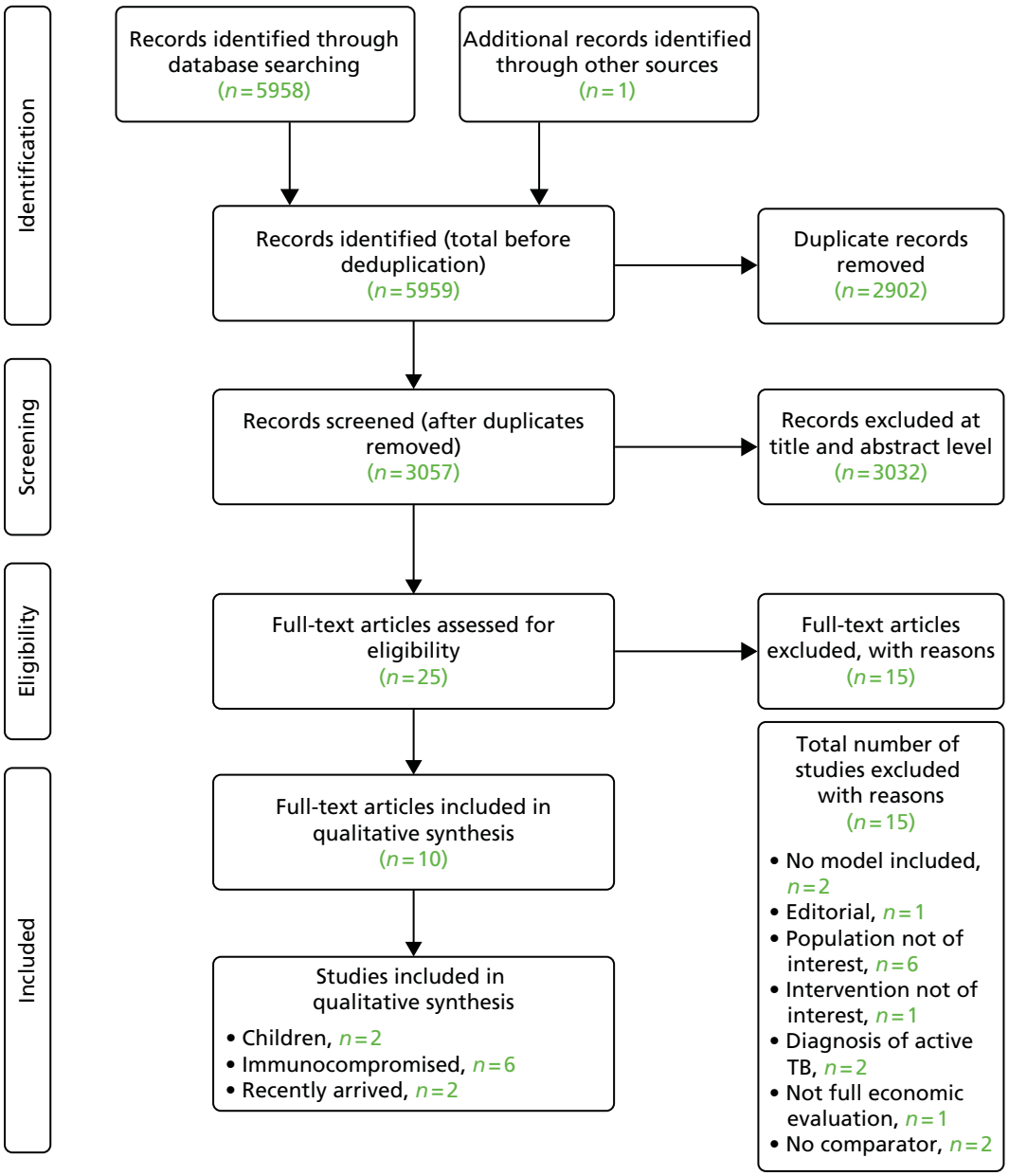


FIGURE 48 Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow diagram.

Summary of the general approaches to modelling latent tuberculosis infection

The general modelling approaches used for the diagnosis of LTBI are presented in the following sections by population of interest and in *Table 26*.

Children

Kowada[197]

Kowada[197] estimated the cost-effectiveness of QFT-GIT compared with the TST and chest radiography for the diagnosis of LTBI in children. The author developed a decision tree structure with Markov nodes to demonstrate the clinical pathway that children would undergo for the diagnosis and treatment of LTBI. The model started with a hypothetical cohort of children receiving one of three diagnostic strategies (QFT-GIT alone, TST alone or chest radiography). The model structure continued with children being in the LTBI/initial active TB or no LTBI health state, characterised by the prevalence of the disease. On positive test results, children received chest radiography to confirm initial active TB. Children who received a negative result on chest radiography were treated for LTBI. Children who adhered to LTBI treatment could develop isoniazid-induced hepatotoxicity. For the state transition model, children entered the model at the no LTBI health state and could remain or progress over time to LTBI, TB or death. Data required to populate the model were obtained from published sources. Estimates of sensitivity and specificity of tests in this population were obtained from a meta-analysis of developed-country studies. Cost data from published sources were adjusted to 2009 Japanese yen and converted to US dollars. The analysis was conducted from the societal perspective and the base-case results were expressed as an incremental cost-effectiveness ratio (ICER) based on the outcome of cost per QALY gained. Kowada[197] conducted one- and two-way sensitivity analyses and populated with data to run the model probabilistically to represent the uncertainty in key model input parameters. The base-case results demonstrated that the QFT-GIT-alone strategy was less costly and more effective than the TST-alone strategy.

Mandalakas *et al.*[203]

Mandalakas *et al.*[203] used a decision tree structure with Markov nodes to estimate the health and economic outcomes of five screening strategies for the diagnosis of MTB infection in young household contacts with an index case. The model started with a cohort of children aged < 5 years who received one of five diagnostic strategies (no test, TST alone, IGRA alone, TST positive followed by IGRA and TST negative followed by IGRA) and continued with children being in the LTBI/initial active TB or no LTBI/no initial TB health state, characterised by the prevalence of the disease. Children with positive test results were eligible for treatment for LTBI and could either accept or refuse treatment. For the Markov model, children entered the model at the LTBI health state and could progress to no infection, initial infection, subsequent infection from future exposures, pulmonary TB, disseminated TB, TB death and death from other causes. The analysis was conducted from the third-party payer and societal perspectives, and the base-case results were reported in terms of an ICER based on the outcome of cost per life-year saved. Base-case results indicate that for those aged 0–2 years the no testing strategy was the dominant strategy whereas for those aged 3–5 years an IGRA following a negative TST was the most effective strategy but was not cost-effective compared with no testing. The authors conducted one-way sensitivity analyses to determine the impact of data uncertainties on the results.

TABLE 26 Summary characteristics of the models comparing IGRAs and the TST in identifying LTBI in children, immunocompromised people and recently arrived immigrants

Study ID, country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention	Outcome measure(s)	Model type	Health states	Results (base-case and sensitivity analysis)
Children							
Kowada 2012,[197] Japan	To assess the cost-effectiveness of school-based TB screening using QFT-GIT vs. TST and CXR	Cost-effectiveness analysis, societal perspective, setting not reported	QFT-GIT	Cost per QALY	Decision tree structure to model the short-term events followed by a Markov modelling structure	Healthy, LTBI, TB and dead	QFT-GIT was less costly and more effective than TST
Mandalakas 2013,[203] South Africa	To estimate the health and economic outcomes of five TB screening strategies	Cost-effectiveness analysis, third-party payer and societal perspectives	IGRA (QFT, T-SPOT.*TB*)	Cost per LYS	Decision tree structure to model the short-term events followed by a Markov modelling structure	LTBI health state and could progress to no infection, initial infection, subsequent infection from future exposures, pulmonary TB, disseminated TB, TB death and death from other causes	In the 0–2 years cohort, the no testing strategy dominated other strategies. In the 3–5 years cohort, the TST negative followed by IGRA was the most effective with a reported ICER of approximately US$233,000 per LYS vs. no testing
Immunocompromised people							
Kowada 2010,[196] Japan	To assess the cost-effectiveness of QFT-GIT vs. TST for TB screening of RA patients prior to initiation of TNF-α antagonist therapy	Cost-effectiveness analysis, societal perspective, setting not reported	QFT-GIT	Cost per QALY	Decision tree model with Markov nodes	No LTBI, LTBI, TB and death	QFT-GIT was less costly and more effective than TST. At society's WTP per QALY, the QFT-GIT testing strategy had a 100% probability of being cost-effective compared with the TST strategy

continued

TABLE 26 Summary characteristics of the models comparing IGRAs and the TST in identifying LTBI in children, immunocompromised people and recently arrived immigrants (*continued*)

Study ID, country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention	Outcome measure(s)	Model type	Health states	Results (base-case and sensitivity analysis)
Kowada 2013,[198] Japan	To assess the cost-effectiveness of QFT-GIT vs. TST and CXR for TB screening of haemodialysis patients	Cost-effectiveness analysis, societal perspective, setting not reported	QFT-GIT	Cost per QALY	Decision tree model with Markov nodes	Maintenance dialysis with no disorder, maintenance dialysis with LTBI, maintenance dialysis with TB and death	QFT-GIT was dominant compared with the TST testing strategy. Results from the sensitivity analysis showed that the base-case results were sensitive to the BCG vaccination rate. At all WTP thresholds, the QFT-GIT testing strategy had a 100% probability of being cost-effective compared with the TST testing strategy
Kowada 2014,[199] Japan	To assess the cost-effectiveness for TB screening of high-risk HIV-positive pregnant women of using IGRAs vs. TST in low-incidence countries	Cost-effectiveness analysis, health service perspective, low incidence of TB country but setting not reported	(1) TST alone, (2) QFT alone, (3) T-SPOT.*TB*, (4) TST followed by QFT and (5) TST followed by T-SPOT.*TB*	Cost per QALY	Decision tree model with Markov nodes	Non-LTBI and non-TB, LTBI, non-MDR TB, MDR TB and death	Base-case results showed that T-SPOT.*TB* is less costly and more effective than other strategies. Sensitivity analysis showed that cost-effectiveness was sensitive to the sensitivity of T-SPOT.*TB*, the sensitivity of QFT, the specificity of T-SPOT.*TB* and the specificity of QFT in close contacts

Study ID, country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention	Outcome measure(s)	Model type	Health states	Results (base-case and sensitivity analysis)
Laskin 2013,[200] USA	To determine the most cost-effective LTBI screening strategy before long-term steroid therapy in a child with new-onset idiopathic nephrotic syndrome	Cost-effectiveness analysis, societal perspective, setting not reported	IGRAs	Cost per QALY	Decision tree structure to model the short-term events followed by a Markov modelling structure	Well, LTBI, TB, nephrotic relapse and dead for the longer-term events	Base-case results showed that IGRA was less costly and produced moderately more QALYs than universal TST
Linas 2011,[201] USA	To estimate the cost-effectiveness of LTBI screening using the TST and IGRAs	Cost-effectiveness analysis, health service, setting not reported	IGRAs and TST	Number needed to screen to prevent one case of active TB, life expectancy, quality-adjusted life expectancy	Markov model	LTBI with INH, LTBI no INH, isoniazid-related hepatitis, < 6 months' INH, 6–8 months' INH, 9 months' INH, active TB, post active TB and death	Base-case results showed that, in people who are taking immunosuppressive medication, neither TST nor IGRA screening was cost-effective compared with the no screening strategy. Similar results were reported for people with ESRD
Swaminath 2013,[202] USA	To compare the performance of TST and QFT-G screening of LTBI among immunosuppressed IBD patients based on prevalence, mortality risk from reactivation TB and costs	Cost-effectiveness, health-care payer, setting not reported	QFT-G	Cost per false-negative case of LTBI avoided, cost per TB death avoided, cost per reactivation TB avoided (this can be derived from the information provided)	Decision tree model	True positive, true negative, false positive, false negative, hepatitis, survive/death hepatitis	Base-case results showed that QFT-G dominated the TST strategy. Additionally, the use of QFT-G would avoid 30 false-negative cases, 4.92 TB reactivations and 1.4 deaths compared with the TST strategy

continued

TABLE 26 Summary characteristics of the models comparing IGRAs and the TST in identifying LTBI in children, immunocompromised people and recently arrived immigrants (*continued*)

Study ID, country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention	Outcome measure(s)	Model type	Health states	Results (base-case and sensitivity analysis)
Recent arrivals from countries with a high incidence of TB							
CG117 2011,[10] UK	To compare the costs and effects of four strategies of testing for people suspected of having LTBI in England and Wales	Cost-effectiveness analysis, NHS and Personal Social Services	(1) TST, (2) IGRA, (3) TST followed by IGRA for people with positive TST and (4) no test (to inform and advise only)	Cost per QALY	Decision tree model	Test results, treatment for LTBI, treatment for TB	Results showed that TST positive followed by IGRA and IGRA testing strategies were associated with ICERs of < £30,000 per QALY compared with no testing. The results from the sensitivity analyses showed that varying the cost of an IGRA (from £50 to £60) changed the direction of the cost-effectiveness results
Pareek 2013,[77] UK	To assess the cost-effectiveness of LTBI screening using different screening modalities at different incidence thresholds in a primary care setting, with and without CXR screening on arrival at port of entry	Cost-effectiveness analysis, NHS, primary care setting	(1) T-SPOT.*TB* alone, (2) QFT-GIT alone, (3) TST plus confirmatory T-SPOT.*TB* (if TST positive), and (4) TST plus confirmatory QFT-GIT (if TST positive)	Cost per case of active TB avoided	Decision tree model	The illustrative modelling structure was presented in a supplementary web appendix but unfortunately, these structures were illegible	Results showed that screening of recently arrived immigrants from countries of origin with a moderate (not defined) TB incidence is likely to be cost-effective for the use of one-step IGRA testing compared with other screening strategies

CXR, chest radiography, IBD, inflammatory bowel disease; ICER, incremental cost-effectiveness ratio; ID, identification; INH, isoniazid-induced hepatotoxicity; LYS, life-year saved; MDR, multidrug resistant; RA, rheumatoid arthritis; WTP, willingness to pay.

Immunocompromised people

Kowada[196]

Kowada[196] used a decision tree structure with Markov nodes to assess the cost-effectiveness of using QFT-GIT alone compared with TST alone to diagnose LTBI in patients with rheumatoid arthritis. The model simulated a pathway for a hypothetical cohort of people with rheumatoid arthritis being screened for LTBI and cost-effectiveness was estimated over a lifetime horizon. The model started with a cohort of people aged 40 years who received either diagnostic strategy and continued with people being in the LTBI/initial active TB or no LTBI/no initial TB health state, characterised by the prevalence of the disease. People with positive or negative results on the TST or positive QFT-GIT results received chest radiography to detect active TB. If active TB was detected they received treatment for active TB, whereas if active TB was not detected they received treatment for LTBI. Here, the author assumed that chest radiography to diagnose initial active TB was 100% sensitive and specific. People who adhered to LTBI treatment were at risk of developing isoniazid-induced hepatotoxicity. Kowada[196] presented an illustrative Markov structure to depict the transitions that could occur between health states. From the structure, people could enter the model from the no LTBI, LTBI or TB health state.

The information required to populate the model was obtained from published sources. However, the author did not comment on/discuss the sources of prevalence of LTBI in this population. Information on the sensitivity and specificity of the tests was obtained from secondary sources and a meta-analysis. All costs included in the model were reported in 2009 Japanese yen and converted to US dollars using the same price year. The primary outcome measure of effectiveness was QALYs gained over a lifetime horizon; however, the author did not elaborate on the descriptive tools used to value these health states. All costs and benefits were discounted at 3% per annum. The analysis was conducted from the societal perspective and results were presented in terms of an ICER expressed as cost per QALYs gained. Kowada[196] conducted one-way and two-way sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, a probabilistic sensitivity analysis (PSA) was undertaken, but the distributions and the cost-effectiveness acceptability curve (CEAC) were not presented. The author demonstrated that QFT-GIT alone was the most cost-effective strategy for the diagnosis of LTBI in people undergoing haemodialysis. The results from the sensitivity analyses showed that the base-case results were robust to changes in model input parameters. Results from the probabilistic analysis showed that IGRA was the preferred option, with a 100% probability of being cost-effective compared with TST at society's willingness to pay of US$50,000 per QALY.

Kowada[198]

In this study Kowada[198] used a decision tree structure with Markov nodes to assess the costs and effects of using QFT-GIT alone, TST alone and chest radiography alone to diagnose LTBI in patients undergoing haemodialysis. The model simulated a pathway for a hypothetical cohort of people with haemodialysis being screened and cost-effectiveness was estimated over a lifetime horizon. The model started with a cohort of people who received one of the three diagnostic tests. People with positive results on the TST or QFT-GIT received chest radiography to detect active TB. If active TB was detected they received treatment for active TB, whereas if active TB was not detected they received treatment for LTBI. The author assumed that chest radiography to diagnose initial active TB was 100% sensitive and specific. People who adhered to LTBI treatment were at risk of developing isoniazid-induced hepatitis. Kowada[198] did not present the illustrative Markov structure but described the clinical health states; however, no further comment was made on how people progressed through these health states. The information required to populate the model was obtained from published sources. The author conducted a review of the literature but did not state whether or not the accuracy of the tests was derived from a meta-analysis. The primary outcome measure of effectiveness was QALYs gained; however, the author did not elaborate on the descriptive tools used to value these health states. The analysis was conducted from the societal perspective and the results were presented in terms of an ICER expressed as cost per QALYs gained. Kowada[198] conducted one-way and two-way sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, PSA was undertaken but the

distributions and the CEAC were not presented. The author demonstrated that QFT-GIT alone was the most cost-effective strategy for the diagnosis of LTBI in haemodialysis patients.

Kowada 2014[199]

Kowada used a decision tree structure with Markov nodes to estimate the cost-effectiveness of IGRAs compared with TST for TB screening in high-risk HIV-positive pregnant women in countries with a low incidence (< 24 cases per 100,000) of TB. The model simulated the pathway for four cohorts (BCG vaccinated during pregnancy, non-BCG vaccinated during pregnancy, BCG vaccinated in the post-partum period and non-BCG vaccinated in the post-partum period) separately and cost-effectiveness was estimated over a 30-year time horizon. The starting point of the model was a hypothetical cohort of women aged 20 years who received one of five (TST alone, QFT-G alone, T-SPOT.*TB* alone, TST positive followed by QFT or TST positive followed by T-SPOT.*TB*) testing strategies. A result was considered positive on TST if the induration was ≥ 5 mm and ≥ 10 mm in those who were non-BCG vaccinated and BCG vaccinated respectively. Women who had positive results on the TST-, QFT-G- or T-SPOT.*TB*-alone strategies received chest radiography to diagnose initial active TB. On the combination strategies, women who received a positive result on TST further received QFT-G or T-SPOT.*TB* and, if the result was positive, received chest radiography to detect initial active TB and received treatment for LTBI/TB. Women who adhered to LTBI treatment were at risk of developing isoniazid-induced hepatotoxicity and were treated accordingly. In the Markov structure, the author considered five health states (non-LTBI and non-TB, LTBI, non-multidrug-resistant TB, multidrug-resistant TB and dead) that women could enter based on proportions from the decision tree and showed the transitions between these health states.

Data required to populate the models were obtained from published sources. The analysis was conducted from the public health payer perspective and results were presented in terms of ICERs expressed as cost per QALYs gained. All costs included in the model were reported in 2012 Japanese yen and converted to US dollars using the same price year. The primary outcome measure of effectiveness was QALYs gained over a 30-year time horizon. All costs and benefits were discounted at 3% per annum. Kowada[199] conducted PSA and one- and two-way sensitivity analyses by changing key model input parameters to determine the impact on the base-case results. The base-case results showed that the TST positive followed by QFT-G strategy was the most cost-effective strategy for the diagnosis of LTBI in occasional screening of HIV-positive pregnant women who were non-BCG vaccinated during pregnancy. Similar results were demonstrated in the other hypothetical cohorts. Results from the PSA showed that the TST followed by QFT-G strategy was the preferred option, with a 100% probability of being cost-effective at all of society's willingness-to-pay levels per QALY. The results from the sensitivity analyses showed that the base-case results were sensitive to changes in the sensitivity of T-SPOT.*TB* and the sensitivity of QFT-G in occasional screening of non-BCG vaccinated pregnant women.

Laskin *et al.*[200]

Laskin *et al.*[200] used a decision tree structure with Markov nodes to determine the most cost-effective screening strategy for children with new-onset idiopathic nephrotic syndrome. The decision tree component of the model represented the pathway that children would undertake in a 6-month time period before they entered into the Markov model. Here, the longer-term events were simulated over a lifetime horizon with 3-month cycle lengths. The starting point of the model was a hypothetical cohort with new onset nephrotic syndrome. Children who received a positive test result were treated for LTBI and were at risk of developing hepatitis. The starting points of the Markov model were derived from the proportions of children with negative TST/IGRA results, children in whom LTBI treatment was successful and those in whom LTBI treatment had failed. The authors assumed that effective LTBI treatment provided long-term protection against LTBI/TB. Data required to populate the model were obtained from published sources. The analyses were conducted from the societal perspective applying an annual discount rate of 3% on costs and benefits. Indirect costs incurred in the analysis included travel time and loss of productivity. Base-case results showed that the no-screen strategy was least costly and more effective than other strategies. However, the results from this study should be interpreted with caution because the discounted and undiscounted costs were similar. The results from the sensitivity analysis showed that the

results were robust when indirect medical costs were excluded from the analysis. The results were sensitive to changes in the prevalence of LTBI in this population, with the questionnaire followed by the IGRA screening strategy being the most cost-effective strategy at a prevalence of > 4.9%. The results from the probabilistic analysis showed that, at a prevalence of 1.1%, no screening was the preferred screening option compared with IGRA, but the authors did not state the willingness-to-pay value used.

Linas *et al.* 2011[201]

Linas *et al.*[201] constructed a decision tree structure with Markov nodes to estimate the cost-effectiveness of using TST compared with IGRAs for the diagnosis of LTBI in various populations. The model begins with a hypothetical cohort of people who received one of three diagnostic strategies (TST alone, IGRA alone or no screening). The model continued with people characterised by their disease status (LTBI/no LTBI). People with a positive IGRA or TST result received treatment for LTBI. The decision tree structure was used to inform on the proportion of people who started in the Markov model structure. The Markov structure started with people in the LTBI with isoniazid treatment state, the LTBI with no treatment state or the active TB health state, and showed the transitions between these health states. People who received treatment for LTBI were at risk of developing isoniazid-induced hepatitis.

Data required to populate the model were obtained from published sources. All costs included were obtained from published sources and presented in 2011 US dollars. The primary outcome was cost per QALY gained over a lifetime horizon. Utility values estimated were based on the Short Form questionnaire-36 items and European Quality of Life-5 Dimensions descriptive systems. The analysis was conducted from the health service perspective and all costs and benefits were discounted at 3% per annum. The authors further conducted one- and two-way sensitivity analyses around the key model input parameters. Results from the analysis showed that, in the HIV-infected cohort, screening with IGRA alone was marginally more costly and effective than the no screening option, with an ICER of $12,800. For people who were on immunosuppressive medication, the reported ICER for TST screening compared with no screening was $129,000. Sensitivity analyses showed that increasing the mean age of the population to 65 years and screening with TST remained cost-effective in people living with HIV infection. The base-case results were sensitive to changes in the estimates of health-related quality of life for people who received treatment for active TB. Screening with TST or IGRA resulted in ICERs that were > $100,000 for people with diabetes or end-stage renal disease.

Swaminath *et al.*[202]

Swaminath *et al.*[202] used a decision tree structure to estimate the costs and benefits of using QFT-G alone compared with TST alone for the diagnosis of LTBI in people with inflammatory bowel disease. The model simulated a cohort of people with moderate to severe active Crohn's disease being treated with immunosuppressive medication. The starting point of the model was a cohort of people who received one of two tests. The structure started from disease status (LTBI/no LTBI) followed by test results. On positive test results people received treatment for LTBI and could further develop isoniazid-induced hepatitis and either survived or died from this event. People who were false negative could have reactivated TB and could survive or die from this event. People who were false positive received treatment and could further develop isoniazid-induced hepatitis. The authors suggested that people with indeterminate results on the QFT-G would immediately receive a second QFT-G test. However, this pathway was not shown in the decision tree structure. Data required to populate the model were obtained from secondary sources. The prevalence of LTBI in this population was obtained from the WHO. The sensitivity and specificity of tests were derived based on information obtained from a few sources and not from a literature review. The analysis was conducted from the health payer perspective and the results were presented in terms of the costs of false-negative cases avoided, TB reactivations and deaths avoided. The authors conducted one-way sensitivity analyses around key model input parameters. They suggested that QFT-G was less costly and more effective than the TST in this population.

Recent arrivals from countries with a high incidence of tuberculosis

Pareek *et al.*[77]

Pareek *et al.*[77] used a decision tree structure to simulate the costs and benefits of using T-SPOT.*TB* alone, QFT-GIT alone, TST plus confirmatory T-SPOT.*TB* (if TST positive) or TST plus confirmatory QFT-GIT (if TST positive) for screening immigrants for LTBI. The illustrative model structure presented by the authors in the supplementary appendix was illegible and hence further comment on/appraisal of the structure/pathways could not be made. The authors suggested that immigrants who were symptomatic at initial screening or who had a positive IGRA/TST result were referred for chest radiography and further clinical assessment. Immigrants with a positive IGRA and/or positive TST result and a normal chest radiograph without any symptoms suggestive of active TB were considered to have LTBI. For a positive TST test, cut-offs of ≥ 6 mm and ≥ 15 mm were used for BCG-unvaccinated and BCG-vaccinated participants, respectively. Additionally, the authors used a non-stratified cut-off of ≥ 10 mm to suggest a positive TST. The data required to populate the model were obtained from an observational study undertaken by the authors and from published sources. To be included in the observational study, participants had to be recently arrived (within the last 5 years) immigrants to the UK, aged ≥ 16 years (with symptoms of TB) or from a country with a TB incidence of ≥ 40 per 100,000 (asymptomatic). Information on the prevalence of LTBI was derived from immigrants aged ≤ 35 years who had been tested with the three screening tests. Cost data from published sources were inflated to 2010 prices using the Consumer Prices Index. The analysis was undertaken from the UK NHS perspective in a primary care setting. The outcome measures included in the analyses were the number of cases of active TB avoided and the number of LTBI cases needed to be treated to prevent one case of active TB, over a 20-year time horizon. The results were presented as cost per active TB cases avoided. Both costs and benefits were discounted at 3.5% per annum. Pareek *et al.*[77] conducted sensitivity analyses on key model input parameters (prevalence of LTBI, progression rate from LTBI to active TB, specificity, proportion of immigrants accepting and adhering to LTBI treatment). The base-case results showed that the screening strategy of no port-of-entry chest radiography and screening with one-step QFT-GIT was cost-effective with an ICER of £21,570 per case of active TB avoided for immigrants whose country of origin had an incidence of TB of 250 per 100,000. For immigrants whose country of origin had an incidence of TB of ≤ 150 per 100,000, the strategy was not cost-effective (at a willingness to pay of £30,000 per QALY). Results from the sensitivity analyses showed that varying the prevalence and the progression rate from LTBI to active TB increased the cost-effectiveness of the one-step QFT-GIT strategy. Reducing the specificity of the test resulted in the one-step T-SPOT.*TB* becoming the most cost-effective strategy. Reducing the proportion of people accepting and adhering to LTBI treatment led to higher cost-effectiveness estimates.

National Collaborating Centre for Chronic Conditions, Centre for Clinical Practice at the National Institute for Health and Care Excellence[10]

The authors of CG117[10] used a decision tree structure to compare the costs and effects of four testing strategies [TST alone, IGRA alone, TST followed by IGRA and no test (to provide information and advice only)] for the diagnosis of LTBI in immigrants from countries with a high prevalence of active TB. The model started with a cohort of recently arrived immigrants who received one of the four testing strategies. In the TST-/IGRA-alone strategies, people who received a positive test result were treated for LTBI. Conversely, a proportion of people who had negative test results were given the BCG vaccination. In the combination strategy, people who tested positive on the TST received a QFT test. Immigrants who had a positive QFT result were treated for LTBI and, of those with a negative result, a proportion were given a BCG vaccination. The end point of the model was the proportion of people developing TB having received a BCG vaccination or treatment for LTBI. Data required to populate the model were obtained from published sources. Sensitivity of the tests was based on two publications and average values were used as estimates. Costs included in the model were those related to the UK NHS and Personal Social Services. All costs were presented in UK pounds sterling in 2008/9 prices. Costs obtained from published sources were inflated using the Hospital and Community Health Services pay and price index. The results showed that a positive TST result followed by IGRA and the IGRA-alone testing strategy were associated with ICERs of $<$ £30,000 per QALY compared with the no-testing strategy. The results from the sensitivity analyses showed that varying the cost of an IGRA (from £50 to £60) changed the direction of the cost-effectiveness results.

Characteristics of the included studies

The characteristics of the models included in these evaluations are summarised in *Table 26*. All of the included studies used an economic model to determine the cost-effectiveness of various strategies for the diagnosis of LTBI. Four[196–199] of the economic evaluations were conducted in Japan, three[200–202] in the USA, two[10,77] in the UK and one[203] in South Africa. Three studies[196–198] compared QFT-GIT only with TST only, two studies[200,201] compared an IGRA with TST but did not indicate the type of IGRA being used, one study[202] compared QFT-G only with TST only and four studies[10,77,199,203] compared various testing strategies (TST alone, QFT alone, QFT-GIT alone, T-SPOT.*TB* alone, TST followed by QFT and TST followed by T-SPOT.*TB*, TST negative followed by IGRA) for the diagnosis of LTBI. Two[197,203] economic evaluations were conducted in children, six[196,198–202] evaluations were conducted in the immunocompromised population and two[10,77] were conducted in the recently arrived population.

Most of the decision-analytical models[196–200,203] used for the analyses were decision tree structures with Markov nodes; three studies[10,77,202] used a decision tree structure alone and one study[201] used a Markov model alone to show diagnostic strategies for detecting LTBI and progression over time to active TB. The health states included in the models represented those that people would experience while being screened for LTBI. In the models with a cohort of children, the health states included healthy, LTBI, TB and dead. There was some variation in the health states used for the immunocompromised population; this may be because of the presence of various diseases/conditions when trying to assess which diagnostic strategy is cost-effective for the diagnosis of LTBI. In the models with a cohort of recently arrived immigrants, the health states included test results, treatment for LTBI and treatment for TB. One of the model structures was illegible in this population.

Model time horizons ranged from 1 year to a lifetime. In the models with children, the time horizon was a lifetime (up to 80 years) with cycle lengths of 6 months[203] and 1 year.[197] In the models with immunocompromised cohorts, the time horizons ranged from 1 year to a lifetime, with 3-month or 1-year cycle lengths, and in the models with a recently arrived cohort, the time horizons ranged from 15 years to 20 years, with annual cycle lengths. The authors stated that the time horizons chosen were long enough to measure the costs and benefits of the diagnostic strategies.

Resource use and costs included in the economic analyses depended on the perspective taken. All studies clearly stated the perspective or viewpoint from which the analysis was undertaken. Five studies[10,77,199,201,202] conducted their analyses from the UK NHS or other national health payer perspective and the remaining five studies[196–198,200,203] conducted their analyses from the societal perspective. The five models[10,77,199,201,202] that presented results based on the health payer perspective included direct costs related to the health service (costs of diagnostic tests, chest radiography and sputum examinations, treatment for LTBI/active TB and treatment for isoniazid-induced hepatotoxicity). Of the five models[196–198,200,203] that presented results based on the societal perspective, three models[196–198] did not include indirect costs or loss of productivity.

Six[10,196–200] studies reported their results in terms of cost per QALY only, three studies[77,202,203] reported their results in terms of cost per life-year saved, cost per false-negative case of LTBI avoided, cost per TB death avoided, cost per reactivation TB case avoided or cost per TB case avoided, and in one study[201] the outcomes were based on the number needed to screen to prevent one case of active TB, life expectancy and QALYs gained. Of the studies that reported results in terms of QALYs, utility values were obtained from published sources to derive QALY estimates. These studies referenced the original source of the utility values but did not elaborate on which descriptive system was used to values these health states. From the base-case results reported in these studies, the consensus was that IGRAs were less costly and more effective than other strategies.

Because of the uncertainty around key model input parameters and assumptions made in the models, all authors conducted sensitivity analyses. Five studies[10,77,201–203] conducted deterministic (one- and two-way) sensitivity analyses alone. The remaining studies[196–200] conducted both deterministic sensitivity analyses and

PSAs. Sensitivity analyses were conducted around changing the prevalence of LTBI, test accuracies (sensitivity and specificity) of diagnostic tests, the costs of the IGRAs, return rates for TST and the progression rate from LTBI to active TB.

This review was used to inform model development for the diagnosis of LTBI in three populations. In the following section we provide an appraisal of the modelling structures, the data used to parameterise the models and the handling of uncertainty. We also consider relevant issues when deriving key model input parameters (prevalence, sensitivity/specificity of diagnostic tests and combination strategies).

Quality assessment of the modelling methods

We present a summary of the reporting quality of the studies included in the current review assessed against the Philips *et al.*[195] checklist in *Appendix 13*.

Structure

The structures of the models included in this review were generally of good quality. In accordance with best practice for developing model structures, studies clearly stated their decision problem and the perspective of the analysis, the objectives of the model, which were consistent with the decision problem, and the structures which represented the clinical pathway people that would follow while being screened for LTBI. However, there were some structural issues noticed. Three studies[196–198] conducted their analyses from the societal perspective but did not include indirect costs or loss of productivity in the analyses. Studies generally stated the location of the analyses but not the setting and this may have an impact on the generalisability of the results. Illustrative model structures were also presented in the majority of the studies but in one study[77] the model structure was illegible. All studies clearly stated and justified their time horizon and cycle lengths.

All authors justified their choice of model structure, which represented coherent pathways of LTBI disease and its treatment. Six models[10,196–200] used decision tree structures with Markov nodes for their analyses, three studies[77,202,203] used decision tree structures alone and one study[201] used a Markov model alone. Of the studies identified, six[10,198–201,203] modelled from the test result first followed by LTBI diagnosis, whereas four[77,196,197,202] modelled from LTBI diagnosis followed by the test result. One study[10] included a proportion of people returning to have their TST result read. One study[202] included a proportion of people with indeterminate test results on an IGRA and assumed that they would receive a second IGRA immediately (not shown in the decision tree). All studies included chest radiography to confirm whether or not active TB was present. All studies also included treatment for LTBI and TB. As a result of adhering to LTBI treatment, all studies included a proportion of people developing isoniazid-induced hepatotoxicity but they did not include any other adverse events from adhering to TB treatment. Studies that included a Markov model[196–200,203] generally used similar health states (no LTBI, LTBI, active TB, reinfection, disseminated TB and dead) to show the possible transitions over time.

Key model input parameters

The methods used to identify relevant information to populate the models were satisfactory in most studies. Studies stated that a literature review was undertaken but did not specify the purpose/aim of the review, that is, to search the literature to inform on the data inputs and/or to inform on the model structure or model design. All studies provided references for their model inputs but they were not clear on the choices between data sources or the quality of information used in the models. This may have been a result of a paucity of information in the literature.

In the four models[77,196,197,202] that started from known disease status, information required at this point was the prevalence of LTBI in the population. Most studies used secondary sources to obtain a point estimate or to derive an estimate of the prevalence of LTBI but they did not elaborate on what the prevalence represented (prevalence of LTBI in contact tracing, prevalence of LTBI based on occasional screening in the

population of interest or prevalence of LTBI that would develop to active TB). Additionally, studies that used multiple sources were not transparent on the methods used to derive an estimate of the prevalence of LTBI.

Test characteristics of the TST and IGRAs were required for all of the models. In most studies[10,77,197,199–203] a literature review was carried out and estimates of sensitivity and specificity were derived based on sources identified. Most studies[10,77,197,199–201] elaborated on the methods used to derive sensitivity and specificity. These methods included calculating an estimate based on an average of sensitivity (and specificity) obtained from the literature, obtaining estimates from sources that conducted a meta-analysis or using Bayesian statistics to calculate an estimate of sensitivity and specificity based on confirmed TB cases. The study[77] that used Bayesian statistics acknowledged that there is no gold standard test available for the diagnosis of LTBI in these populations and provided equations used to derive sensitivity and specificity. Studies that included a combination strategy,[10,199] for example TST positive followed by IGRA, did not elaborate on the methods used to derive the sensitivity and specificity of a test conditional on an initial positive/negative result.

All costs required for the models were justified and referenced. Costs obtained from published literature were inflated using the appropriate indices. All authors clearly stated the unit costs used in the models, but some authors[196,198–200] did not elaborate on the resources used to estimate the unit costs, especially for the treatment of LTBI/active TB. All authors stated the perspective of the analyses, but in some studies[196–198] the costs included did not reflect the viewpoint/perspective of the analyses. All authors, when necessary, discounted costs and benefits using the appropriate rates.

In the models that reported their results in terms of QALYs,[10,196–201] authors provided the references used to obtain the utility weights. However, the majority of the authors[196–200] did not elaborate on the descriptive tools/measures used to value these health states in these populations. Additionally, authors did not elaborate whether or not the sources of utility information used were relevant to their population of interest.

Uncertainty and assumptions

Uncertainty is unavoidable in economic modelling. Briggs and Gray[204] and Philips *et al.*[195] have outlined methods to handle the four main types of uncertainty (methodological, structural, parameter and generalisability). All of the models attempted to address uncertainty, but none of these studies addressed all types of uncertainty. All of the studies undertook univariate or multivariate sensitivity analysis on key model input parameters. Four studies[196–199] also undertook PSA for joint uncertainty in model parameters to assess the impact on the base-case results.

To have a workable model structure to conduct these analyses, all studies except that by Kowada[199] clearly stated the simplifying assumptions of their models. In general, these assumptions outlined in the studies appeared to be feasible but were strong in some cases. One study[77] assumed that testing with an IGRA would not lead to an indeterminate result whereas in CG117[10] the authors assumed that treatment of LTBI/TB was adhered to by the population and that it would not lead to any adverse events.

Conclusion

The evidence base described here offers insight on the decision-analytic models available to determine the cost-effectiveness of an IGRA compared with the TST for the diagnosis of LTBI in children, immunocompromised people and people from countries with a high incidence of active TB. We identified 10 model-based economic evaluations across these three populations. The majority of these models included immunocompromised or immunosuppressed populations, with the evidence available for the other two populations being sparse. The majority of the models used decision tree structures with Markov nodes to simulate a cohort of people being tested for LTBI.

We appraised these models against frameworks on best practice for reporting an economic evaluation and economic modelling. In general, all models performed well in terms of defining the decision problem, including the study perspective, outlining the choice of comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. These models all add to the existing literature but are subject to limitations. First, the majority of the studies indicated the location of the study but did not state the setting of the analysis and this may limit the generalisability of the results. Second, the majority of the studies used QALYs as the outcome measure and referenced the source of the utility values. However, the authors did not provide commentary on the descriptive tools used to value these health states. Third, the perspective of the analysis was stated in all studies; however, some of the resource use and costs reported did not reflect the viewpoint of the analysis. Fourth, the majority of the studies were transparent with regard to the methods used to identify information to populate the models, but it was unclear if any quality assessment of the information was undertaken. Finally, all models explored uncertainty around key model input parameters by undertaking one- and two-way sensitivity analyses but no attempt was made to explore the other types of uncertainty: methodological, structural or generalisability. Other concerns relate to the derivation of prevalence, test accuracy and transition probabilities; most studies did not elaborate on these statistical/pre-model analyses.

In *Chapter 6* we outline the development of a de novo model that includes two stages to inform on the cost-effectiveness of various strategies for the diagnosis of LTBI in our populations of interest.

Chapter 6 Health economics methods and results

Objective

The objective of the economic evaluation was to compare the cost-effectiveness of various screening strategies for the diagnosis of LTBI in immunocompetent children, people who are immunocompromised or at risk of immunosuppression and people who are recent arrivals from countries with a high incidence of active TB.

Currently in the UK, the following strategies are recommended to diagnose people with LTBI:[10]

- *Children*. Offer a Mantoux test to children aged 2–15 years. If positive, follow up with an IGRA.
- *Immunocompromised*. For people who are HIV negative, offer an IGRA alone or an IGRA with a concurrent Mantoux test. If either test is positive perform a clinical assessment to exclude active TB and treat.
- *Recently arrived immigrants*. Offer an IGRA alone or a dual strategy for people aged 16–35 years. If either test is positive, refer to a TB specialist to exclude active TB and treat.
- *General population*. Offer an IGRA alone or IGRA testing for people whose Mantoux test shows positive results.

Developing the model structure

To assess the cost-effectiveness of various strategies for the diagnosis of LTBI, we developed an economic model using R (version 3.1.1; The R Foundation for Statistical Computing, Vienna, Austria).

The model was developed with clinical input and represents, as far as possible, the clinical pathways that people would take while being screened for LTBI. The model structure for the child population is presented in *Figure 49*. The model was structured in two stages: diagnosis of LTBI and disease progression to active TB. The first stage of the model represents the clinical pathway that people would take in a 1-year time period before entering the infectious disease model. For this stage we used a decision tree structure for the diagnosis of LTBI. Four diagnostic strategies were examined in the model for each population:

- TST alone
- IGRA alone
- combinations of TST and IGRA
- simultaneous testing.

These strategies being compared were derived based on the strategies outlined in CG117[10] and with input from the TB Guideline Development Group. The model begins with people receiving one of these diagnostic strategies (see *Figure 49*). The branches to the right of the decision node (square symbol) represent the strategies being compared (see *Figures 50–54* for the child population and *Appendix 15*, *Figures 60–74*, for all other populations). People begin in one of the possible health states to the right of the chance nodes (circle symbols). The decision tree is modelled from individuals who have LTBI that progresses to active TB/no LTBI, followed by the probability of test results. However, in clinical practice the test result is known before LTBI is diagnosed. Modelling the test result first followed by disease category or vice versa makes no mathematical difference in terms of the expected values calculated for each diagnostic strategy.[205] In the following sections we describe each strategy in detail.

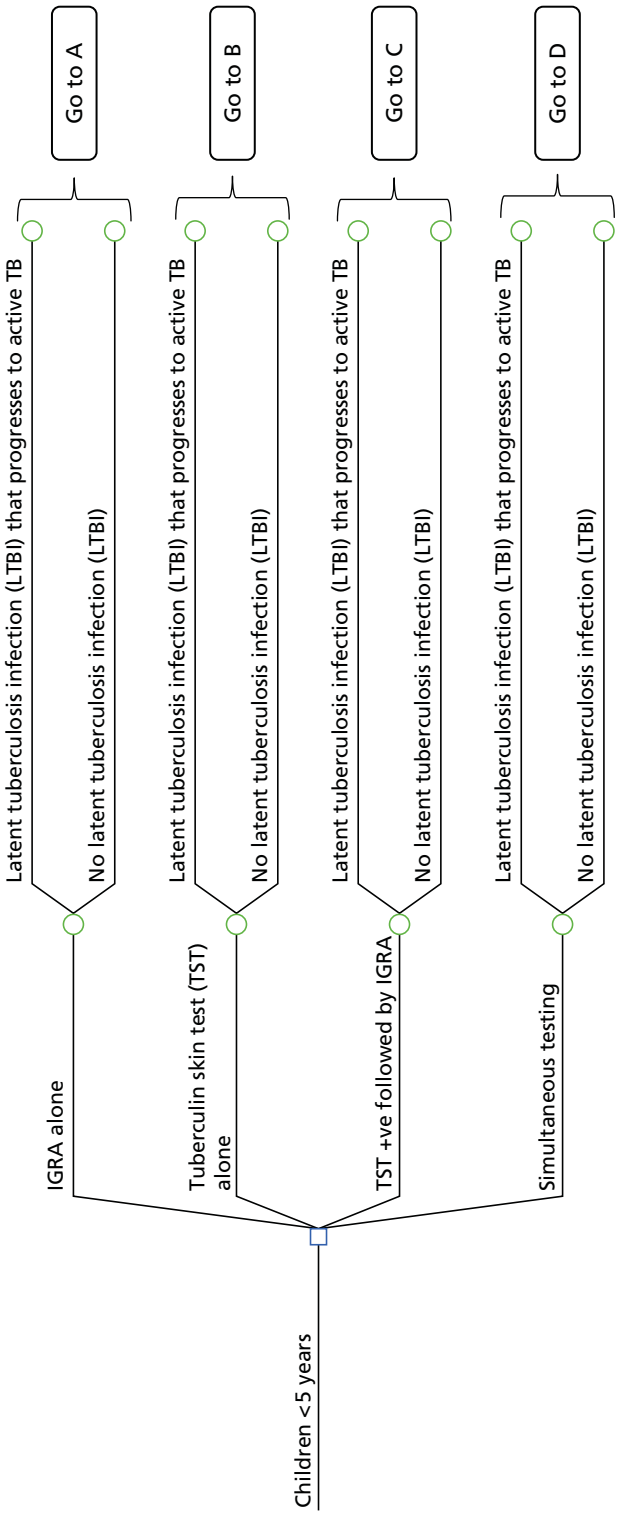


FIGURE 49 Decision tree structure for the child population.

*Tuberculin skin test-alone strategy (*Figure 50*)*

When screening with a TST, an individual may or may not return to have the test results interpreted (TST not read). Adults with positive TST results (induration ≥ 5 mm/10 mm) are assessed for initial active TB by chest radiography and sputum examination. Children with positive TST results are assessed for active TB by chest radiography and, if that is positive, a gastric lavage procedure. Those who have a positive result on chest radiography and sputum examination are treated for active TB. We assumed here that chest radiography and sputum examination are 100% accurate at diagnosing people who have initial active TB. People who adhere to TB treatment in the immunocompromised or recently arrived population may develop hepatitis and can survive or die from this adverse event. In the model with a cohort of children, we assumed that they would not develop hepatitis because it is a rare adverse event in this population.[203] People who have a negative result on chest radiography and sputum examination (LTBI) can either accept or refuse to be treated for LTBI. Those who accept LTBI treatment may adhere/not adhere to treatment. If the TST is not read or the TST results are negative, the individual is not followed up.

*Interferon gamma release assay-alone strategy (*Figure 51*)*

When screening with an IGRA alone, an individual may have a determinate or an indeterminate result. Adults with a determinate result and who are IGRA positive are assessed for initial active TB by chest radiography and sputum examination. Children with positive IGRA results are assessed for active TB by chest radiography and, if that is positive, a gastric lavage procedure. Those who have a positive result on chest radiography and sputum examination are treated for active TB. Those who have a negative result on chest radiography and sputum examination (LTBI) can either accept or refuse to be treated for LTBI. People who accept LTBI treatment can adhere or not adhere to treatment. People with an indeterminate IGRA result receive a second IGRA test, which is the same as the initial IGRA test. If the IGRA result is negative or both IGRA tests are indeterminate, the individual is not followed up.

*Combined strategy (*Figure 52*)*

For children and the recently arrived population, those who had their TST results interpreted, and whose results are positive, receive an IGRA test. Children with determinate, positive IGRA results receive chest radiography and, if positive, the gastric lavage procedure before a sputum examination for the assessment of active TB. Children with negative chest radiography/sputum examination results are either treated or not treated for LTBI. Children with indeterminate results receive a second IGRA test, which is the same as the initial IGRA test. If the TST is not read or the TST is negative, the individual is not followed up. Recent arrivals with determinate, positive IGRA results are assessed for active TB by chest radiography and sputum examination. If there is a positive result on chest radiography and sputum examination, they are treated for active TB. Those who have a negative result on chest radiography and sputum examination (LTBI) can either accept or refuse to be treated for LTBI. If people accept LTBI treatment, they may adhere/not adhere to treatment. People with an indeterminate IGRA result receive a second IGRA test, which is the same as the initial IGRA test. These people follow similar pathways to those who received one IGRA test. At most, people will receive two IGRA tests. If the TST result is not read, the TST result is negative, the IGRA result is negative or both IGRA tests are indeterminate, the individual is not followed up.

Conversely, in the immunocompromised group, people receive an IGRA test first. Those who have a positive result on the IGRA test receive chest radiography and sputum examination to detect initial active TB. Those with a positive result on chest radiography and sputum examination are treated for active TB. Those who have a negative result can accept or refuse treatment for LTBI. People who have accepted and adhered to LTBI treatment may develop hepatitis and can survive or die from this adverse event.

Individuals with a negative IGRA result undergo a TST test. People here follow similar pathways as those who received the TST-alone strategy. Those with an indeterminate IGRA result receive a second IGRA test, which is the same as the initial IGRA test. These people follow similar pathways to those who received one IGRA test. At most, people will receive two IGRA tests. If the IGRA result is negative, both IGRA tests are indeterminate, the TST result is negative or the TST result has not been read, the individual is not followed up.

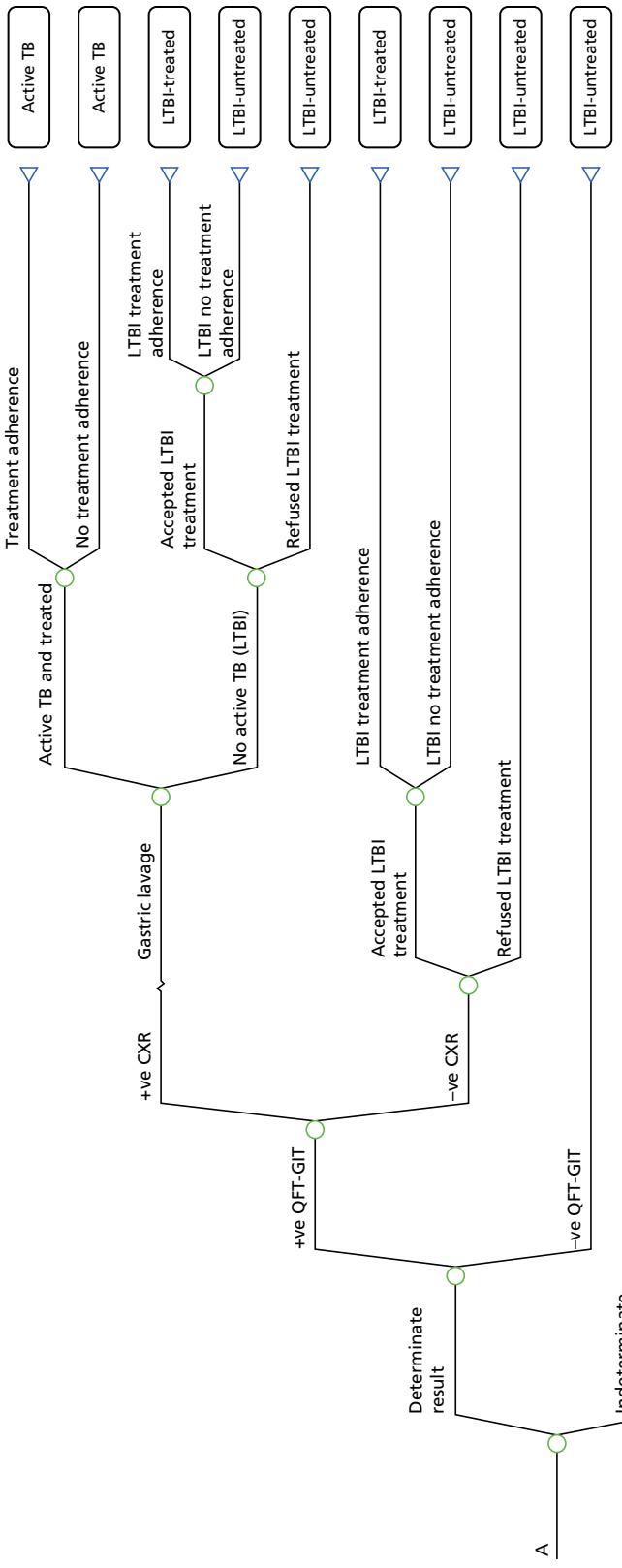


FIGURE 50 Pathway for the TST-alone diagnostic strategy in children. –ve, negative; +ve, positive; CXR, chest radiography.

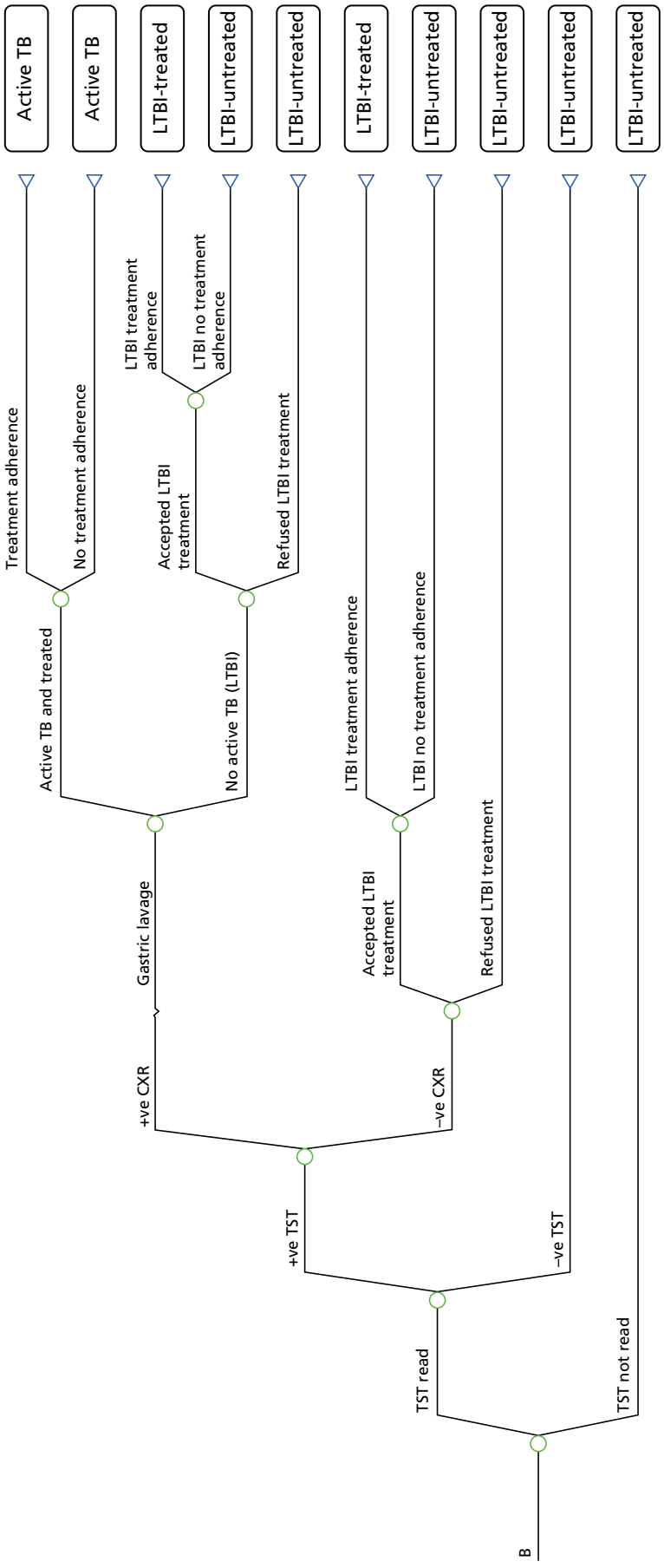


FIGURE 51 Pathway for the IGRA-alone diagnostic strategy in children. –ve, negative; +ve, positive; CXR, chest radiography.

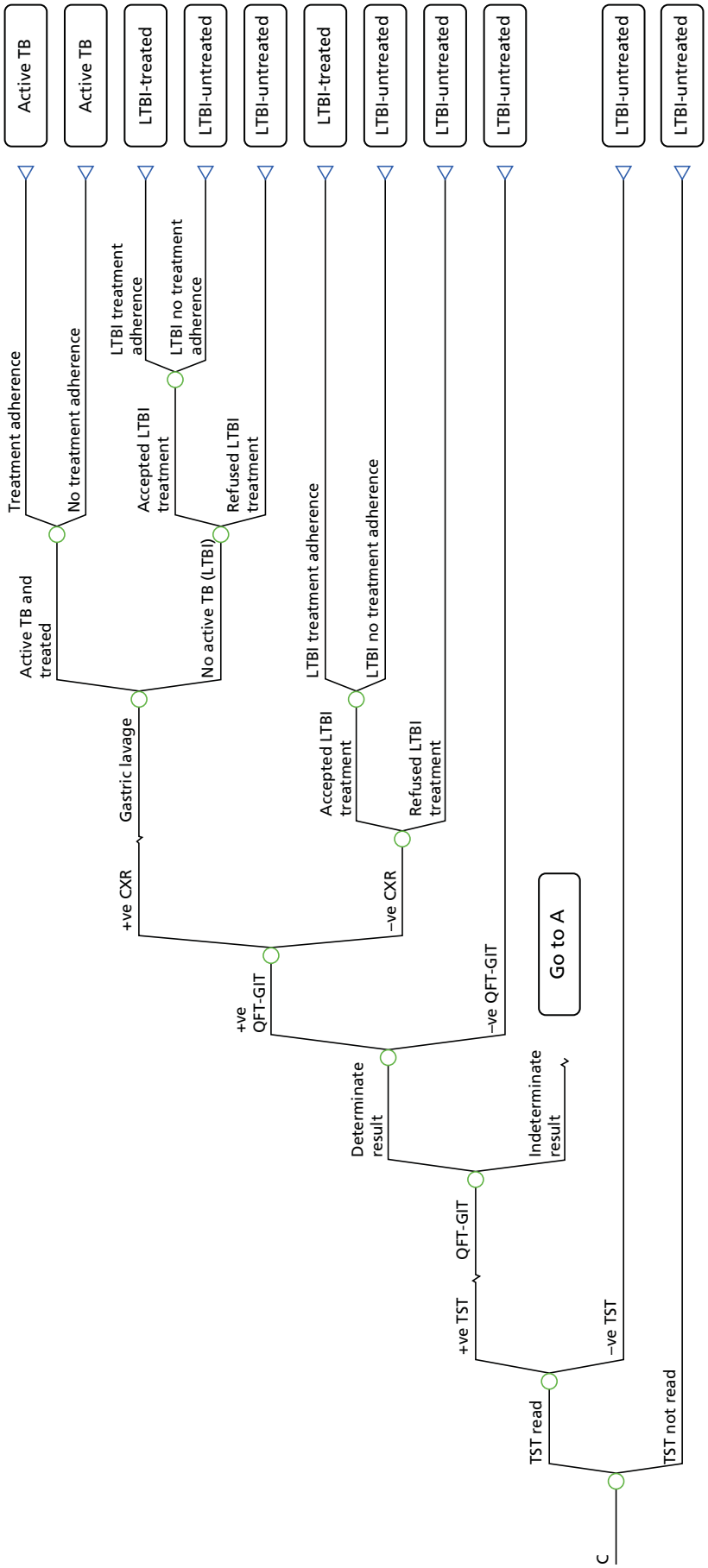


FIGURE 52 Pathway for the diagnostic strategy TST positive followed by IGRA in children. –ve, negative; +ve, positive; CXR, chest radiography.

*Simultaneous testing strategy (*Figures 53 *and* 54*)*

When screening with an IGRA and a TST, people can have a combination of test results: a determinate result on the IGRA and the TST read, a determinate result on the IGRA and the TST not read, an indeterminate result on the IGRA and the TST read or an indeterminate result on the IGRA and the TST not read. Children with a positive result on either test receive chest radiography and, if positive, the gastric lavage procedure and sputum examination to detect initial active TB. For the other populations, those with a positive result on either test receive chest radiography and, if positive, a sputum examination to detect active TB. If the IGRA result is indeterminate and the TST is not read, the individual is not followed up.

Stage 2 of the model is a disease progression model looking at progression between no TB/LTBI, LTBI that will progress to active TB and active TB, as well as secondary infections in other individuals caused by people with active TB. The basic model structure is shown in *Figure 55*. This structure is the same for people who are/are not being treated for LTBI/active TB, although the transmission probabilities are different in each of these cases. The outputs of the decision tree are used to determine the proportions of people who start in each state, specifically:

1. active TB
2. LTBI – treated for LTBI
3. LTBI – untreated
4. no TB/LTBI – treated for LTBI
5. no TB/LTBI – untreated.

The model used was a discrete event simulation, modelling individual patients, built using R (version 3.1.1). An initial simulation, starting with an identical cohort of 500,000 individuals in each arm, was run using the mean values of each parameter. To account for parameter uncertainty, we also ran a Monte Carlo simulation, consisting of 2000 different sampled parameter sets, each run on a starting sample of 100,000 individuals. An individual's event risks at any time point are determined by their age, TB status and current treatment and remain constant until one of these factors changes.

People who begin the model with LTBI and who are not treated will develop active TB at a later point (from the definition of LTBI in our model as LTBI that progresses to active TB). The mean delay between the diagnostic test and progression to active TB was estimated from the systematic review, with individual activation times simulated assuming a constant activation rate over time. People who begin the model with LTBI and who are treated for LTBI have a certain probability of not developing active TB in the future (the effectiveness of the treatment – assumed to be 6 months of isoniazid), with activation times for those whose treatment is unsuccessful sampled as above.

Age-specific all-cause mortality rates were taken from UK-specific data in the Human Mortality Database[206] and applied to all individuals in the model. Age-specific utilities for individuals without TB were calculated using data from the Health Survey for England.[207] When an individual develops active TB, they have an immediate, age-specific probability of death, over that of all-cause mortality. Recovery rates from active TB were calculated from the mean length of an active TB episode, assuming a constant probability of recovery over time. Individuals with resolved TB have an annual probability of relapse, with subsequent activations having the same probability as the initial episode.

For each TB activation (primary or relapse), individuals generate a certain number of secondary cases of LTBI that will progress to active TB, sampled from a Poisson distribution. These cases are assumed to occur in the general population; hence, the age of the secondarily infected individuals was simulated from the average age distribution of active TB cases in the UK. These secondary cases were assumed to be identical (in terms of probability of death, average length of active TB episode, utility loss, number of secondary cases generated) to similarly aged individuals in the initial population. We did not simulate secondary cases of LTBI that do not progress to active TB as we have also not considered these in our initial population.

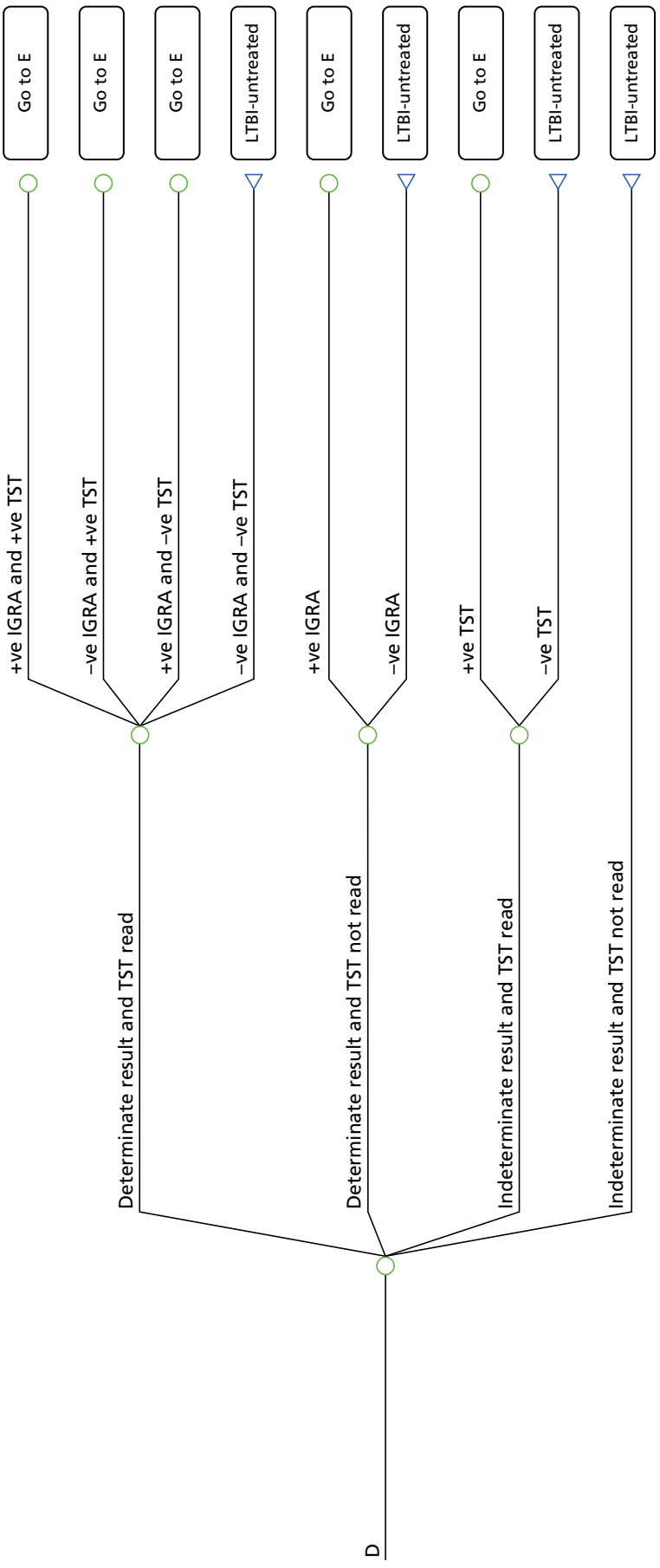


FIGURE 53 Decision tree structure for the child population receiving the simultaneous testing strategy. –ve, negative; +ve, positive.

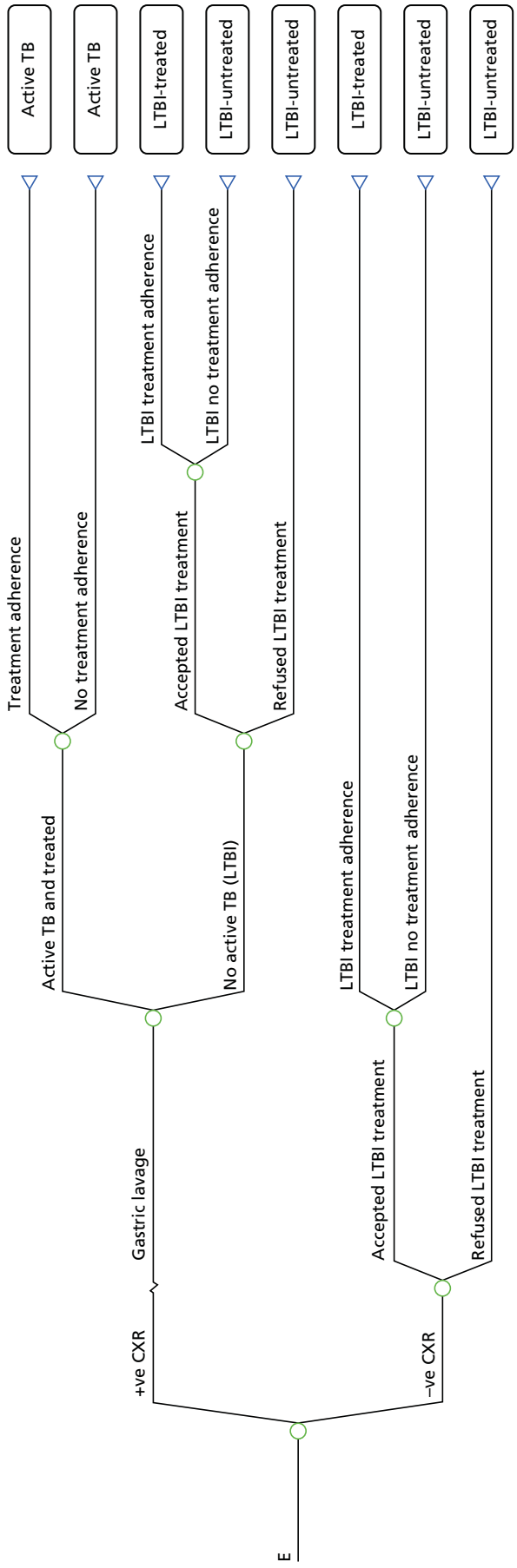


FIGURE 54 Pathway for the simultaneous testing strategy in children. –ve, negative; +ve, positive; CXR, chest radiography.

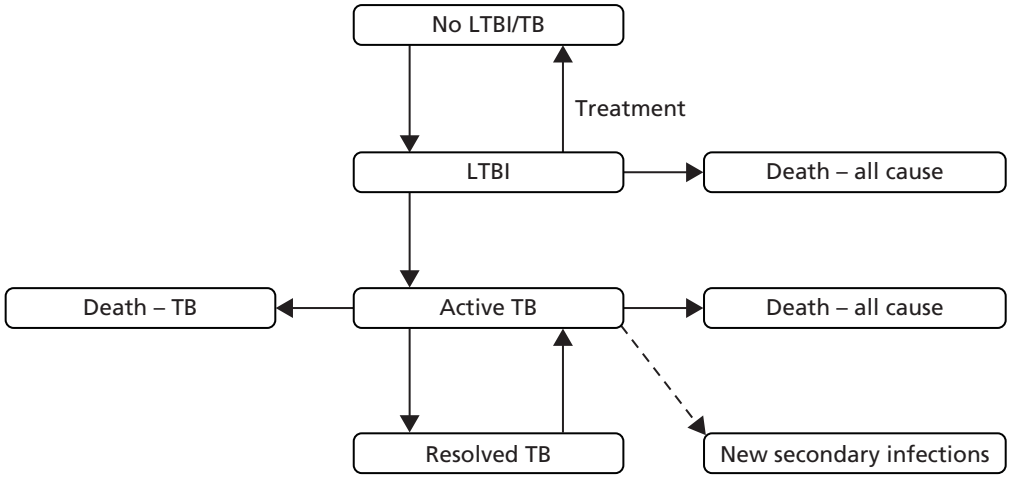


FIGURE 55 Dynamic transmission model.

As the model is run, any new cases of LTBI generated are included in the disease progression model from that time forward. Costs and QALYs are accrued by individuals according to the length of time that they spend in each state of the model. Unlike a traditional economic model, it is not possible to continue running the simulation until all individuals have died, as there is a continuous stream of new individuals being added as a result of new infections. Consequently, the simulation was run for 100 years, with discounting meaning that any results over a longer time horizon than this are unlikely to make a meaningful difference to the outcome. The parameters for the discrete event simulation are presented in *Table 27* for the child population and in *Tables 64* and *65* (see *Appendix 16*) for the immunocompromised and recently arrived populations respectively.

Model assumptions

A number of assumptions were required to develop a workable model structure to enable the analyses to be undertaken:

1. We assumed that our population is similar to the population in the clinical effectiveness studies, but excluding studies with populations with a high incidence of active TB.
2. People being assessed for initial active TB undergo chest radiography and, if positive, receive a sputum examination.
3. Children being assessed for initial active TB undergo chest radiography and, if positive, undergo a gastric lavage procedure.
4. The sputum examination is 100% accurate when diagnosing initial active TB.
5. Individuals with a second indeterminate result on the IGRA test are at the same risk of developing active TB as those with a false-negative result.
6. People who have been diagnosed with initial TB accept treatment.
7. People who do not adhere to LTBI treatment take medication for 1 month.
8. People who do not adhere to LTBI treatment are not at risk of developing isoniazid-induced hepatotoxicity.
9. People who do not adhere to active TB treatment take medication for 1 month.
10. Children are not at risk of developing hepatitis as a result of treatment for active TB or LTBI.
11. No health loss is experienced by people with LTBI who do not progress to active TB.

TABLE 27 Model input parameters required for the child population

Variable	Base-case value	Range for SA	PSA distribution	Source
Probabilities				
Prevalence of LTBI	0.0288	0.0206–0.0384	[a]	Derived from the current clinical effectiveness study
Sensitivity TST (≥ 5 mm)	0.7280	0.6059–0.7294	[a]	
Specificity TST (< 5 mm)	0.4903	0.4796–0.5008	[a]	
Sensitivity TST (≥ 10 mm)	0.5351	0.3821–0.6769	[a]	
Specificity TST (< 10 mm)	0.7481	0.3434–0.7618	[a]	
Sensitivity QFT-GIT	0.6884	0.5856–0.7820	[a]	
Specificity QFT-GIT	0.6103	0.6030–0.6176	[a]	
Sensitivity T-SPOT.*TB*	0.500	0.0245–0.9764	[a]	
Specificity T-SPOT.*TB*	0.7758	0.6738–0.8640	[a]	
Sensitivity of QFT-GIT conditional on positive TST (LTBI arm)	0.6775	0.4674–0.9233	[a]	
Specificity of QFT-GIT conditional on positive TST (no LTBI arm)	0.3213	0.3073–0.3353	[a]	
Sensitivity of QFT-GIT conditional on negative TST (LTBI arm)	0.7031	0.1122–0.9921	[a]	
Specificity of QFT-GIT conditional on negative TST (no LTBI arm)	0.9108	0.9013–0.9200	[a]	
Sensitivity of CXR for diagnosing active TB	0.7800	Not reported	Not varied	Kumar *et al.*[208]
Specificity of CXR for diagnosing active TB	0.5100	Not reported	Not varied	Kumar *et al.*[208]
Determinate QFT-GIT	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
Determinate T-SPOT.*TB*	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
TST read	0.9400	0.6–1.00	Beta(164,10.5)	Pareek *et al.*[77]
Initial active TB	0.00001	–	Not varied	Laskin *et al.*[200]
TB treatment adherence	1.0000	–	Not varied	Pareek *et al.*[77]
Accepting LTBI treatment	0.9400	0.50–1.00	Beta(141,9)	CG117[10]
Adherence to LTBI treatment	0.8000	0.50–0.90	Beta(41,10)	Kowada[198]
Isoniazid-induced hepatitis after TB treatment	0.0040	0.001–0.010	Beta(2.7,664)	Assumption
Death from isoniazid-induced hepatitis	0.00002	0.00001–0.0001	Beta(0.5,25125)	Pooran *et al.*[209]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	–	Log-normal (–1.065,0.842)	White and Jit[210]
Average number of secondary cases from one index case	0.2	0.1–0.3	Log-normal (–1.609,0.354)	Pareek *et al.*[6]

continued

TABLE 27 Model input parameters required for the child population (*continued*)

Variable	Base-case value	Range for SA	PSA distribution	Source
Average delay from infection to activation (secondary cases)	2.88	–	Log-normal (1.058,0.333)	Okuonghae[211]
Annualised reactivation rate from resolved TB	0.013	0.004–0.025	Beta(7,513)	Oxlade *et al.*[212]
Case fatality rate for active TB (0–4 years)	0.0477	–	Beta(628,12543)	Crofts *et al.*[213]
Case fatality rate for active TB (5–14 years)	0.0034	–	Beta(1,290)	Crofts *et al.*[213]
Case fatality rate for active TB (15–44 years)	0.0018	–	Beta(1,564)	Crofts *et al.*[213]
Case fatality rate for active TB (45–64 years)	0.0476	–	Beta(125,2500)	Crofts *et al.*[213]
Case fatality rate for active TB (65+ years)	0.1755	–	Beta(413,1940)	Crofts *et al.*[213]
Resource use and costs (£)				
TST	17.48	–	Not varied	Pooran *et al.*[209]
QFT-GIT	48.73	–	Not varied	Pooran *et al.*[209]
T-SPOT.*TB*	59.57	–	Not varied	Pooran *et al.*[209]
CXR	35.00	–	Not varied	NHS reference costs 2012/13[214]
Gastric lavage procedure	916.00	–	Not varied	NHS reference costs 2012/13[214]
Sputum examination	7.00	–	Not varied	NHS reference costs 2012/13[214]
Cost of adherence to active TB treatment	5461.12	–	Gamma (10.41,524.6)	Bothamley *et al.*[215]
Cost of non-adherence to active TB treatment	910.19	–	Not varied	Assumption
Cost of adherence to LTBI treatment	677.07	–	Uniform (511.69,842.45)	NHS drug tariff[216]
Cost of non-adherence to LTBI treatment	112.85	–	Uniform (85.24,140.41)	Assumption
Treatment of isoniazid-induced hepatitis	389.51	–	Gamma (7.13,55.64)	Pareek *et al.*[77]
Utility decrements				
Active TB (while on treatment)	0.15[b]	Not reported	Gamma (11.2,0.0134)	Derived from Kowada[197]
Treatment for LTBI	0.001	–	Uniform (0,0.002)	Derived from Kowada[197]
Other				
Discount rate per annum (costs and QALYs)	3.5%			

CXR, chest radiography; SA, sensitivity analysis.
a Calculated from posterior distributions generated by Markov chain Monte Carlo methods.
b QALY decrement for people being treated for active TB.

Data required for the model

The model was populated with clinical information from the current clinical effectiveness review and supplemented with information from secondary sources. Information required to parameterise the model included prevalence, sensitivity and specificity, adverse events, resource use, and costs and utilities. We acknowledge here that there is no gold standard test for a LTBI diagnosis. Hence, we have used clinical information from studies in this review that reported information on confirmed cases of active TB (the proportion of untreated individuals who go on to develop active TB at a later date).

All of the data available for the child population were based on studies in which there was previous contact with an index case. We therefore restricted our analysis to this population both because of the lack of data and because it was thought unlikely that a general screening programme for all children, irrespective of contact, would ever be introduced.

Prevalence

In this analysis, prevalence was defined as the proportion of people who have LTBI that will progress to active TB, assuming that they are not treated. We derived estimates for this LTBI prevalence criterion based on empirical data from the three cohorts separately. We used WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK) to conduct Bayesian Markov chain Monte Carlo (MCMC) simulation to derive the prevalence of LTBI in each cohort using the following formula:

$$\text{Probability of a positive result} = (\text{test sensitivity} \times \text{prevalence of LTBI}) + [(1 - \text{test specificity}) \times (1 - \text{prevalence of LTBI})]. \quad (1)$$

Rearranging the above equation for prevalence of LTBI:

$$\text{Prevalence of LTBI} = \text{probability of a positive result} - (1 - \text{test specificity})/[(\text{test sensitivity}) - (1 - \text{test specificity})]. \quad (2)$$

To avoid overestimating the prevalence of LTBI that progresses to active TB, we excluded studies with populations with a high incidence (≥ 40 cases per 100,000) of active TB. For the recently arrived population, we derived the prevalence from all studies on recent arrivals found in the clinical effectiveness review, which included people with LTBI who progressed to active TB.

Performance of screening tests (sensitivity and specificity)

The sensitivities and specificities of the various strategies were derived based on information obtained from longitudinal studies in people who received testing and developed active TB. Therefore, our calculated sensitivities and specificities represent the sensitivities and specificities of detecting people with LTBI that will progress to active TB, not the sensitivities and specificities of detecting LTBI in general. Bayesian MCMC was used to derive posterior distributions for test performance assuming weakly informative priors to derive the sensitivity and specificity of the diagnostic tests by population. Estimates for sensitivity and specificity were derived for TST (≥ 5 mm), TST (≥ 10 mm), QFT-GIT and T-SPOT.*TB*.

To synthesise the clinical evidence in WinBUGS, there were three main components of the model: the statistical model, priors and data. *Appendix 17* provides the WinBUGS code for the child population.

Statistical model

In our models we have used distributions to represent the unknown variables in the model. For the evidence synthesis for children, immunocompromised people and recent arrivals we used the binomial distribution to derive the sensitivities and specificities of TST, QFT-G, QFT-GIT and T-SPOT.*TB*. We chose the binomial distribution because we were interested in the probability p of the number of successes (people with positive/negative results that progressed to active TB) from n number of longitudinal studies.

First, we were interested in the probability p_{pos} of the number of positive test results from n longitudinal studies and, second, we were interested in the probability p_{apos} of the number of positive results that progressed to active TB from n number of positive test results. Likewise, we were interested in the probability p_{aneg} of a negative result progressing to active TB.

Logical expressions were built into the model to represent the relationship between the probability of a positive result, the prevalence of LTBI, test sensitivity and test specificity (see *Appendix 17*).

We initially explored both fixed- and random-effects models. However, for two of the populations (children and immunocompromised people) the random-effects models did not converge (most likely because in a number of studies either no individuals or only a very small number of individuals progressed to active TB). Hence, for consistency, we used the fixed-effects model for the three populations.

Priors

We stated in the WinBUGS model the prior distribution to be used. We chose the uniform distribution because all possible combinations of positive and negative test results have an equal a priori probability of occurring. In our WinBUGS code we added a logic expression to inform the model that the sensitivity of TST (≥ 5 mm) is greater than the sensitivity of TST (≥ 10 mm), which is greater than the sensitivity of TST (≥ 15 mm). Likewise, the specificity of TST (< 5 mm) is lower than the specificity of TST (< 10 mm), which is lower than the specificity of TST (< 15 mm). We included this logic expression because the TST is a single test with various cut-off thresholds for a positive result and, by definition, TST (≥ 5 mm) would be more sensitive and less specific than TST (≥ 10/15 mm).

Data

Observed data from longitudinal studies identified in the clinical effectiveness review were entered into the model in a list format. Data included the number of people being tested, the number of people with positive results, the number of people with positive results who were untreated and who developed active TB and the number of people with negative results who developed active TB. *Tables 67–72* (see *Appendix 18*) show the information obtained from the clinical effectiveness studies. The term 'not applicable' was used to represent any missing values. After compiling the model, we specified distributions from which to sample initial values for the model.

To obtain accurate posterior probabilities we used 60,000 simulations; a burn-in period of 30,000 simulations was used. Output from the remaining 30,000 simulations represented the posterior mean, along with its posterior standard deviation, posterior median and 95% credible intervals. Convergence of the model was assessed using a visual inspection of the sample trace plots (see *Appendix 17*).

The results of the meta-analysis are presented in *Table 28*. The sensitivity and specificity of TST (≥ 5 mm) for the diagnosis of LTBI in children were estimated at 72.80% and 49.03%, respectively. In the immunocompromised group we derived estimates of 32.42% and 74.22% for the sensitivity and specificity of TST (≥ 5 mm), respectively. In the recently arrived immigrants group we derived estimates of 93.56% and 50.11% for the sensitivity and specificity of TST (≥ 5 mm), respectively. In the models we have not stratified by BCG status and hence we used a cut-off of ≥ 5 mm to define a positive TST.

Similar methods were used to derive the sensitivity and specificity of TST (≥ 10 mm) in these populations. The sensitivity and specificity of QFT-GIT for the diagnosis of LTBI in children were estimated at 68.84% and 61.03%, respectively. In the immunocompromised group we derived estimates of 55.48% and 82.27% for sensitivity and specificity, respectively, and in the recently arrived group we derived estimates of 59.15% and 79.29% for sensitivity and specificity, respectively. In the models we used QFT-GIT values as the base-case values for the analysis because the majority of the studies compared QFT-GIT with the TST.

TABLE 28 Diagnostic accuracy of various tests for diagnosing LTBI that progresses to active TB

Test	Sensitivity (95% credible interval) (%)	Specificity (95% credible interval) (%)
Children		
TST (≥ 5 mm)	72.80 (60.59 to 72.94)	49.03 (47.96 to 50.08)
TST (≥ 10 mm)	53.51 (38.21 to 67.69)	74.81 (34.34 to 76.18)
QFT-GIT	68.84 (58.56 to 78.20)	61.03 (60.30 to 61.76)
T-SPOT.*TB*	50.00 (2.45 to 97.64)	77.58 (67.38 to 86.40)
Immunocompromised people		
TST (≥ 5 mm)	32.42 (11.19 to 58.48)	74.22 (72.88 to 75.57)
TST (≥ 10 mm)	16.82 (2.52 to 38.99)	83.97 (78.99 to 88.31)
QFT-GIT	55.48 (24.73 to 83.73)	82.27 (80.52 to 83.96)
T-SPOT.*TB*	66.65 (35.17 to 91.44)	68.46 (63.46 to 73.37)
Recent arrivals from countries with a high incidence of TB		
TST (≥ 5 mm)	93.56 (77.86 to 99.77)	50.11 (47.90 to 52.29)
QFT-GIT	59.15 (35.84 to 81.42)	79.29 (77.80 to 80.73)
T-SPOT.*TB*	70.01 (39.78 to 92.42)	39.92 (34.39 to 45.54)

Resource use and costs

The resource use and costs included were those directly incurred by the NHS. Costs for diagnostic tests, chest radiography, gastric lavage, sputum examination, treatment of LTBI/TB and isoniazid-induced hepatitis were all included in the analysis. Societal costs (indirect costs, loss of productivity or cost of death) were not included. The unit costs are presented in *Table 27*. The majority of the cost information used in the analyses was obtained from secondary sources. The costs for QFT-GIT (testing kit, consumables, processing and phlebotomy) and the TST (disposables, administration and reading) were obtained from Pooran *et al.*[209] Estimated costs for chest radiography, the gastric lavage procedure and sputum examination were obtained from NHS reference costs 2012/13.[214] Estimated costs for the treatment of LTBI were obtained from the NHS drug tariff 2015[216] and in consultation with a clinical expert (see *Appendix 16*). Costs for the treatment of TB were obtained from Bothamley *et al.*[215] (see *Appendix 16*). Management of LTBI included further blood tests (full blood count and liver function tests), doctor and nurse outpatient visits, and treatment with 300 mg of isoniazid daily for 6 months. Estimated costs for treating isoniazid-induced hepatitis were obtained from Pareek *et al.*[77] All costs were adjusted to 2012/13 prices using the Hospital and Community Health Services pay and price index[217] and discounted at a rate of 3.5% per annum, as recommended by NICE.[91]

Outcomes

Two different outcome measures were used in the analysis, QALYs and diagnostic error avoided. To calculate QALYs, age-related utility weights for the general population were obtained from the Health Survey for England[207] and the utility decrement of 0.15 for people who received treatment for active TB was derived from the published literature.[197] With respect to the diagnostic error avoided, we did not require any effectiveness information; the true-positive and true-negative cases were given the value of 1 and we reserved the value of 0 for an error (false positives and false negatives) in the diagnosis.

Analysis

The models were constructed to assess the cost-effectiveness of various strategies for the diagnosis of LTBI in three populations (children, immunocompromised people and recently arrived immigrants). The models estimated the mean costs and effects associated with each diagnostic strategy. For children, we began with a hypothetical cohort of children aged 5 years, whereas for the recently arrived and immunocompromised populations the starting distributions were representative of the UK recent arrival and UK general populations respectively.[218] The analysis was undertaken from a NHS perspective in a primary care setting and outcomes were reported as ICERs, expressed in terms of cost per diagnostic error avoided and cost per QALY gained. Because using QALYs allows trade-offs between the harms of false negatives and the harms of false positives, which are treated as equal in a cost per error avoided analysis, our primary conclusions are drawn from the ICERs expressed as cost per QALY gained. Univariate sensitivity analyses and PSAs were undertaken to assess the impact of the uncertainty of model input parameters.

Probabilistic sensitivity analysis

A PSA was undertaken to determine the joint uncertainty in the key model input parameters of prevalence, sensitivity and specificity, and expected QALYs. We undertook the PSA based on an outcome of cost per QALY only. In the PSA, each model parameter is assigned a distribution, reflecting the amount and pattern of its variation, and cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. In total, 2000 sets of parameters were simulated, each of which was run on a starting cohort of 100,000 individuals. Because of the considerable heterogeneity of the studies included in our meta-analysis, the results from the PSA, which explicitly includes the impact of that uncertainty, were considered to provide more plausible estimates of costs and outcomes than our single simulation based on mean parameter values. Therefore, costs and outcomes used to produce ICERs were calculated as the means of the costs and outcomes in each of the 2000 PSA simulations. The distributions used in the PSA are presented in *Table 27*. We also calculated the probability that each strategy is the most cost-effective at a willingness to pay of £20,000 per QALY.

Results of the cost-effectiveness modelling

The results of the cost-effectiveness modelling of various strategies for the diagnosis of LTBI in the three populations, based on the outcomes of cost per diagnostic error avoided and cost per QALY gained, are presented in the following sections.

Model 1: children

The results from the 250,000 patient simulations, based on the mean value of each parameter, are presented in *Tables 29* and *30*. *Table 29* shows the mean per patient cost (including both the initial cohort and subsequent secondary cases) for each of the six strategies as well as a breakdown of the total cost into diagnosis, LTBI treatment, active TB and hepatitis costs. *Table 30* shows the incidence rates of active TB in the initial cohort, the numbers of secondary infections, mean life-years and mean QALYs for each of the strategies.

The primary results, based on the 2000 Monte Carlo simulations, are presented in *Tables 31* (diagnostic accuracy) and *32* (QALYs). Considering diagnostic accuracy, the TST (≥ 10 mm)-alone strategy dominated the TST (≥ 5 mm) negative followed by QFT-GIT, TST (≥ 5 mm), QFT-GIT and TST (≥ 5 mm) positive followed by QFT-GIT strategies. The TST (≥ 10 mm) strategy had a mean cost of approximately £272 with a corresponding diagnostic error of 0.2449 compared with a mean cost of approximately £306 and a diagnostic error of 0.2322 for the T-SPOT.*TB*-alone strategy. The ICER for T-SPOT.*TB* compared with TST (≥ 10 mm) indicates the additional cost required to avoid one diagnostic error. The results for the simultaneous testing strategy and the TST (≥ 10 mm) followed by QFT-GIT are not presented because these results were dominated by the sequential testing strategy and TST (≥ 5 mm) followed by QFT-GIT, respectively.

TABLE 29 Mean costs and cost breakdown based on a single simulation using mean parameter values (2012/13 prices)

Strategy	Mean cost (£)	Mean diagnosis cost (£)	Mean LTBI cost (£)	Mean active TB cost (£)	Mean hepatitis cost (£)
TST (≥ 5 mm)	362.47	58.28	192.57	111.55	0.07
TST (≥ 10 mm)	298.42	48.02	119.89	130.42	0.09
QFT-GIT	357.38	83.61	160.22	113.48	0.07
T-SPOT.*TB*	328.97	80.90	113.21	134.76	0.10
TST (≥ 5 mm) positive then QFT-GIT	360.47	83.16	134.23	142.98	0.10
TST (≥ 5 mm) negative then QFT-GIT	389.24	114.98	196.17	78.03	0.06

TABLE 30 Mean QALYs and life-years gained (discounted), incidence of active TB and numbers of secondary infections

Strategy	Mean QALYs (discounted)	Mean life-years (discounted)	Number of active TB cases (initial cohort)	Number of active TB cases (secondary)
TST (≥ 5 mm)	23.095	27.036	4722	1133
TST (≥ 10 mm)	23.090	27.035	5521	1332
QFT-GIT	23.093	27.036	4804	1149
T-SPOT.*TB*	23.091	27.036	5620	1349
TST (≥ 5 mm) positive then QFT-GIT	23.091	27.036	5653	1367
TST (≥ 5 mm) negative then QFT-GIT	23.097	27.037	4150	996

TABLE 31 Results from the analysis based on cost per diagnostic error avoided (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	False positives	False negatives	Effectiveness (diagnostic error)[a]	Incremental diagnostic error	ICER (£)
TST (≥ 5 mm) negative followed by QFT-GIT	361.42	NA	0.5032	0.0040	0.5072	NA	Dominated
TST (≥ 5 mm)	339.26	–22.16	0.4654	0.0084	0.4740	–0.0332	Dominated
QFT-GIT	324.07	–15.19	0.3790	0.0091	0.3880	–0.0860	Dominated
TST (≥ 5 mm) positive followed by QFT-GIT	324.12	0.05	0.3040	0.0154	0.3194	–0.0686	Dominated
TST (≥ 10 mm)	271.66	–52.46	0.2307	0.0142	0.2449	–0.0745	NA
T-SPOT.*TB*	306.09	34.43	0.2172	0.0150	0.2322	–0.0127	2711.02

NA, not applicable.
a Results include only the initial test population simulated and not secondary cases as diagnostic accuracy is a relevant criterion only for those in the initial, tested population.

TABLE 32 Results from the analysis based on cost per QALY (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	Mean QALYs[a]	Incremental QALYs	ICER (£)	Probability most cost-effective[b]
TST (≥ 10 mm)	300.21	NA	23.088	NA	NA	0.032
T-SPOT.*TB*	332.46	32.25	23.091	0.003	Extendedly dominated	0.122
TST (≥ 5 mm) positive followed by QFT-GIT	366.45	33.99	23.092	0.001	Dominated	0.045
QFT-GIT	361.03	–5.42	23.095	0.002	8249 (vs. TST ≥ 10 mm)	0.210
TST (≥ 5 mm)	371.14	10.09	23.096	0.001	11,255 (vs. QFT-GIT)	0.269
TST (≥ 5 mm) negative followed by QFT-GIT	393.03	21.89	23.097	0.001	18,871	0.322

NA, not applicable.
a Results are for the initial simulated population and any secondary TB cases generated. These values are based on the mean of the PSA simulations to take into account parameter uncertainty.
b Based on a willingness to pay of £20,000 per QALY; results derived from PSA simulations.

The QALY outcomes of the Monte Carlo simulations showed that the TST (≥ 10 mm) diagnostic strategy alone was the least costly strategy and the TST (≥ 5 mm) negative followed by QFT-GIT was the most effective strategy for the diagnosis of LTBI in this population. The QFT-GIT-alone diagnostic strategy had a mean cost of £361 with corresponding QALYs of 23.095, whereas the TST (≥ 5 mm)-alone strategy had a mean cost of £371 and 23.096 QALYs. The ICER of £11,255 indicates the additional cost required to gain an extra QALY. In terms of the joint uncertainty in the expected mean costs and QALYs, the results show that TST (≥ 5 mm) negative followed by QFT-GIT is the most cost-effective strategy at a willingness to pay of £20,000 per QALY in 32% of the simulations followed by TST (≥ 5 mm) (27%) and QFT-GIT (21%).

The results of the univariate sensitivity analyses are presented in *Table 33*. In each scenario we present costs and QALYs for each of the three most effective strategies [QFT-GIT, TST (≥ 5 mm) and TST (≥ 5 mm) negative followed by QFT-GIT]. We also show which of the three strategies was the most cost-effective in each scenario, assuming a willingness to pay of £20,000 per QALY. In the majority of scenarios, as in the base case, the TST (≥ 5 mm) negative followed by QFT-GIT strategy was the most cost-effective strategy. However, decreases in prevalence, the sensitivity of the TST, the effectiveness of LTBI treatment or the disutility associated with active TB, as well as increases in the sensitivity of QFT-GIT, all led to QFT-GIT being the most cost-effective option. Conversely, decreases in the sensitivity of QFT-GIT led to the TST (≥ 5 mm) being selected as the most cost-effective option.

Finally, *Figure 56* presents CEACs for each of the same three strategies, showing the proportion of simulations in which each has the highest net benefit at different willingness-to-pay thresholds.

TABLE 33 Univariate sensitivity analyses

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (TST ≥ 5 mm) (£)	QALYs (TST ≥ 5 mm)	Cost (TST ≥ 5 mm negative then QFT-GIT) (£)	QALYs (TST ≥ 5 mm negative then QFT-GIT)	Most cost-effective strategy (WTP £20,000 per QALY)
Base case		361.03	23.095	371.17	23.096	393.03	23.097	TST (≥ 5 mm) negative then QFT-GIT
Prevalence	0.0206	329.42	23.104	336.83	23.104	363.87	23.105	QFT-GIT
	0.0384	397.36	23.087	406.60	23.091	422.86	23.093	TST (≥ 5 mm) negative then QFT-GIT
Sensitivity: IGRAs	QFT-GIT 0.5856, QFT-GIT following negative TST 0.1122	368.16	23.089	363.76	23.096	397.13	23.095	TST (≥ 5 mm)
	QFT-GIT 0.7820, QFT-GIT following negative TST 0.9921	369.69	23.100	357.12	23.096	388.54	32.099	QFT-GIT
Specificity: IGRAs	QFT-GIT 0.6030, QFT-GIT following negative TST 0.9013	368.46	23.095	363.76	23.096	393.43	23.097	TST (≥ 5 mm) negative then QFT-GIT
	QFT-GIT 0.6176, QFT-GIT following negative TST 0.9200	354.02	23.095	379.48	23.096	393.98	23.097	TST (≥ 5 mm) negative then QFT-GIT
Sensitivity: TST ≥ 5mm	0.6059	361.03	23.095	379.54	23.095	395.48	23.096	QFT-GIT
	0.7294	361.03	23.095	368.47	36.098	392.62	23.099	TST (≥ 5 mm) negative then QFT-GIT
Specificity: TST ≥ 5mm	0.4796	361.03	23.095	374.27	23.096	395.75	23.097	QFT-GIT
	0.5008	361.03	23.095	361.28	23.096	383.20	23.097	TST (≥ 5 mm) negative then QFT-GIT
Effectiveness of LTBI treatment (proportion of cases of active TB prevented)	0.392	384.94	23.092	395.23	23.093	420.81	23.093	QFT-GIT
	0.805	349.73	32.097	358.29	23.099	377.78	23.100	TST (≥ 5 mm) negative then QFT-GIT

continued

TABLE 33 Univariate sensitivity analyses (*continued*)

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (TST ≥ 5 mm) (£)	QALYs (TST ≥ 5 mm)	Cost (TST ≥ 5 mm negative then QFT-GIT) (£)	QALYs (TST ≥ 5 mm negative then QFT-GIT)	Most cost-effective strategy (WTP £20,000 per QALY)
Cost of LTBI treatment (£0)	511.69	321.89	23.095	324.13	23.096	345.11	23.097	TST (≥ 5 mm) negative then QFT-GIT
	842.45	400.17	23.095	418.21	23.096	440.95	23.097	TST (≥ 5 mm) negative then QFT-GIT
Cost of active TB treatment (£0)	2664.38	302.91	23.095	314.25	23.096	343.07	23.097	TST (≥ 5 mm)
	9244.44	419.15	23.095	428.09	23.096	432.99	23.097	TST (≥ 5 mm) negative then QFT-GIT
Utility decrement – active TB	0.75	361.03	23.090	371.17	23.091	393.03	23.092	TST (≥ 5 mm) negative then QFT-GIT
	0.95	361.03	23.099	371.17	23.099	393.03	23.100	QFT-GIT
Number of secondary TB cases per index case	0	324.07	23.105	339.26	23.105	361.42	23.106	QFT-GIT

WTP, willingness to pay.

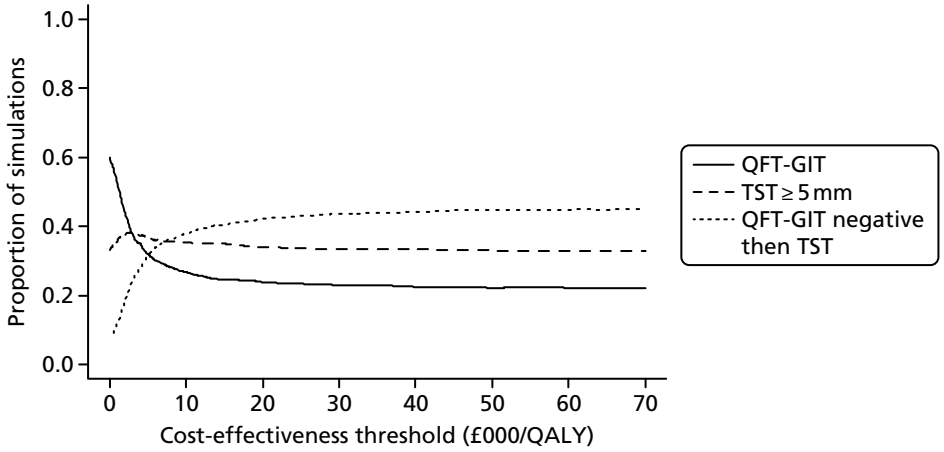


FIGURE 56 Cost-effectiveness acceptability curves for the child population, showing the proportion of simulations in which each strategy is the most cost-effective at different willingness-to-pay thresholds.

Model 2: immunocompromised people

The results from our 250,000 patient simulations, based on the mean value of each parameter, are presented in *Tables 34* and *35*. *Table 34* shows the mean per patient cost (including both the initial cohort and subsequent secondary cases) for each of the six strategies as well as a breakdown of the total cost into diagnosis, LTBI treatment, active TB and hepatitis costs. *Table 35* shows the incidence rates of active TB in the initial cohort, the numbers of secondary infections, mean life-years and mean QALYs for each of the strategies.

The primary results, based on the 2000 Monte Carlo simulations, are presented in *Tables 36* (diagnostic accuracy) and *37* (QALYs). Considering diagnostic accuracy, QFT-GIT dominated the QFT-GIT negative followed by TST (≥ 5 mm), T-SPOT.*TB* and TST (≥ 5 mm) strategies. The TST (≥ 10 mm) strategy had a mean cost of approximately £236 with a corresponding diagnostic error of 0.1641 whereas the QFT-GIT positive followed by TST (≥ 5 mm) strategy had a mean cost of approximately £253 and a diagnostic error of 0.1047. The ICER of £297 per diagnostic error avoided for the QFT-GIT positive followed by TST (≥ 5 mm) strategy compared with the TST (≥ 10 mm) strategy shows the additional cost required to avoid a diagnostic error. We have not presented the results for the simultaneous testing strategies because these strategies were dominated by the equivalent sequential strategies.

TABLE 34 Mean costs and cost breakdown based on a single simulation using mean parameter values (2012/13 prices)

Strategy	Mean cost (£)	Mean diagnosis cost (£)	Mean LTBI cost (£)	Mean active TB cost (£)	Mean hepatitis cost (£)
TST (≥ 5 mm)	272.79	28.59	127.86	116.00	0.35
TST (≥ 10 mm)	266.96	24.35	88.91	153.50	0.20
QFT-GIT	252.93	58.67	97.50	96.52	0.24
T-SPOT.*TB*	287.83	61.04	134.28	92.10	0.41
QFT-GIT positive then TST (≥ 5 mm)	286.49	67.91	63.95	154.51	0.12
QFT-GIT negative then TST (≥ 5 mm)	315.00	79.99	145.50	89.08	0.43

TABLE 35 Mean QALYs and life-years gained (discounted), incidence of active TB and numbers of secondary infections

Strategy	Mean QALYs (discounted)	Mean life-years (discounted)	Number of active TB cases (initial cohort)	Number of active TB cases (secondary)
TST (≥ 5 mm)	15.527	33.018	4826	1158
TST (≥ 10 mm)	15.526	33.017	5228	1251
QFT-GIT	15.532	33.018	4086	987
T-SPOT.*TB*	15.532	33.018	3772	902
QFT-GIT positive then TST (≥ 5 mm)	15.526	33.017	5271	1254
QFT-GIT negative then TST (≥ 5 mm)	15.534	33.018	3671	886

TABLE 36 Results from the analysis based on cost per diagnostic error avoided (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	False positives	False negatives	Effectiveness (diagnostic error)[a]	Incremental diagnostic error	ICER (£)
QFT-GIT negative then TST (≥ 5 mm)	287.77	NA	0.3100	0.0066	0.3166	NA	Dominated
T-SPOT.*TB*	252.01	–35.76	0.3080	0.0072	0.3152	–0.0018	Dominated
TST (≥ 5 mm)	249.33	–2.68	0.2371	0.0155	0.2526	–0.0626	Dominated
QFT-GIT	234.41	–14.92	0.1734	0.0084	0.1814	–0.0712	NA
TST (≥ 10 mm)	236.11	1.70	0.1474	0.0167	0.1641	–0.0173	98.27 (vs. QFT-GIT)
QFT-GIT positive then TST (≥ 5 mm)	253.77	17.66	0.0876	0.0171	0.1047	–0.0594	297.31 (vs. TST ≥ 10 mm)

NA, not applicable.
a Results include only the initial test population simulated and not secondary cases as diagnostic accuracy is a relevant criterion only for people in the initial, tested population.

TABLE 37 Results from the analysis based on cost per QALY (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	Mean QALYs[a]	Incremental QALYs	ICER (£)	Probability most cost-effective[b]
TST (≥ 10 mm)	269.42	NA	15.516	NA	Dominated	0.046
QFT-GIT positive then TST (≥ 5 mm)	289.31	19.89	15.516	0.000	Dominated	0.052
TST (≥ 5 mm)	276.01	–13.30	15.517	0.001	Dominated	0.067
QFT-GIT	258.61	–17.40	15.523	0.006	NA	0.187
T-SPOT.*TB*	280.90	12.29	15.524	0.001	10,402.63 (vs. QFT-GIT)	0.249
QFT-GIT negative then TST (≥ 5 mm)	318.26	37.36	15.526	0.002	18,746.01 (vs. T-SPOT.*TB*)	0.399

NA, not applicable.
a Results are for the initial simulated population and any secondary TB cases generated. These values are based on the mean of the PSA simulations to take into account parameter uncertainty.
b Based on a willingness to pay of £20,000 per QALY; results derived from PSA simulations.

The QALY outcomes of our Monte Carlo simulations showed that TST (≥ 10 mm), QFT-GIT positive followed by TST (≥ 5 mm) and TST (≥ 5 mm) were dominated by the QFT-GIT-alone strategy, which had a mean cost of £259 with corresponding QALYs of 15.523. The ICER reported for the T-SPOT.*TB*-alone strategy shows the additional cost required to gain 1 extra QALY compared with the QFT-GIT strategy. At a willingness to pay of £20,000 per QALY, the QFT-GIT negative followed by TST (≥ 5 mm) had the highest net benefit in the largest proportion of simulations (40%), followed by the T-SPOT.*TB* (25%) and QFT-GIT-alone (19%) strategies. All other strategies had the largest net benefit in < 7% of the simulations.

The results of the univariate sensitivity analyses are presented in *Table 38*. In each scenario we present costs and QALYs for each of the three strategies that were not strictly dominated by another strategy in the primary results. We also show which of the three strategies was the most cost-effective in each scenario, assuming a willingness to pay of £20,000 per QALY. In the scenarios in which the importance of test sensitivity was equal to or higher than that in the base case, the QFT-GIT negative followed by TST (≥ 5 mm) strategy was consistently the most cost-effective strategy at a willingness to pay of £20,000 per QALY. In the scenarios in which the relative importance of test specificity was increased (by decreasing LTBI prevalence, decreasing the effectiveness of LTBI treatment, increasing the cost of LTBI treatment, decreasing the cost of active TB or ignoring the impact of secondary TB cases), QFT-GIT often became the most cost-effective strategy.

Finally, *Figure 57* presents CEACs for each of the three non-dominated treatment strategies, showing the proportion of simulations in which each has the highest net benefit at different willingness-to-pay thresholds.

Model 3: recent arrivals from countries with a high incidence of tuberculosis

The results from our 250,000 patient simulations, based on the mean value of each parameter, are presented in *Tables 39* and *40*. *Table 39* shows the mean per patient cost (including both the initial cohort and subsequent secondary cases) for each of the six strategies as well as a breakdown of the total cost into diagnosis, LTBI treatment, active TB and hepatitis costs. *Table 40* shows the incidence rates of active TB in the initial cohort, the numbers of secondary infections, mean life-years and mean QALYs for each of the strategies.

The primary results, based on the 2000 Monte Carlo simulations, are presented in *Tables 41* (diagnostic accuracy) and *42* (QALYs). Considering diagnostic accuracy, the QFT-GIT-alone strategy was the least costly strategy and the TST (≥ 5 mm) positive followed by QFT-GIT strategy was the most effective. The QFT-GIT strategy had a mean cost of approximately £266 with a corresponding diagnostic error of 0.2113, whereas the TST (≥ 5 mm) positive followed by QFT-GIT strategy had a mean cost of approximately £277 and a diagnostic error of 0.1955. The ICER for the TST (≥ 5 mm) positive followed by QFT-GIT strategy compared with the QFT-GIT-alone strategy shows an additional cost of £692 to avoid one diagnostic error. We have not presented the results for the simultaneous testing strategies because these strategies were dominated by the equivalent sequential strategies.

The QALY outcomes of our Monte Carlo simulations showed that the QFT-GIT strategy dominated the TST (≥ 5 mm) positive followed by QFT-GIT and T-SPOT.*TB* strategies. TST (≥ 5 mm) had a mean cost of £299 with corresponding QALYs of 19.922. TST (≥ 5 mm) negative followed by QFT-GIT was more expensive than the TST (≥ 5 mm) strategy, with corresponding QALYs of 19.923 and an ICER of £58,720 compared with TST (≥ 5 mm). At a willingness to pay of £20,000 per QALY, the TST (≥ 5 mm) strategy had the highest net benefit in the largest proportion of simulation (47%) followed by the TST (≥ 5 mm) negative then QFT-GIT strategy (28%) and the QFT-GIT-alone strategy (18%). All other strategies had the largest net benefit in < 5% of the simulations.

TABLE 38 Univariate sensitivity analyses

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (T-SPOT.*TB*) (£)	QALYs (T-SPOT.*TB*)	Cost (QFT-GIT negative then TST ≥ 5 mm) (£)	QALYs (QFT-GIT negative then TST ≥ 5 mm)	Most cost-effective strategy (WTP £20,000 per QALY)
Base case		258.61	15.523	280.90	15.524	318.26	15.526	QFT-GIT negative then TST (≥ 5 mm)
Prevalence	0.0152	228.77	15.537	258.47	15.537	293.19	15.539	QFT-GIT
	0.0306	301.73	15.508	315.09	15.510	355.47	15.513	QFT-GIT negative then TST (≥ 5 mm)
Sensitivity: IGRAs	QFT-GIT 0.2473, T-SPOT.*TB* 0.3517	275.95	15.516	295.74	15.517	330.35	15.522	QFT-GIT negative then TST (≥ 5 mm)
	QFT-GIT 0.8373, T-SPOT.*TB* 0.9144	243.54	15.529	271.36	15.530	308.81	15.531	QFT-GIT
Specificity: IGRAs	QFT-GIT 0.8052, T-SPOT.*TB* 0.6346	268.55	15.523	305.26	15.524	324.82	15.526	QFT-GIT negative then TST (≥ 5 mm)
	QFT-GIT 0.8396, T-SPOT.*TB* 0.7331	247.43	15.523	268.69	15.524	312.34	15.526	QFT-GIT
Sensitivity: TST ≥ 5 mm	TST following negative IGRA 0.0121	258.61	15.523	280.90	15.524	321.89	15.526	QFT-GIT negative then TST (≥ 5 mm)
	TST following negative IGRA 0.7989	258.61	15.523	280.90	15.524	314.87	15.526	QFT-GIT negative then TST (≥ 5 mm)
Specificity: TST ≥ 5 mm	TST following negative IGRA 0.3909	258.61	15.523	280.90	15.524	342.16	15.526	T-SPOT.*TB*
	TST following negative IGRA 0.4993	258.61	15.523	280.90	15.524	291.20	15.526	QFT-GIT negative then TST (≥ 5 mm)
Effectiveness of LTBI treatment (proportion of cases of active TB prevented)	0.392	272.49	15.518	294.85	15.519	334.58	15.521	QFT-GIT
	0.805	249.77	15.528	273.12	15.530	309.56	15.534	QFT-GIT negative then TST (≥ 5 mm)
Cost of LTBI treatment (£)	511.69	235.90	15.523	249.62	15.524	284.37	15.526	QFT-GIT negative then TST (≥ 5 mm)
	842.45	281.32	15.523	312.18	15.524	352.15	15.526	QFT-GIT

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (T-SPOT.*TB*) (£)	QALYs (T-SPOT.*TB*)	Cost (QFT-GIT negative then TST ≥ 5 mm) (£)	QALYs (QFT-GIT negative then TST ≥ 5 mm)	Most cost-effective strategy (WTP £20,000 per QALY)
Cost of active TB treatment (£)	2664.38	207.18	15.523	233.73	15.524	272.64	15.526	QFT-GIT
	9244.44	323.48	15.523	344.70	15.524	379.97	15.526	QFT-GIT negative then TST (≥ 5 mm)
Utility decrement – active TB	0.75	258.61	15.520	280.90	15.522	318.26	15.524	QFT-GIT negative then TST (≥ 5 mm)
	0.95	258.61	15.526	280.90	15.526	318.26	15.528	QFT-GIT negative then TST (≥ 5 mm)
Number of secondary TB cases per index case	0	234.41	15.536	252.01	15.536	287.77	15.38	QFT-GIT

WTP, willingness to pay.

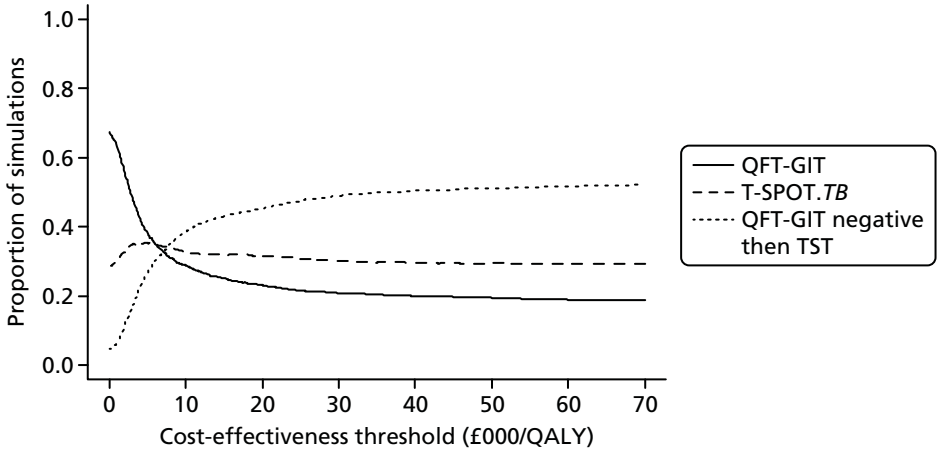


FIGURE 57 Cost-effectiveness acceptability curves for the immunocompromised population, showing the proportion of simulations in which each strategy is the most cost-effective at different willingness-to-pay thresholds.

TABLE 39 Mean costs and cost breakdown based on a single simulation using mean parameter values (2012/13 prices)

Strategy	Mean cost (£)	Mean diagnosis cost (£)	Mean LTBI cost (£)	Mean active TB cost (£)	Mean hepatitis cost (£)
TST (≥ 5 mm)	310.00	34.19	203.04	72.09	0.68
QFT-GIT	295.11	57.72	114.42	122.50	0.47
T-SPOT.*TB*	432.95	77.45	259.89	94.74	0.86
TST (≥ 5 mm) positive then QFT-GIT	310.83	78.88	101.04	130.07	0.84
TST (≥ 5 mm) negative then QFT-GIT	363.64	74.15	219.87	68.91	0.72

TABLE 40 Mean QALYs and life-years gained (discounted), incidence of active TB and number of secondary infections

Strategy	Mean QALYs (discounted)	Mean life-years (discounted)	Number of active TB cases (initial cohort)	Number of active TB cases (secondary)
TST (≥ 5 mm)	19.929	24.160	2883	705
QFT-GIT	19.924	24.158	4329	1041
T-SPOT.*TB*	19.922	24.158	4289	998
TST (≥ 5 mm) positive then QFT-GIT	19.915	24.157	4522	1091
TST (≥ 5 mm) negative then QFT-GIT	19.931	24.160	2756	660

TABLE 41 Results from the analysis based on cost per diagnostic error avoided (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	False positives	False negatives	Effectiveness (diagnostic error)[a]	Incremental diagnostic error	ICER (£)
T-SPOT.*TB*	374.60	NA	0.5669	0.0071	0.5740	NA	Dominated
TST (≥ 5 mm) negative then QFT-GIT	325.81	–48.79	0.4680	0.0016	0.4696	–0.1044	Dominated
TST (≥ 5 mm)	277.46	–48.35	0.4566	0.0025	0.4391	–0.0305	Dominated
QFT-GIT	265.87	–11.59	0.2015	0.0098	0.2113	–0.2278	NA
TST (≥ 5 mm) positive then QFT-GIT	276.80	10.93	0.1846	0.0109	0.1955	–0.0158	691.77

NA, not applicable.
a Results include only the initial test population simulated and not secondary cases as diagnostic accuracy is a relevant criterion only for people in the initial, tested population.

TABLE 42 Results from the analysis based on cost per QALY (2012/13 prices)

Strategy	Mean cost[a] (£)	Incremental cost (£)	Mean QALYs[a]	Incremental QALYs	ICER (£)	Probability most cost-effective[b]
TST (≥ 5 mm) positive then QFT-GIT	300.10	NA	19.909	NA	Dominated	0.032
T-SPOT.*TB*	400.12	100.02	19.915	0.006	Dominated	0.042
QFT-GIT	291.13	–108.99	19.917	0.002	NA	0.177
TST (≥ 5 mm)	298.75	7.62	19.922	0.005	1524 (vs. QFT-GIT)	0.469
TST (≥ 5 mm) negative then QFT-GIT	353.47	54.72	19.923	0.001	58,720 (vs. TST ≥ 5 mm)	0.280

NA, not applicable.
a Results are for the initial simulated population and any secondary TB cases generated. These values are based on the mean of the PSA simulations to take into account parameter uncertainty.
b Based on a willingness to pay of £20,000 per QALY; results derived from PSA simulations.

The results of the univariate sensitivity analyses are presented in *Table 43*. In each scenario we present costs and QALYs for the three strategies that were not strictly dominated by another strategy in the primary results. We also show which of the three strategies was the most cost-effective in each scenario, assuming a willingness to pay of £20,000 per QALY. In the majority of scenarios, as in our base case, the TST (≥ 5 mm)-alone strategy was the most cost-effective strategy. However, a decrease in the prevalence of LTBI, increase in the sensitivity of QFT-GIT and decrease in the sensitivity of the TST all led to strategies involving QFT-GIT becoming the most cost-effective.

Finally, *Figure 58* presents CEACs for each of the three non-dominated treatment strategies, showing the proportion of simulations in which each has the highest net benefit at different willingness-to-pay thresholds.

TABLE 43 Univariate sensitivity analyses

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (TST ≥ 5 mm) (£)	QALYs (TST ≥ 5 mm)	Cost (TST ≥ 5 mm negative then QFT-GIT) (£)	QALYs (TST ≥ 5 mm negative then QFT-GIT)	Most cost-effective strategy (WTP £20,000 per QALY)
Base case		291.13	19.917	298.75	19.922	353.47	19.923	TST (≥ 5 mm)
Prevalence	0.0150	250.19	19.930	271.80	19.931	326.65	19.932	QFT-GIT
	0.0345	342.56	19.904	331.53	19.910	389.21	19.912	TST (≥ 5 mm)
Sensitivity: IGRAs	QFT-GIT 0.3584, QFT-GIT following negative TST 0.0225	309.31	19.913	298.75	19.922	354.82	19.922	TST (≥ 5 mm)
	QFT-GIT 0.8172, QFT-GIT following negative TST 0.9724	271.22	19.921	298.75	19.922	353.18	19.923	QFT-GIT
Specificity: IGRAs	QFT-GIT 0.7780, QFT-GIT following negative TST 0.9555	299.23	19.917	298.75	19.922	355.66	19.923	TST (≥ 5 mm)
	QFT-GIT 0.8073, QFT-GIT following negative TST 0.9893	283.62	19.918	298.75	19.922	349.92	19.923	TST (≥ 5 mm)
Sensitivity: TST ≥ 5 mm	0.7786	291.13	19.917	303.86	19.920	354.48	19.922	TST (≥ 5 mm) negative then QFT-GIT
	0.9977	291.13	19.917	297.08	19.924	352.08	19.924	TST (≥ 5 mm)
Specificity: TST ≥ 5 mm	0.4790	291.13	19.917	311.44	19.922	363.91	19.923	TST (≥ 5 mm)
	0.5229	291.13	19.917	288.84	19.922	344.32	19.923	TST (≥ 5 mm)
Effectiveness of LTBI treatment	0.392	302.35	19.915	311.22	19.918	369.71	19.919	TST (≥ 5 mm)
	0.805	283.73	19.919	279.48	19.925	334.96	19.926	TST (≥ 5 mm)
Cost of LTBI treatment (£)	511.69	264.48	19.917	251.46	19.922	302.26	19.923	TST (≥ 5 mm)
	842.45	317.78	19.917	346.04	19.922	404.68	19.923	TST (≥ 5 mm)

Parameter varied	Value	Cost (QFT-GIT) (£)	QALYs (QFT-GIT)	Cost (TST ≥ 5 mm) (£)	QALYs (TST ≥ 5 mm)	Cost (TST ≥ 5 mm negative then QFT-GIT) (£)	QALYs (TST ≥ 5 mm negative then QFT-GIT)	Most cost-effective strategy (WTP £20,000 per QALY)
Cost of active TB treatment (£)	2664.38	228.40	19.917	261.83	19.922	318.18	19.923	TST (≥ 5 mm)
	9244.44	375.99	19.917	348.69	19.922	401.21	19.923	TST (≥ 5 mm)
Utility decrement – active TB	0.75	291.13	19.911	298.75	19.917	353.47	19.918	TST (≥ 5 mm)
	0.95	291.13	19.923	298.75	19.926	353.47	19.927	TST (≥ 5 mm)
Number of secondary TB cases per index case	0	265.87	19.928	277.46	19.931	325.81	19.932	TST (≥ 5 mm)

WTP, willingness to pay.

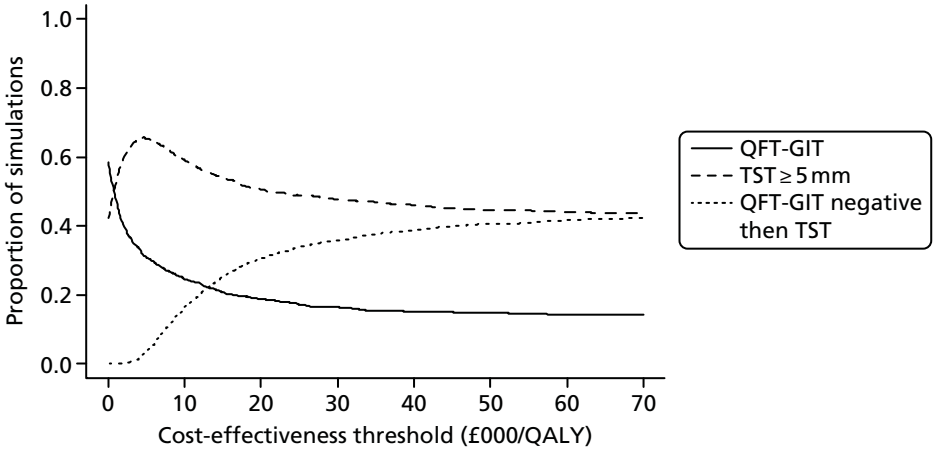


FIGURE 58 Cost-effectiveness acceptability curves for the recently arrived population, showing the proportion of simulations in which each strategy is the most cost-effective at different willingness-to-pay thresholds.

Exploring sensitivity and specificity

Clearly, key drivers of differences between the models are sensitivity and specificity. To illustrate the impact that these parameters have on the outputs of our models, *Figure 59* shows graphs of sensitivity and specificity plotted against costs, QALYs and net monetary benefit (at £20,000 per QALY) for each of the six strategies that were simulated in the child population.

These graphs show, at first sight, the counterintuitive result that increased specificity is associated with lower QALYs and lower net monetary benefit whereas higher sensitivity is associated with higher costs. This is because of the high levels of correlation between sensitivity and specificity (specifically, higher sensitivity is associated with lower specificity) in the strategies that were simulated. Therefore, both sets of graphs are in fact showing the same result, namely that, as sensitivity increases and specificity decreases, this leads to higher QALYs, higher costs and, on balance, a higher net monetary benefit.

To try and remove the effect of this sensitivity/specificity correlation, instead of using the different strategies we used the outputs of the PSA simulations for one of these strategies. This gave us 2000 realisations of sensitivity, specificity, costs and QALYs and, as each of these sensitivity/specificity pairs was a sample from the posterior distribution of our MCMC, we would expect lower correlations between sensitivity and specificity than when comparing between different strategies. We then ran a linear regression model for costs and QALYs, with sensitivity and specificity as the predictor variables. The results of this regression model are shown in *Table 44*.

In this model, in which we jointly estimated the impact of both sensitivity and specificity on outcomes, the results are much more intuitive. Increases in both sensitivity and specificity lead to increases in QALYs and decreases in costs, with increases in sensitivity providing the largest QALY gains and increases in specificity the largest cost reductions. It should be noted that the output data from the PSA simulation very likely do not conform to the necessary assumptions (linearity, additivity, etc.) for linear regression and the models contain a lot of noise because of the impact of varying other parameters and so the actual values of these parameters should be treated with extreme caution. Nevertheless, they do give an indicative picture of what the key drivers of difference between the models are.

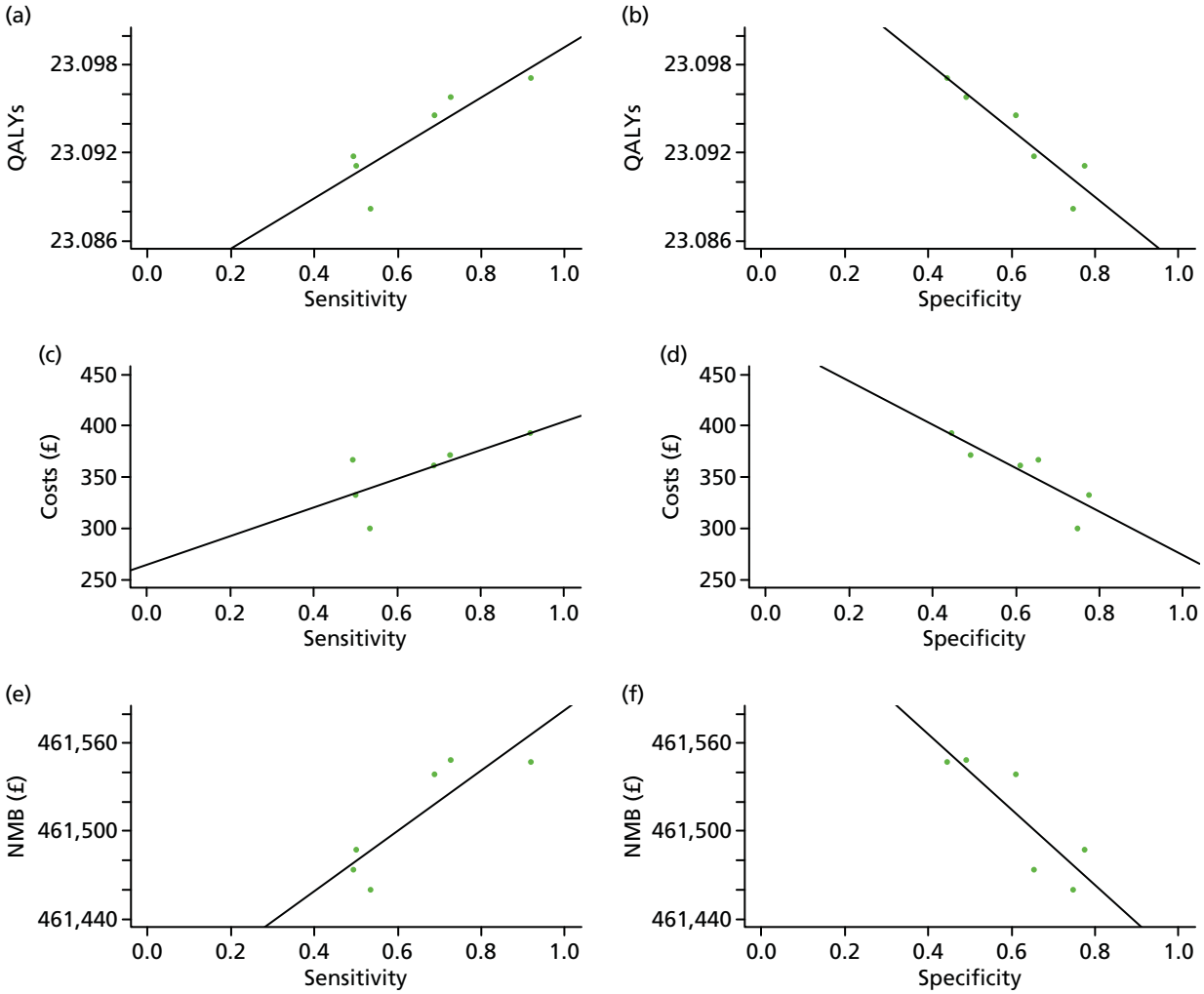


FIGURE 59 Sensitivity and specificity plotted against costs, QALYs and net monetary benefit (NMB) (at £20,000 per QALY) for each of the six strategies in the child population. (a) Sensitivity against QALYs; (b) specificity against QALYs; (c) sensitivity against costs; (d) specificity against costs; (e) sensitivity against NMB; and (f) specificity against NMB. NMB, net monetary benefit.

TABLE 44 Results of the linear regression model

Parameter	Costs (£)	QALYs
Intercept	578.72	23.080
Sensitivity	–0.99	0.00015
Specificity	–2.60	0.00001

Discussion and conclusion

The results based on the outcome of cost per diagnostic error avoided showed that, in the child population, the TST (≥ 10 mm) strategy dominated all strategies except for the T-SPOT.*TB* strategy alone. T-SPOT.*TB* compared with TST (≥ 10 mm) was more effective but more expensive, with an ICER of approximately £2711 per diagnostic error avoided. A breakdown of effectiveness showed that the T-SPOT.*TB* strategy resulted in fewer false-positive cases (0.2172) than the TST (≥ 10 mm) strategy (0.2307), but a larger number of false-negative cases (0.0150 vs. 0.0142). If the T-SPOT.*TB* strategy were to be used in this population to diagnose LTBI that progresses to active TB, this would lead to a slight reduction in the number of children being overtreated for LTBI. In the immunocompromised population, QFT-GIT dominated QFT-GIT negative followed by TST, T-SPOT.*TB* and TST (≥ 5 mm) in terms of diagnostic errors avoided. The results showed that QFT-GIT resulted in fewer false positives and fewer false negatives than the other strategies. The use of TST (≥ 10 mm) in this population was more effective, with overall diagnostic errors avoided of 0.1641. A breakdown of this effectiveness showed that TST (≥ 10 mm) resulted in fewer false-positive but more false-negative results. Likewise, the combination strategy QFT-GIT positive followed by TST (≥ 5 mm) produced fewer false-positive results but more false-negative results. In the population of recent arrivals from countries with a high incidence of TB, QFT-GIT dominated the T-SPOT.*TB*, TST (≥ 5 mm) negative followed by QFT-GIT and TST (≥ 5 mm) strategies. TST (≥ 5 mm) positive followed by QFT-GIT had an ICER of £692 per diagnostic error avoided compared with QFT-GIT, with more false negatives and fewer false positives.

The cost per QALY outcomes are summarised in terms of the probability of each strategy being the most cost-effective (at a given threshold). We used a willingness-to-pay threshold of £20,000 per QALY, a standard threshold that is used in the UK. The results in the child population showed that TST (≥ 5 mm) is marginally more effective than the QFT-GIT-alone strategy, with an ICER of approximately £11,255 per QALY, and has a 27% probability of being the most cost-effective strategy at a willingness to pay of £20,000 per QALY. The most effective strategy was TST (≥ 5 mm) negative followed by QFT-GIT, which was the most cost-effective strategy in 32% of the simulations. The results in the immunocompromised population showed that QFT-GIT negative followed by TST (≥ 5 mm) was the most effective strategy, with an ICER of approximately £18,746 compared with T-SPOT.*TB*, and is the most cost-effective strategy in 40% of the simulations. In the population of recent arrivals, TST (≥ 5 mm) dominated the TST (≥ 5 mm) positive followed by QFT-GIT, T-SPOT.*TB* and QFT-GIT strategies, and had a probability of 47% of being cost-effective at a willingness to pay of £20,000 per QALY.

Based on the current clinical evidence on people with LTBI without treatment that progressed to active TB as well as expert opinion used to develop the model structures, the results demonstrate that TST (≥ 5 mm) was slightly more cost-effective than QFT-GIT in the child population. In the immunocompromised population the results based on cost per QALY showed that QFT-GIT negative followed by TST (≥ 5 mm) was the most cost-effective strategy. In the recent arrivals population the results based on cost per QALY showed that TST (≥ 5 mm) dominated the TST (≥ 5 mm) positive followed by QFT-GIT, T-SPOT.*TB* and QFT-GIT-alone strategies.

Chapter 7 Discussion

The purpose of the current review was to compare the clinical effectiveness and cost-effectiveness of new screening tests for LTBI (IGRAs vs. TST) in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of TB. We aimed to address the following questions:

1. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in children?
2. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in people who are immunocompromised or at risk of immunosuppression?
3. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying LTBI in people who are recent arrivals from countries with a high incidence of TB?

In this chapter, the principal findings of the clinical effectiveness and cost-effectiveness reviews and economic evaluation are interpreted alongside an assessment of the strengths and limitations of the review and the individual studies. Areas of uncertainty, implications for further research and implications for practice are highlighted.

Main findings

Clinical effectiveness review

There is no gold standard for the accurate diagnosis of LTBI. The existing screening tests for LTBI (IGRAs and TST) provide indirect assessment of the presence of LTBI by relying on a host's immunological response to TB antigens. The evaluation of the comparative effectiveness of IGRAs and TST in accurately identifying LTBI has been a challenging task because of the absence of a gold standard for direct estimation of the screening tests' accuracy indices (i.e. sensitivity and specificity) and the tests' own limitations.[11–13,16,27,56,57] To address this issue, many studies have tried to estimate and compare the measures of association between the test results (i.e. TST and/or IGRAs) and constructs of validity for LTBI (e.g. duration/proximity of exposure to a person with active TB, risk of development of active TB).[11,18,58,60]

This review identified and appraised a large amount of evidence (53 new studies since CG117[10] and 37 studies from CG117[10]) comparing IGRAs with TST for identifying LTBI in children, immunocompromised people and recently arrived immigrants from countries with a high TB incidence. Overall, the limited evidence from prospective studies in children showed no significant difference in the performance of QFT-GIT and TST 5 mm in predicting LTBI. However, QFT-GIT was significantly better than TST 10 mm in predicting LTBI. In children, IGRAs (QFT-GIT/G) demonstrated similar sensitivity to and slightly better specificity than those of TST 5 mm. Moreover, IGRAs tended to have a greater sensitivity but lower specificity than those of TST 10 mm/15 mm. As the predictive value of a test is a function of its sensitivity, the greater predictive ability of IGRAs than of TST 10 mm in predicting LTBI (as a proxy for developing active TB) could be explained by the better sensitivity of the former. Based on the exposure studies in children, IGRAs outperformed the TST in identifying LTBI in the setting of low TB burden but not in the setting of high TB burden. This finding is consistent with a growing body of evidence showing reduced sensitivity and specificity of IGRAs in high compared with low TB burden areas, the former represented mostly by developing countries where BCG vaccination is given at birth.[44,59,219–221] This heterogeneity in test performance could be explained by a higher frequency of exposure to MTB, different transmission dynamics, malnutrition, comorbidity, people coinfected with HIV, exposure to NTMs and helminthic infection in high TB burden settings.[105,220,221] Moreover, in high TB burden settings (mostly developing countries), the specificity of the TST is not greatly reduced because BCG vaccination is given mostly at birth without repeating it. In contrast, in some low TB burden settings (e.g. developed countries), BCG vaccination with booster shots may be offered after infancy, which is known to compromise TST specificity.[220]

Evidence comparing IGRAs with TST in predicting the incidence of active TB in immunocompromised people was insufficient and inconclusive. The forest plot of 21 exposure-based studies showed a large variation in the performance of IGRAs compared with the TST across different clinical subgroups. In general, QFT-GIT and T-SPOT.*TB* performed better than TST 5 mm/10 mm in identifying LTBI among people undergoing haemodialysis and in those with hepatitis C. In contrast, in patients with HIV/AIDS, QFT-GIT was significantly worse than TST 10 mm at identifying LTBI. One explanation of this finding could be the reduced sensitivity of IGRA to detect LTBI because of CD4+ T-lymphocyte depletion in those with HIV-induced immunosuppression, leading to a high proportion of indeterminate IGRA results. Interestingly, it is not clear whether or not QFT-GIT and TST are differentially affected by CD4 depletion.[40,220,222,223] Evidence on the comparative performance of IGRAs and TST in people with lupus erythematosus, those with immune-mediated inflammatory diseases before antiTNF-α therapy, solid organ transplantation candidates and kidney transplant recipients was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates. The agreement between IGRAs and the TST in immunocompromised people was low.

There was no significant difference in the performance of the IGRAs and TST in identifying LTBI among recently arrived people from countries with a high TB burden. QFT-GIT demonstrated greater specificity but lower sensitivity than the TST. Similarly, there was no evidence indicating a differential effect of BCG vaccination on IGRA (QFT, T-SPOT.*TB*) and TST positivity. Limited evidence indicated that both concordance and kappa were greater among BCG-unvaccinated people (or among people who have/have not been vaccinated) than among BCG-vaccinated people.

In general, the degree of agreement (measured by the kappa statistic) between the IGRAs and the TST across the three subgroups of children, immunocompromised people and those recently arrived from high TB burden areas was low. Several studies indicated better between-test (IGRAs vs. TST) concordance and agreement in unvaccinated than in BCG-vaccinated people. The higher rates of discordance between the IGRAs and the TST in BCG-vaccinated populations could be explained by the TST having reduced specificity (i.e. a higher false-positive rate) because of its cross-reactivity with antigens that are common to both MTB and the BCG vaccine.[219] Overall, there was no clear and convincing evidence indicating a differential effect of BCG vaccination on IGRA and TST positivity. The evidence, if reported, was conflicting and inconclusive, with most studies indicating non-significant differences in the odds of test positivity (with great uncertainties) for the IGRAs and TST between BCG-vaccinated and BCG non-vaccinated people.

Cost-effectiveness review

Ten studies[10,77,196–203] reported evidence on decision-analytical models to determine the cost-effectiveness of IGRAs compared with TST for the diagnosis of LTBI in the three populations of interest. The majority of these models were in the immunocompromised population. These results highlight that there is a paucity of evidence available for children and recently arrived populations. The majority of the models used decision tree structures with Markov nodes to simulate a cohort of people being tested for LTBI.

We appraised these models against frameworks for best practice for reporting model-based economic evaluations. All performed well in terms of defining the decision problem, including the study perspective, outlining the choice of comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. These models all add insight to the existing literature but were subject to some limitations. First, the majority of the studies stated the location of the study but not the setting of the analysis and this may limit the generalisability of the results. Second, the majority of the studies used QALYs as the outcome measure but did not elaborate on the descriptive tool used to value health states. Third, the perspective of the analysis was stated in all studies but the resource use and costs reported did not reflect the viewpoint of the analysis in some studies. Finally, all models explored uncertainty around key model input parameters but no attempt was made to explore methodological, generalisability or structural uncertainty. Other concerns relate to the derivation of prevalence, test accuracy and transition probabilities; most studies did not elaborate on these statistical/pre-model analyses.

Economic evaluation

In the child population, the TST negative followed by QFT-GIT strategy had the lowest proportion of false-negative results and the T-SPOT.*TB* strategy had the lowest proportions of false-positive results and overall errors. TST (≥ 10 mm) was the strategy with the lowest overall cost whereas TST (≥ 5 mm) negative followed by QFT-GIT produced the highest QALYs, was the most cost-effective at a willingness to pay of £20,000 per QALY and had the highest probability of being the most cost-effective strategy.

In the immunocompromised population, the QFT-GIT negative followed by TST (≥ 5 mm) strategy had the lowest proportion of false-negative results and the QFT-GIT positive followed by TST (≥ 5 mm) strategy had the lowest proportions of false-positive results and overall errors. QFT-GIT was the strategy with the lowest overall cost whereas the QFT-GIT negative followed by TST (≥ 5 mm) strategy produced the highest QALYs, was the most cost-effective at a willingness to pay of £20,000 per QALY and had the highest probability of being the most cost-effective strategy.

In the recently arrived population, the TST (≥ 5 mm) negative followed by QFT-GIT strategy had the lowest proportion of false-negative results and the TST (≥ 5 mm) positive followed by QFT-GIT strategy had the lowest proportions of false-positive results and overall errors. QFT-GIT was the strategy with the lowest overall cost, the TST (≥ 5 mm) negative followed by QFT-GIT strategy produced the highest QALYs and the TST (≥ 5 mm) strategy was the most cost-effective at a willingness to pay of £20,000 per QALY and had the highest probability of being the most cost-effective strategy.

Current findings compared with those from other systematic reviews

In general, our findings agreed with those from three other systematic reviews[59,91,221] in showing that IGRAs have improved specificity and a greater ability to predict LTBI relative to the TST in the setting of low (but not high) TB burden in children. All three previous reviews also highlight the lack or insufficient amount of evidence and heterogeneity in estimates, methodology and clinical characteristics across the studies that were reviewed.

The findings of this review could not be directly compared with those of several previously published systematic reviews for the following reasons: (1) our review results were stratified by children, immunocompromised people and those recently arrived from high TB burden countries, whereas other reviews[18,44,57,58,219,224] did not analyse these three populations; (2) unlike other studies[40,219,222] we did not use prevalent culture-positive active TB as a proxy for LTBI; (3) one review[224] included in-house IGRAs, which we did not; (4) one review[222] compared QFT-GIT with T-SPOT.*TB* only; and (5) two reviews[225,226] reported no relevant outcomes.

Current results compared with those from other cost-effectiveness studies

When comparing our model with others from the literature, it is important to note that our definitions of sensitivity and specificity are not the same as those used in most studies. In the absence of a gold standard we have used LTBI that progresses to active TB, rather than any LTBI, as in previously published papers, and hence the numbers derived for sensitivity and specificity are not comparable. In addition, most of the previously published papers did not include sequential testing as a possible strategy and so we have to restrict our comparisons to the results for the TST- and IGRA-alone strategies only.

In the immunocompromised population, previous studies[196,198,200,202] indicated that, when using a single test, IGRAs were preferable to TST, a conclusion that our results concur with. In the child population our results agree with those of Mandalakas *et al.*[203] in that the TST (≥ 5 mm) negative followed by IGRA strategy was the most effective; however, they disagree with those of Kowada[197] who found QFT-GIT to be

more cost-effective than the TST, the opposite of our conclusion. Finally, in the recently arrived population, Pareek *et al.*[77] found QFT-GIT to be more cost-effective than the TST whereas we found the reverse, with the TST (≥ 5 mm) strategy being the most cost-effective strategy.

The reasons for these differences, other than those that always apply (different populations modelled, different parameter values used, etc.), can be found in the different underlying structures of the models. First, Kowada[197] considered only primary cases of TB and not secondary infections. From our univariate sensitivity analyses in the child population we see that, when we set our secondary infection rate to zero, we also find the QFT-GIT strategy to be the most cost-effective strategy. When comparing IGRAs with the TST in the recently arrived population, Pareek *et al.*[77] used indurations of 10 mm and 6/15 mm (stratified by BCG status). Our results for the recently arrived population are based on an induration of 5 mm, a value not modelled in the Pareek *et al.*[77] study, and therefore differences in conclusions may be explained by these different thresholds used.

It is important to note that our model is designed to evaluate only which is the most cost-effective diganostic strategy, conditional on a decision having been made to test. It does not say anything about whether or not testing itself, compared with no testing, is cost-effective and should be undertaken in these populations. Research addressing this question (testing/no testing) has recently been published.[210] This model and our model were built to address fundamentally different questions, in different populations, and hence the results obtained from them cannot be directly compared. In particular, the inclusion criteria for studies in the two reviews were entirely different (our criteria included only studies on TSTs vs. IGRAs whereas their criteria included only studies on treatment vs. no treatment) and hence papers included in one review will have been specifically excluded from the other.

Considering parameter inputs to the models, identical parameter values were used for the effectiveness of LTBI treatment and case fatality rates for active TB, with very similar values used for the costs of active TB, differing by only 2%. The costs of managing hepatitis differed more substantially (by around £200), but as isoniazid-induced hepatitis contributed only a small fraction to the costs in our model this is unlikely to make a major impact. As progression to active TB was calculated using different methods in the two models, it is not possible to compare the input parameters directly. However, by restricting the comparison to a subsample of the full population that can be extracted from both models, we can compare the number of active TB cases that each predicts. In particular, for a sample of patients aged 51–65 years with a positive TST result, the White and Jit[210] model predicts 2091 active TB cases per 100,000 in treated patients and 5928 active TB cases per 100,000 untreated patients. Our model, in contrast, predicts 1736 cases per 100,000 treated patients and 5372 cases per 100,000 untreated patients. These differences are most likely explained simply by the different data used to populate the two models. However, if the incidence rate used in the White and Jit[210] study is believed to be more accurate, this would have the effect of increasing the prevalance of LTBI in our starting population, the net effect of which can be explored from our univariate sensitivity analyses.

Strengths and limitations of the evidence

The assessment, comparison and interpretation of the clinical effectiveness of the existing tests in identifying LTBI is hampered by the absence of a gold standard for diagnosing LTBI. The evidence relied mostly on indirect measures of association derived between the test results (i.e. TST and/or IGRAs) and constructs of validity for LTBI (e.g. duration/proximity of exposure to a person with active TB, risk of development of active TB). Moreover, the existing commercially available screening tests for LTBI are imperfect in that they measure a host's immunological response to TB antigens, which may be affected by a number of factors other than LTBI and which differ from study to study (such as previous BCG vaccination, inter-/intrarater variability in interpretation of test results, boosting, conversion, reversion, different cut-offs for test positivity, assay manufacturing, pre-analytical processing and/or incubation delay). Thus, the findings of this review warrant a cautious interpretation.

Although we appraised and summarised a large amount of evidence, much of it was inconclusive because of unexplained heterogeneity in the effect estimates, poor reporting, missing data and great uncertainty around the effect estimates for the association between test results and the constructs of validity for LTBI. One of the difficulties in the assessment and interpretation of test performance (IGRAs vs. TST) in correctly detecting LTBI is the inconsistent use of definitions for high compared with low risk for LTBI (i.e. construct of validity). The heterogeneity in the measures of association between test results and previous exposure to TB observed even at within-study level could be the result of inadequate definition of the construct of validity for LTBI (e.g. previous exposure definition may not represent the true presence of LTBI), exposure misclassification (e.g. not all people exposed to a TB case will become infected) or both. Furthermore, some but not all of the observed heterogeneity in the parameters of test performance (e.g. sensitivity, specificity, DORs, between-test agreement) could be explained by study setting, type of population, type of test and the outcome characteristics. Some heterogeneity, especially with regard to the sensitivity and specificity estimates derived from previous TB exposure-based categories, could not be explained, thereby rendering some of our findings inconclusive. These factors were compounded by the scarcity of evidence in analyses stratified by population, type of IGRA test and TST threshold.

Another concern in interpreting the evidence relates to the ROB and methodological quality of the individual studies. In general, most studies were rated as being at high or moderate ROB (incidence studies) or of low methodological quality (exposure studies). Apart from the issues highlighted above, various sources of bias may have independently distorted the review findings and their interpretation. For example, results from the studies that we reviewed may have been biased because of diagnostic review bias (i.e. lack of blinding or knowledge of the IGRA/TST results influencing the ascertainment of exposure status or diagnosis of incident active TB), selection bias (i.e. study sample distorted with respect to previous TB exposure or disease spectrum because of an inadequate sampling frame, inadequate participant recruitment, non-participation and exclusions at study baseline), partial verification bias (i.e. incomplete outcome data assessment because of indeterminate IGRA results, missing TB exposure data, withdrawals and/or losses to follow-up) and incorporation bias (i.e. incorporation of IGRA/TST results as a criterion for the diagnosis of LTBI or incident active TB).[18,44,90,227]

Although the results from the incidence studies merit more credibility given their prospective design and standard and uniform ascertainment of the outcome (i.e. diagnosis of incident active TB), this evidence was scarce, the studies included small sample sizes and their follow-up was not long enough to document and evaluate the predictive ability of the tests more reliably. Moreover, the use of incident case of active TB as the validity construct for the presence of LTBI may also lead to misclassification as not all LTBI cases will develop into active TB or some seemingly incident cases of active TB (assumed to have developed from LTBI) may actually be people with newly acquired TB infection (prevalent active TB cases).

One of the limitations of this review was that we excluded non-English-language publications, which might have led to language-related bias in the estimates. However, none of the six excluded studies (see *Appendix 6*) (two in Turkish, two in Chinese, one in Spanish and one in Persian) would have been eligible for inclusion in the clinical part of this review as three included mixed samples not stratified by the subgroups of interest, one was a cost-effectiveness study and two did not use the LTBI constructs, such as previous exposure group or incidence of progression to active TB. Therefore, we believe that these language-based exclusions would not have had any impact on our findings.

Strengths and limitations of the current reviews and economic evaluation

We undertook a systematic review to identify all relevant studies providing evidence on the clinical effectiveness of IGRAs compared with the TST for identifying LTBI in the prespecified populations. The main strengths of this review were the application of systematic comprehensive searches, study screening, data extraction, use of relevant quality/ROB assessment tools for different study designs and the stratified analyses (by children, immunocompromised people and those recently arrived from high TB burden countries, subgroups defined by clinical condition, type of IGRA, TST threshold, high vs. low TB burden area and study setting). Our review, unlike other systematic reviews,[40,219,222] avoided including studies that used invalid constructs for LTBI, such as culture-confirmed active TB. Instead, this review focused on studies that defined the construct of LTBI either through the incidence of active TB or through study participants' previous exposure to index TB cases (e.g. risk categories defined by exposure proximity, duration and/or relationship to index TB case).

Our economic evaluation analyses are based on test accuracy data obtained from the current clinical effectiveness review, which represents the best available information on the accuracy of tests for LTBI that progresses to active TB. Our analyses represent the work of a multidisciplinary team, which includes input from clinical experts to develop the model structure. Additionally, considerable efforts were made to identify the most appropriate model input parameters to be used in the decision-analytic model.

The main limitation of the clinical effectiveness review is that full additional data extraction and quality assessment were not undertaken for studies included in CG117.[10] Moreover, because of a lack of relevant reported evidence, it was not possible to evaluate the effectiveness of the two-step testing procedure (using both IGRAs and TST) for identifying people with LTBI. Another limitation was our inability to stratify the study findings by BCG vaccination status; the individual study publications failed to report their results separately for vaccinated and non-vaccinated populations; even though this may have been an important distinguishing feature in the effectiveness of the different tests. The proportions of people vaccinated with BCG varied considerably in the included studies such that it was not possible to dichotomise populations into, for example, vaccinated and non-vaccinated. In any case, further stratification by BCG status was not feasible because of the scarcity of the data. With regard to the economic evaluation, we applied a unit cost for people being tested with the TST. The unit cost included the costs of the test consumables, administering the test and reading the result. We applied this cost both to people who had their TST result read and to those who did not have their result read. This had the effect of inflating the cost of an unread TST result. In addition, the model took into account the need for two clinic visits for the TST; however, it did not take into account the need for skilled operators and the wide intraobserver variability in interpretation. IGRAs require one visit, need fewer skilled personnel for interpretation and have less reliance on observer interpretation. Second, to our knowledge there are no systematic reviews on the accuracy of chest radiography for identifying people who have active TB. In our model we used the sensitivity and specificity from the study by Kumar *et al.*[208] for the accuracy of chest radiography for identifying the presence/absence of active TB in our three populations. This may over/underestimate the diagnostic accuracy of chest radiography in these populations. Third, detailed resource use information with regard to treatment for LTBI was unavailable in the literature. We therefore estimated resource use for LTBI treatment using input from our clinical advisors and this may have resulted in either over- or underestimation of resource use.

Chapter 8 Conclusion

The review draws attention to the clinical effectiveness evidence published since CG117.[10] The research adds to the existing literature but highlights the poor quality of the evidence. Surprisingly, the results show that the two different generations of tests are broadly equivalent, although the results vary in a number of different settings and subgroups. The limitations in the evidence (e.g. absence of a gold standard for LTBI diagnosis, ROB in individual studies, scarcity of evidence, test administration/interpretation, variation in the exposure-based definitions of the LTBI construct, limitations of the screening tests) and heterogeneity in IGRA performance relative to TST performance limit the applicability of the review findings. Generally, the findings from population-based setting studies conducted in countries of low TB burden would be more applicable to the UK's routine general practice of LTBI screening. The findings of this review underscore the variability of test performance across clinical conditions within the immunocompromised population, thereby limiting the applicability of test results from one subgroup (e.g. those with HIV infection or rheumatoid arthritis) to another (e.g. those with hepatitis C or lupus erythematosus).

The review of the cost-effectiveness evidence enabled the identification of previously published methodology before we developed our model structure to determine the cost-effectiveness of IGRAs compared with TST for the diagnosis of LTBI. These models offer insight and, in general, performed well against the frameworks on best practice for reporting a model-based economic evaluation, but were subjected to some limitations. Areas of concern included the perspective of the analysis, the handling of uncertainty in the models, the derivation of prevalence, test accuracy and transition probabilities; most studies did not elaborate on these statistical/pre-model analyses.

In the population of children who had had contact with an index case, the results based on the outcome of cost per diagnostic error avoided showed that the TST (≥ 10 mm) strategy dominated all strategies except for the T-SPOT.*TB* strategy alone. T-SPOT.*TB* compared with TST (≥ 10 mm) was more effective but more expensive, with an ICER of approximately £2710 per diagnostic error avoided. The TST (≥ 5 mm) strategy was slightly more effective than the QFT-GIT-alone strategy, with an ICER of approximately £11,260 per QALY, and had a 26.9% probability of being cost-effective at a willingness to pay of £20,000 per QALY.

In the immunocompromised population, QFT-GIT dominated QFT-GIT negative followed by TST (≥ 5 mm), T-SPOT.*TB* and TST (≥ 5 mm) strategies in terms of diagnostic errors avoided. The QFT-GIT positive followed by TST (≥ 5 mm) strategy was the most effective strategy. The results in terms of cost per QALY showed that the QFT-GIT negative followed by TST (≥ 5 mm) strategy was the most effective strategy, with an ICER of approximately £18,750 compared with T-SPOT.*TB*, and had a 40% probability of being cost-effective at a willingness to pay of £20,000.

In the recent arrivals from countries with a high incidence of TB, the QFT-GIT strategy dominated all strategies except for TST (≥ 5 mm) positive followed by QFT-GIT. The TST (≥ 5 mm) positive followed by QFT-GIT strategy was more costly and resulted in more diagnostic errors avoided, with an ICER of approximately £690 compared with the QFT-GIT-alone strategy. The results in terms of cost per QALY showed that QFT-GIT dominated the T-SPOT.*TB* and TST (≥ 5 mm) positive followed by QFT-GIT strategies and had an 18% probability of being cost-effective at a willingness to pay of £20,000 per QALY. The TST (≥ 5 mm) strategy had the highest probability (47%) of being cost-effective at a willingness to pay of £20,000.

Implications for service provision and local commissioning

The results of the health economic analysis show which diagnostic strategy is likely to be the most cost-effective for the diagnosis of LTBI that progresses to active TB.

Our results do not show whether or not screening compared with no screening is likely to be cost-effective nor do they demonstrate which IGRA (e.g. QFT-GIT vs. T-SPOT.*TB*) is more cost-effective.

Our findings should be interpreted by clinicians, commissioners and policy makers with caution because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made. Clinicians should be mindful of the variation in performance of the different testing strategies among different populations.

Suggested research priorities

A key priority is to conduct research in populations from both high and low TB burden countries to explore and confirm whether the inconsistent performance of IGRAs is real or whether it represents a chance finding. The natural history of the condition needs to be clarified. Prospective population-based studies with an adequate sample size and follow-up should be conducted in people at high risk for TB. These studies should employ standard diagnostic methodology and criteria for ascertaining incident cases of active TB. Research is also needed to clarify the role of serial as opposed to single cross-sectional testing in light of the comparative effectiveness of IGRAs and the TST for the diagnosis of LTBI; future studies need to evaluate the utility of two-step compared with single testing to maximise both sensitivity and specificity for identifying people with LTBI. Although strain and infectivity data have not been used in the present analyses because they were not available, they are relevant to future research.

Consensus-based standard criteria or a multivariable risk prediction model for the construct of LTBI should be developed. This would provide a standard set of all of the component exposures to classify people into high or low risk for LTBI. This would improve retrospective or cross-sectional studies of previous TB exposure by facilitating standardised definitions across different studies and would allow for more objective comparisons between IGRAs and the TST in terms of detecting LTBI in subgroups of interest.

There is very little evidence on the roles of IGRAs and the TST for the diagnosis of LTBI in different clinical subgroups of immunocompromised people (e.g. those with HIV infection or hepatitis C, solid organ transplant recipients, those with rheumatoid arthritis) and future research could be directed at providing this. Finally, more efforts need to be directed at identifying new more accurate markers of LTBI.

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Peter Auguste conducted the clinical effectiveness systematic review (screening and retrieving papers, assessing papers against the inclusion criteria, appraising the quality of papers and abstracting information from papers for synthesis), the cost-effectiveness systematic review and the health economic analysis, and wrote the discussion section.

Alexander Tsertsvadze wrote the background section, conducted the clinical effectiveness systematic review (screening and retrieving papers, assessing papers against the inclusion criteria, appraising the quality of papers and abstracting information from papers for synthesis) and the clinical effectiveness analysis, wrote the clinical effectiveness results section, conducted the cost-effectiveness systematic review and wrote the discussion section.

Joshua Pink conducted the health economic analysis and wrote the discussion section.

Rachel Court developed the search strategy and undertook the searches.

Farah Seedat wrote the background section.

Tara Gurung conducted the clinical effectiveness systematic review (screening and retrieving papers, assessing papers against the inclusion criteria, appraising the quality of papers and abstracting information from papers for synthesis).

Karoline Freeman conducted the clinical effectiveness systematic review (screening and retrieving papers, assessing papers against the inclusion criteria, appraising the quality of papers and abstracting information from papers for synthesis) and wrote the clinical effectiveness results section.

Sian Taylor-Phillips provided support for the clinical effectiveness analysis.

Clare Walker wrote the background section and the discussion.

Jason Madan provided support for the cost-effectiveness analysis.

Ngianga-Bakwin Kandala provided support for the clinical effectiveness analysis.

Aileen Clarke wrote the discussion section and provided clinical and methodological input.

Paul Sutcliffe co-ordinated the review, conducted the clinical effectiveness systematic review (screening and retrieving papers, assessing papers against the inclusion criteria, appraising the quality of papers and abstracting information from papers for synthesis) and wrote the discussion section.

All authors were involved in writing draft and final versions of the report.

Data sharing statement

All data in this report were already in the public domain; therefore, there are no data to share.

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Appendix 1 Search strategies and results from 2011

Main searches

Diagnosis of latent tuberculosis infection using interferon gamma release assays based on M. tuberculosis*-specific antigens*

Databases were searched to answer questions relating to the diagnosis of LTBI using IGRAs based on *M. tuberculosis*-specific antigens (ESAT-6, CFP 10 and TB7.7), including the following commercially available assays:

- QFT-GIT
- QFT-G
- T-SPOT.*TB*.

The diagnostic utility of these assays, alone or in combination with a tuberculin skin test, was compared with that of the TST alone.

The database searches were undertaken between 7 and 14 December 2009. The databases searched were:

- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process & Other Non-Indexed Citations (Ovid)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO*host*)
- Database of Abstracts of Reviews of Effects (CRD)
- Health Technology Assessment database (CRD)
- The Cochrane Library (Wiley)
- Cochrane Register of Diagnostic Test Accuracy Studies (Wiley)
- Medion
- Aggressive Research Intelligence Facility.

The MEDLINE search strategy is presented below. It was translated for use in the databases listed above.

Ovid MEDLINE 1950 to November Week 3 2009

1. (laten* adj3 (tb* or tubercul*)).tw.
2. ltb*.tw.
3. Tuberculosis, Pulmonary/
4. Tuberculosis/
5. Mycobacterium tuberculosis/
6. or/1-5 (123029)
7. IGRA*.tw.
8. IGT*.tw.
9. (interferon adj3 gamma adj3 (release* or test* or assay*)).tw.
10. ((y-interferon or interferon-y) adj3 (release* or assay* or test*)).tw.
11. (quantiferon adj3 gold*).tw.
12. (quantiferon adj3 (in tube or test*)).tw.
13. QFT*.tw.
14. t spot*.tw.

15. Interferon-gamma/
16. (enzyme* adj3 link* adj3 immunosorbent adj3 (test* or assay*)).tw.
17. ELISA*.tw.
18. (ELISPOT* or (enzyme* adj3 link* adj3 immunospot)).tw.
19. (ESAT6* or ESAT-6* or ESAT 6*).tw.
20. (early adj3 secret* adj3 antigen adj3 target-6).tw.
21. (CFP10* or (culture adj3 filtrate adj3 protein-10)).tw.
22. "TB7.7".tw.
23. Fluorospot*.tw.
24. "region of difference".tw.
25. Enzyme-Linked Immunosorbent Assay/
26. or/7-25
27. 6 and 26
28. mass screening/
29. (screen* adj3 (program* or mass or population* or disease*)).tw.
30. 28 or 29
31. 30 and 6
32. 27 or 31
33. Animals/ not Humans/
34. 32 not 33
35. limit 34 to english language

Health economics

The following sources were searched to identify economic evaluations and quality-of-life data relating to IGRAs for LTBI:

- Health Economics Evaluations Database (Wiley)
- NHS Economic Evaluation Database (NHS EED) (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process & Other Non-Indexed Citations (Ovid)

The searches were undertaken on 5 and 6 January 2009.

The MEDLINE search strategy is presented below. It was translated for use in other databases.

Ovid MEDLINE 1950 to December Week 4 2009

1. (laten* adj3 (tb* or tubercul*)).tw.
2. ltb*.tw.
3. Tuberculosis, Pulmonary/
4. Tuberculosis/
5. Mycobacterium tuberculosis/
6. or/1-5
7. IGRA*.tw.
8. IGT*.tw.
9. (interferon adj3 gamma adj3 (release* or test* or assay*)).tw.
10. ((y-interferon or interferon-y) adj3 (release* or assay* or test*)).tw.
11. (quantiferon adj3 gold*).tw.
12. (quantiferon adj3 (in tube or test*)).tw.
13. QFT*.tw.
14. t spot*.tw.
15. Interferon-gamma/

16. (enzyme* adj3 link* adj3 immunosorbent adj3 (test* or assay*)).tw.
17. ELISA*.tw.
18. (ELISPOT* or (enzyme* adj3 link* adj3 immunospot)).tw.
19. (ESAT6* or ESAT-6* or ESAT 6*).tw.
20. (early adj3 secret* adj3 antigen adj3 target-6).tw.
21. (CFP10* or (culture adj3 filtrate adj3 protein-10)).tw.
22. "TB7.7".tw.
23. Fluorospot*.tw.
24. "region of difference".tw.
25. Enzyme-Linked Immunosorbent Assay/ [Double click to insert footer here] 23 of 315
26. or/7-25
27. 6 and 26
28. mass screening/
29. (screen* adj3 (program* or mass or population* or disease*)).tw.
30. 28 or 29
31. 30 and 6
32. 27 or 31
33. Animals/ not Humans/
34. 32 not 33
35. limit 34 to english language
36. Economics/
37. exp "Costs and Cost Analysis"/
38. Economics, Dental/
39. exp Economics, Hospital/
40. exp Economics, Medical/
41. Economics, Nursing/
42. Economics, Pharmaceutical/
43. Budgets/
44. exp Models, Economic/
45. Markov Chains/
46. Monte Carlo Method/
47. Decision Trees/
48. econom$.tw.
49. cba.tw.
50. cea.tw.
51. cua.tw.
52. markov$.tw.
53. (monte adj carlo).tw.
54. (decision adj2 (tree$ or analys$)).tw.
55. (cost or costs or costing$ or costly or costed).tw.
56. (price$ or pricing$).tw.
57. budget$.tw.
58. expenditure$.tw.
59. (value adj2 (money or monetary)).tw.
60. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
61. or/36-60
62. "Quality of Life"/
63. quality of life.tw.
64. "Value of Life"/
65. Quality-Adjusted Life Years/
66. quality adjusted life.tw.
67. (qaly$ or qald$ or qale$ or qtime$).tw.
68. disability adjusted life.tw. (571)

69. daly$.tw.
70. Health Status Indicators/
71. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
72. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
73. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
74. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
75. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
76. (euroqol or euro qol or eq5d or eq 5d).tw.
77. (qol or hql or hqol or hrqol).tw.
78. (hye or hyes).tw.
79. health$ year$ equivalent$.tw.
80. utilit$.tw.
81. (hui or hui1 or hui2 or hui3).tw.
82. disutili$.tw.
83. rosser.tw.
84. quality of wellbeing.tw.
85. quality of well-being.tw.
86. qwb.tw.
87. willingness to pay.tw.
88. standard gamble$.tw.
89. time trade off.tw.
90. time tradeoff.tw.
91. tto.tw.
92. or/62-91
93. 61 or 92
94. 35 and 93

Appendix 2 Search strategies and results 2014

The objective of the search strategies was to identify literature on the diagnosis of LTBI using IGRAs compared with other methods. The following sources were searched: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, The Cochrane Library via Wiley, Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index – Science (CPCI-S), Medion, ClinicalTrials.gov, WHO ICTRP, conferences and websites.

The bibliographic database searches were undertaken on 9 and 10 April 2014 and were updated on 2 December 2014 using the same strategies. Supplementary searches were undertaken between 10 June and 5 August 2014.

MEDLINE

Update search

Ovid MEDLINE 1946 to November Week 3 2014, searched 2 December 2014.

The search in *Table 45* was rerun with the following limit:

Line 24 = limit 23 to ed=20140312-20141202 (222)

Total = 1288 + 222 = 1510.

TABLE 45 Ovid MEDLINE 1946 to April week 1 2014, searched 9 April 2014

	Search term	Number of hits
1	(laten* adj3 (tb* or tubercul*)).tw.	2701
2	ltb*.tw.	6939
3	tubercul*.tw.	158,617
4	Tuberculosis/	51,049
5	Latent Tuberculosis/	866
6	Tuberculosis, Pulmonary/	63,874
7	Mycobacterium tuberculosis/	35,401
8	1 or 2 or 3 or 4 or 5 or 6 or 7	195,420
9	quantiferon*.tw.	819
10	QFT*.tw.	557
11	t spot*.tw.	261
12	exp Enzyme-Linked Immunosorbent Assay/	122,317
13	Interferon-gamma Release Tests/	377
14	((interferon* or IFN*) adj3 gamma* adj3 (release* or test* or assay*)).tw.	3856
15	((y-interferon or interferon-y) adj3 (release* or test* or assay*)).tw.	7
16	IGRA*.tw.	448
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	126,234
18	8 and 17	3840
19	Latent Tuberculosis/di	576

continued

TABLE 45 Ovid MEDLINE 1946 to April week 1 2014, searched 9 April 2014 (*continued*)

	Search term	Number of hits
20	18 or 19	4061
21	Animals/ not Humans/	3,812,070
22	20 not 21	3480
23	limit 22 to english language	3014
24	limit 23 to ed=20091207-20140409	1288

MEDLINE In-Process & Other Non-Indexed Citations

Update search

Ovid MEDLINE In-Process & Other Non-Indexed Citations 1 December 2014, searched 2 December 2014.

The search in *Table 46* was rerun with the following limit:

Line 15 = limit 14 to ed=20140312-20141202 (19)

Total = 263 + 19 = 282.

TABLE 46 Ovid MEDLINE In-Process & Other Non-Indexed Citations 8 April 2014, searched 9 April 2014

	Search term	Number of hits
1	(laten* adj3 (tb* or tubercul*)).tw.	312
2	ltb*.tw.	340
3	tubercul*.tw.	10,405
4	1 or 2 or 3	10,625
5	quantiferon*.tw.	121
6	QFT*.tw.	83
7	t spot*.tw.	42
8	(enzyme* adj3 link* adj3 (immunosorbent or immunospot) adj3 (test* or assay*)).tw.	3522
9	((interferon* or IFN*) adj3 gamma* adj3 (release* or test* or assay*)).tw.	148
10	((y-interferon or interferon-y) adj3 (release* or test* or assay*)).tw.	1
11	IGRA*.tw.	102
12	5 or 6 or 7 or 8 or 9 or 10 or 11	3778
13	4 and 12	281
14	limit 13 to english language	263

EMBASE

Update search

EMBASE 1980 to 2014 Week 48, searched 2 December 2014.

The search in *Table 47* was rerun with the following limits:

Line 25 = imit 24 to dd=20140409-20141202 (364)

Line 26 = limit 24 to em=201414-201448 (387)

Line 27 = 25 or 26 (387)

Total = 2483 + 387 = 2870.

TABLE 47 Ovid EMBASE 1980 to 2014 week 14, searched 9 April 2014

	Search term	Number of hits
1	(laten* adj3 (tb* or tubercul*)).tw.	3880
2	ltb*.tw.	8397
3	tubercul*.tw.	175,055
4	tuberculosis/	87,819
5	latent tuberculosis/	1696
6	lung tuberculosis/	62,789
7	Mycobacterium tuberculosis/	47,234
8	1 or 2 or 3 or 4 or 5 or 6 or 7	227,447
9	quantiferon*.tw.	1477
10	QFT*.tw.	871
11	t spot*.tw.	442
12	enzyme linked immunospot assay/	5911
13	*enzyme linked immunosorbent assay/	14,220
14	exp interferon gamma release assay/	1062
15	((interferon* or IFN*) adj3 gamma* adj3 (release* or test* or assay*)).tw.	1925
16	((y-interferon or interferon-y) adj3 (release* or test* or assay*)).tw.	12
17	IGRA*.tw.	841
18	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	23,387
19	8 and 18	3410
20	latent tuberculosis/di	573
21	19 or 20	3619
22	animal/ not human/	1,176,853
23	21 not 22	3556
24	limit 23 to english language	3171
25	limit 24 to dd=20091207-20140409	2280
26	limit 24 to em=200900-201414	2482
27	25 or 26	2483

The Cochrane Library

All results 108: Cochrane reviews 0, other reviews 19, trials 53, methods studies 0, technology assessments 6, economic evaluations 30, Cochrane Groups 0.

Update search

The Cochrane Library via Wiley, searched 2 December 2014.

The search in *Table 48* was rerun with the following limit:

Line 21 = #18 or #19 Publication Year from 2014 to 2014 (11)

All results 11: Cochrane reviews 0, other reviews 3, trials 7, methods studies 0, technology assessments 0, economic evaluations 1, Cochrane Groups 0.

Total = 108 + 11 = 119.

TABLE 48 The Cochrane Library via Wiley, searched 9 April 2014

	Search term	Number of hits
#1	(laten* near/3 (tb* or tubercul*)):ti,ab,kw	186
#2	ltb*:ti,ab,kw	270
#3	tubercul*:ti,ab,kw	3404
#4	MeSH descriptor: [Tuberculosis] this term only	598
#5	MeSH descriptor: [Latent Tuberculosis] this term only	53
#6	MeSH descriptor: [Tuberculosis, Pulmonary] this term only	824
#7	MeSH descriptor: [Mycobacterium tuberculosis] this term only	306
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	3632
#9	quantiferon*:ti,ab,kw	44
#10	QFT*:ti,ab,kw	22
#11	t next spot*:ti,ab,kw	15
#12	MeSH descriptor: [Enzyme-Linked Immunosorbent Assay] explode all trees	2107
#13	MeSH descriptor: [Interferon-gamma Release Tests] this term only	31
#14	((interferon* or IFN*) near/3 gamma* near/3 (release* or test* or assay*)):ti,ab,kw	164
#15	((y-interferon or interferon-y) near/3 (release* or test* or assay*)):ti,ab,kw	0
#16	IGRA*:ti,ab,kw	22
#17	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	2260
#18	#8 and #17	145
#19	MeSH descriptor: [Latent Tuberculosis] this term only and with qualifier(s): [Diagnosis - DI]	31
#20	#18 or #19	154
#21	#18 or #19 Publication Date from 2009 to 2014	108

Science Citation Index Expanded and Conference Proceedings Citation Index – Science

Update search

Science Citation Index Expanded (SCI-EXPANDED) 1970 to present and Conference Proceedings Citation Index – Science (CPCI-S) 1990 to present via Web of Knowledge, searched 2 December 2014.

The search in *Table 49* was rerun with the following limit:

Timespan = 2014

#14 = 277

Total = 3314 + 277 = 3591.

TABLE 49 Science Citation Index Expanded (SCI-EXPANDED) 1970 to present and Conference Proceedings Citation Index – Science (CPCI-S) 1990 to present via Web of Knowledge, searched 9 April 2014

	Search term	Number of hits
#14	(#13) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2014	1608
#13	#4 and #12 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	3139
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	63,467
#11	TS=IGRA* Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	601
#10	TS=((y-interferon or interferon-y) NEAR/3 (release* or test* or assay*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	5
#9	TS=((interferon* or IFN*) NEAR/3 gamma* NEAR/3 (release* or test* or assay*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	5812
#8	TS=(enzyme* NEAR/3 link* NEAR/3 (immunosorbent or immunospot) NEAR/3 (test* or assay*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	56,262
#7	TS=((t-spot*) OR (t NEAR/1 spot*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	464
#6	TS=QFT* Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	1894
#5	TS=quantiferon* Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	949
#4	#1 or #2 or #3 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	108,863
#3	TS=tubercul* Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	103,332
#2	TS=ltb*Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	6278
#1	TS=(laten* NEAR/3 (tb or tubercul*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	3314

Medion

Searched 10 June 2014.

Search 1

Searched in subset of Medion – systematic reviews of diagnostic studies.

Signssymp - selected:

- divers, other, general,
- Laboratory tests

Abstract:

- Tuberculosis

Total: 33.

Search 2

Searched in subset of Medion – systematic reviews of diagnostic studies.

Signssymp - selected:

- divers, other, general,
- Laboratory tests

Abstract:

- tb

Total: 37.

Both searches

- Total of both searches after duplicates removed: 47.
- Saved to Microsoft Word® 2010 (Microsoft Corporation, Redmond, WA, USA) and removed 19 pre-2009 reviews, leaving 28.
- Checked against results of other database searching in EndNote and removed 11 duplicates.
- Total unique records: 17.

World Health Organization International Clinical Trials Registry Platform

Searched 5 August 2014.

Advanced search:

(quantiferon* or QFT* or t-spot* or interferon* or IFN* or gamma* or y-interferon or interferon-y or IGRA*) in Title

AND

(tuberculosis or latent tb) in Condition

Total: 10.

ClinicalTrials.gov

Searched 5 August 2014.

(quantiferon* OR QFT* OR t-spot* OR interferon* OR IFN* OR gamma* OR y-interferon OR interferon-y OR IGRA*) AND (tuberculosis or "latent tb")

Excluded unknown status.

Total: 41.

Conferences

Specific conference proceedings, selected with input from a clinical expert (Professor Jeremy Hawker, Public Health England, 29 April 2014), were searched on 24 and 25 June 2014 for the last 5 years:

- European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) [http://ecdc.europa.eu/en/ESCAIDE/about_ESCAIDE/Pages/previous_conferences.aspx (accessed 25 June 2014)]
- PHE Annual Conference (previously Health Protection Agency Annual Conference) (www.phe-events.org.uk/hpa/frontend/reg/thome.csp?pageID=117557&eventID=286&eventID=286)
- 5 Nations Health Protection Conference [http://5nations.org.uk/?page_id=44 (accessed 13 January 2016)]
- Federation of Infection Societies Annual Conference [http://fis-infection.org.uk/ (accessed 13 January 2016), e.g. www.actiononinfection.com/abstracts-and-poster-walk/ (accessed 25 June 2014)]
- British Thoracic Society [www.brit-thoracic.org.uk/bts-learning-hub/bts-summer-and-winter-meetings/summer-meeting-2014/ (accessed 13 January 2016)]
- Annual Conferences of the Union North America Region [www.bc.lung.ca/association_and_services/union.html (accessed 25 June 2014)].

Websites

Websites of specific organisations, selected with input from a clinical expert (Professor Jeremy Hawker), were checked for relevant literature on 25 June 2014:

- PHE (including old Health Protection Agency site) [www.gov.uk/government/organisations/public-health-england (accessed 13 January 2016) and www.hpa.org.uk/ (accessed 25 June 2014)].
- Centers for Disease Control and Prevention (Atlanta) [www.cdc.gov/ (accessed 13 January 2016)].
- European Centre for Disease Prevention and Control [www.ecdc.europa.eu/en/Pages/home.aspx and www.ecdc.europa.eu/en/activities/diseaseprogrammes/programme_tuberculosis/Pages/index.aspx (accessed 25 June 2014)].
- World Health Organization [www.who.int/en/ (accessed 13 January 2013) and http://dosei.who.int/uhtbin/cgisirsi/tXRt5oo9vL/245820007/60/86/X (accessed 25 June 2014)].
- British Thoracic Society [(www.brit-thoracic.org.uk/ (accessed 13 January 2016)].
- Cellestis (manufacturer of QFT-G and QFT-GIT) [www.cellestis.com/ (accessed 13 January 2016)].
- Oxford Immunotec (manufacturer of T-SPOT.*TB*) [www.oxfordimmunotec.com/ (accessed 13 January 2016)].

Appendix 3 Data extraction table for included primary study reports

Name of first reviewer:
Name of second reviewer:

Study details
First author surname year of publication:
Country:
Study design:
Study setting (e.g., outbreak investigation, community-based - specify):
Number of centres:
Total length of follow up (if applicable):
Funding (government/private/manufacturer/other - specify):
Aim of the study
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Participants
Recruitment dates:
Total N of recruited patients:
Inclusion criteria:
Exclusion criteria:
Total N of excluded patients:
Total N of patients tested with both IGRA and TST:
Total N of patients with valid results for both IGRA and TST:
Methods of active TB diagnosis (if applicable):
Outcomes (study-based) list:
Characteristics of participants (total study sample)
Mean (range or SD) age (years):
Women (n [%]):
Race/ethnicity (n [%]):
Geographic origin (n[%]):
BCG vaccination (n [%]):
History of anti-TB treatment (n [%]):
Total incidence of active TB (n [%]):
Chest radiography (yes/no):
Clinical examination (yes/no):
Morbidity (n [%]):
Co-morbidity (n [%]):
Type of during-study treatment (n [%]):

Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (specify):					
TST:					
Test 3 (specify)					

Total N of patients with valid results for both IGRA and TST:

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	
Exposed 1 **(specify)**:	
Exposed 2 **(specify)**:	
Exposed 3 **(specify)**:	
Exposed 4 **(specify)**:	

Tests				
	Assay used, methodology, timing for test measurement, manufacturer		**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA				
TST				

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +				TST +			
IGRA -				TST -			
indeterminate				indeterminate			
Total				Total			

Test performance parameters	
IGRA	**TST**
Sensitivity =	Sensitivity =
Specificity =	Specificity =
PPV =	PPV =
NPV =	NPV =
Cumulative Incidence $_{IGRA+}$ =	Cumulative Incidence $_{TST+}$ =
Cumulative Incidence $_{IGRA-}$ =	Cumulative Incidence $_{TST-}$ =
Cumulative Incidence Ratio $_{IGRA}$ =	Cumulative Incidence Ratio $_{TST}$ =
Incidence density rate $_{IGRA+}$ =	Incidence density rate $_{TST+}$ =
Incidence density rate $_{IGRA-}$ =	Incidence density rate $_{TST-}$ =
Incidence density rate ratio $_{IGRA}$ =	Incidence density rate ratio $_{TST}$ =

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios =
Ratio of incidence density rate ratios =
Other reported measure =

Association between test results and levels of TB exposure (if applicable)							
IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +				TST +			
IGRA -				TST -			
indeterminate				indeterminate			
Total				Total			

Test performance parameters	
IGRA	**TST**
Sensitivity =	Sensitivity =
Specificity =	Specificity =
PPV =	PPV =
NPV =	NPV =
DOR (for T^+ calculated) =	DOR (for T^+ calculated) =
OR (crude; for T^+ reported) =	OR (crude; for T^+ reported) =
OR (regression-based; reported) = List of covariates:	OR (regression-based; reported) = List of covariates:
Other reported measure =	Other reported measure =

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) =

Ratio of OR (crude; for T^+ reported) =			
Ratio of ORs (regression-based; reported) =			
Other reported measure =			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST +	TST -	Total
IGRA +			
IGRA -			
indeterminate			
Total			
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify):			
TST + threshold:			
Parameters			
Kappa =			
% concordance =			
% discordance =			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +			
IGRA -			
indeterminate			
Total			
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify):			
TST + threshold:			
Parameters			
Kappa =			
% concordance =			
% discordance =			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +			
IGRA -			
indeterminate			
Total			
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify):			
TST + threshold:			
Parameters			
Kappa =			
% concordance =			
% discordance =			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**	
IGRA:			
TST:			
Test 3 (specify):			
Conclusions			

Authors:
Reviewers:
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Appendix 4 Quality assessment and risk of bias

TABLE 50 Quality assessment for the exposure studies

Study ID (burden)	Recruitment of subjects [consecutive (yes), arbitrary or unreported (no)]	Blinding of test results from exposure [blinded (yes), not blinded or unreported (no)]	Description of index test and threshold [adequate (yes), inadequate or unreported (no)]	Definition and description of exposure [adequate (yes), inadequate or unreported (no)]	Sample attrition [adequate (yes),[a] inadequate or unreported (no)]	Overall quality score of satisfactory features[b]

ID, identification.
a ≥ 90% of participants were included in the follow-up analysis (yes response) and < 90% were classified as 'no response'.
b Studies with one or two 'yes' ratings = low quality; studies with three 'yes' ratings = moderate quality; studies with four or five 'yes' ratings = high quality.
Source: adapted from Dinnes *et al.*[44] The item 'study design' was removed from the original checklist as all studies were considered to be retrospective; furthermore, the item 'sample attrition' was added.

TABLE 51 Risk of bias of the incidence studies

Study ID (first author, year, ref. ID):						
Reviewer 1:						
Reviewer 2:						
Domain of bias	**Question**	**Issues to consider for judging overall rating of ROB**	**Comments (if issue not satisfied)**	**Rating (yes, partial, no, unsure)**	**ROB (high, moderate, low)**
Study design	Prospective (yes/no)?	Prospective (low ROB), cross-sectional (moderate ROB), case–control (high ROB)			
Study participation (risk of selection bias)	Does the study sample adequately represent the population of interest? How likely is it that the relationship between the test result and the outcome is different for participants and eligible non-participants?	The source population is adequately described			
		The sampling frame and recruitment are adequately described			
		The period and place of recruitment are adequately described			
		Inclusion and exclusion criteria are adequately described			
		The baseline study sample is adequately described			
		Adequate participation in the study by eligible individuals			
		Participants were consecutively enrolled			

continued

TABLE 51 Risk of bias of the incidence studies (*continued*)

Domain of bias	Question	Issues to consider for judging overall rating of ROB	Comments (if issue not satisfied)	Rating (yes, partial, no, unsure)	ROB (high, moderate, low)
Study attrition (risk of selection bias)	Do the study data available (participants not lost to follow-up) adequately represent the study sample? How likely is it that the relationship between the test results and the outcome is different for completing and non-completing participants?	The response rate (i.e. proportion of study sample completing the study and providing outcome data) is adequate Attempts to collect information on participants who dropped out are described Reasons for loss to follow-up are provided Participants lost to follow-up are adequately described for key characteristics There are no important differences between key characteristics and outcomes between participants who completed the study and those who did not			
Prognostic factor measurement (risk of exposure measurement bias)	Was the test measured in a similar way for all participants? How likely is it that the measurement or knowledge of the outcome influenced the test results?	A clear definition or description of the test is provided (e.g. type, assay, threshold for positivity and method of measurement) The method of test conduct was adequate and test results were ascertained adequately (e.g. raters were blinded to outcomes in relation to construct validity, previous test ratings, clinical or other characteristics not intended to be a part of the test) Test thresholds used are appropriate The method and setting of the test measurement are the same for all study participants An adequate proportion of the study sample has complete data of the test results Appropriate methods of imputation are used for missing data on test results			

TABLE 51 Risk of bias of the incidence studies (*continued*)

Domain of bias	Question	Issues to consider for judging overall rating of ROB	Comments (if issue not satisfied)	Rating (yes, partial, no, unsure)	ROB (high, moderate, low)
Outcome/ construct measurement (ROB in misclassification of individuals in relation to construct validity groups)	Was the outcome of interest (i.e. exposure to MTB, incidence of active TB, definition of low-risk population) measured in a similar way for all participants? How likely is differential measurement of the outcome (e.g. outcome measurement related to the test results)?	A clear definition of outcomes is provided, including duration of follow-up and level and extent of the outcome construct			
		The method of outcome measurement used is valid and reliable to limit misclassification bias (e.g. blinded measurement, adequate methods of outcome/construct ascertainment – exposure proximity plus duration considered)			
		The method and setting of outcome/construct measurement are the same for all study participants			
Study confounding (ROB related to confounding)	Were important potential confounding factors appropriately accounted for? How likely is bias because of confounding?	All important confounders, including treatments (key variables in the conceptual mode) are defined and measured			
		All important confounders are accounted for at the design and/or analysis stage			
Statistical analysis and reporting (ROB related to the analysis and selective reporting)	Was the statistical analysis appropriate and were all primary outcomes reported? How likely is bias related to the statistical analysis and presentation of the results?	There is sufficient presentation of data to assess the adequacy of the analysis			
		The strategy for model building (i.e. inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model			
		The selected statistical model is adequate for the design of the study			
		There is no selective reporting of results			
Total ROB (high, medium, low)					

ID, identification.
Source: adapted from Hayden *et al.*[90]

TABLE 52 Definitions for ROB ratings for each domain of bias: the QUIPS tool[a]

Domain of bias	Definitions for ROB ratings		
	High ROB	Moderate ROB	Low ROB
Study design	Case–control study	Cross-sectional study	Prospective cohort study
Study participation	The relationship between the test results and the construct/ outcome is very likely to be different for participants and eligible non-participants	The relationship between the test results and the outcome may be different for participants and eligible non-participants	The relationship between the test results and the outcome is unlikely to be different for participants and eligible non-participants
Study attrition	The relationship between the test results and the construct/ outcome is very likely to be different for completing and non-completing participants	The relationship between the test results and the construct/ outcome may be different for completing and non-completing participants	The relationship between the test results and the outcome is unlikely to be different for completing and non-completing participants
Prognostic factor measurement	The measurement of the test is very likely to be different for different levels of the outcome/ construct of interest	The measurement of the test may be different for different levels of the outcome/construct of interest	The measurement of the test is unlikely to be different for different levels of the outcome/ construct of interest
Outcome measurement/ construct	The measurement of the outcome/construct is very likely to be different related to the baseline level of the test	The measurement of the outcome/construct may be different related to the baseline level of the test	The measurement of the outcome/construct is unlikely to be different related to the baseline level of the test
Study confounding	The observed association between the test and the outcome/construct is very likely to be distorted by another factor related to prognostic factor and outcome	The observed association between the test and the outcome/construct may be distorted by another factor related to prognostic factor and outcome	The observed association between the test and the outcome/construct is unlikely to be distorted by another factor related to prognostic factor and outcome
Statistical analysis and reporting	The reported results are very likely to be spurious or biased related to analysis or reporting	The reported results may be spurious or biased related to analysis or reporting	The reported results are unlikely to be spurious or biased related to analysis or reporting

a Adapted from Hayden *et al.*[90]

Appendix 5 Studies included in the clinical effectiveness review 2011[10]

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Children

TABLE 53 Studies in children included in CG117[10]

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Brock 2004[156]	Observational. Done in Denmark on Danish School population	125 mean age of 17 years. 85 not BCG vaccinated. Subjects nearest contact case also 17 asked to participate	Stratified by high and low exposure. High exposure contained individuals with close contact to the index case either through household, school class or local choir that index case regularly attended. Low exposure comprised 40 students from two other classes at the school with no connection to the index case	IGRA (QFT-G)	TST PPD RT23 (2 tuberculin units were used)	Determined concordance between the tests in both levels of exposure. And also in both BCG and non-BCG vaccinated individuals. Overall kappa = 0.866	Not determined	Not reported	Study demonstrated that IGRA is similar in performance to TST in detecting LTBI in young non-BCG vaccinated individuals

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Chun 2008[157]	Observational conducted in South Korea	Aged up to 15 years. Patients visiting a children's hospital. All children but one had been BCG vaccinated	Divided into four groups according to contact status 1. Close contact group residing in the same house as active TB index case 2. Casual contact group; those with exposure outside household 3. Control group; TST positive healthy children with no contact history 4. Children with symptoms suggestive of TB as a potential cause	IGRA (QFT-G)	TST PPD RT23 (2 tuberculin units were used)	Close contacts: kappa 0.19 for 5 mm and 0.529 for 10 mm. (B) Kappa 0.378 for 10 mm. A significantly higher rate of positive QFT-G results was evident for the close contact group. 8/42, 19% as compared with the control group 3 subjects 1/65, 1.5% $p < 0.05$. Majority of indeterminate QFT-G results were from group 4 who were suffering from medical conditions that could be associated with impaired immune function at the time of testing	Not determined	Not reported	Authors found that in children with no exposure to TB, the QFT-G was positive in only one of the 65 children, although all of them were positive by the TST at 5 mm and 64.6% at 10 mm. They also found that there was a significant relationship between higher responses to mitogen-positive control and increasing age of the children
Connell 2006[158]	Observational study. Australia. Some children born in high prevalence countries 52%	Children aged < 18 years with a high risk of latent TB infection	Contact with high risk as defined by siblings or parents recently diagnosed with TB disease, clinical suspicion of TB disease and those recently immigrated from high prevalence of TB	IGRA (QFT-G) 0.35 IU/ml positive response	TST PPD 10 IU of tuberculin. Positive if 15 mm in individuals with evidence of prior BCG, > 5 mm in TB contacts regardless of BCG and > 10 mm for all others	Concordance between TST and IGRA poor overall k = 0.3. 70% of TST positives were negative by IGRA. 65% of TST positives had a known TB contact	Not determined	John Burge Trust, VIC, Australia	Recommended further studies to clarify predictive values

continued

TABLE 53 Studies in children included in CG117[10] (*continued*)

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Connell 2008[159]	Observational study. Australia/ Australia and some born in high prevalence countries. 52% BCG vaccinated	96 children from 6 months of age to 19 years. Children who were at risk of latent TB or with suspected TB infection were eligible for inclusion. At risk was defined as a recent TB contact and/or recent immigration from a country of high prevalence of TB	38 participants had LTBI TST positive with no additional symptoms. 49 patients TST negative with no confirmation of active TB Contacts were either household or non-household	IGRA (QFT-G), T-SPOT.*TB*	TST PPD 10 IU of tuberculin. Positive > 10 mm	Out of 100 patients, 38 were TST positive of which 16 were household contacts, 6 non-household contacts and 6 had no known contacts to active TB. 49 were TST negative, of which 10 were household contacts, 1 non-household contact and 38 had no known contacts with active TB	Authors conclude the need for longitudinal studies for determination of predictive values	Not reported	Interesting how latent and uninfected participants were defined. LTBI: those who were TST positive but with no other symptoms and chest radiograph not suggestive of TB. Uninfected: defined as a well-child with negative TST or child with symptoms potentially suggestive of TB but in whom investigations for TB were negative or a child with an alternative diagnosis and complete recovery in the absence of specific TB treatment

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Hansted 2009[160]	Observational study done in Lithuania. All participants were BCG vaccinated	10–17 year olds	Study subjects who had been in contact with a case of infectious TB were divided into three groups. (1) Culture confirmed; (2) high-risk group; those living with a family member with infectious TB or having contact with such a person at school. Those in this group were free from symptoms. (3) Low risk; those who have no identifiable risk of TB(no known risk of contact with TB patient, no symptoms and no complaints	IGRA (TSPOT.*TB*)	TST Mantoux test SSI PPD RT-23, 2TU positive if > 10 mm	60% high-risk TST positive. 17.8% IGRA positive Calculated RR 3.375. For the low risk 65.4% were TST positive while 9.6% were IGRA positive. Calculated RR 6.8. The total number of discordant results was 54 out of 97 subjects in both high-risk and low-risk populations. Out of 61 TST positive patients 51 were IGRA negative	Not recorded	No records of funding	Authors conclude that identifying latent TB in children using this method is useful, especially in countries like Lithuania which have a high incidence of TB despite a high coverage with BCG vaccination
Higuchi 2007[162]	Observational prospective. Japan. Japanese students all BCG vaccinated	349 aged 15–16 years. Patients were all male and previously BCG vaccinated. They attended the same high school as a student diagnosed with active TB	Students stratified into two groups those with close contact (sharing of classes with index case; 210) and those with limited contact (not attending classes with the index case; 139)	QFT-G. Considered positive when > 0.35 IU/ml	TST (defined standard test dose of tuberculin PPD equivalent to 2.5 tuberculin units). Erythema used instead of induration. An erythema of > 30 mm considered positive for a BCG vaccinated individual	The distribution of TST responses in both close and limited contacts was similar. ($p = 0.20$)	Follow up of 91 students with positive TST but negative QFT-G showed no signs of active TB after 3.5 years of follow up	Ministry of Health Labour and Welfare Japan	Partial verification only patients with positive TST were tested with QFT-G. Authors suggest that similar positive rates of TST in both strata of exposed groups suggest limited transmission of MTB

continued

TABLE 53 Studies in children included in CG117[10] (*continued*)

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Higuchi 2009[161]	Prospective observational study Japan. Participants from Japan BCG vaccination done	313 participants between the ages of 8–12 years. In a Japanese school	Participants were exposed to an index case in the school. Close contact participants were those who had daily contact (at 90 hours contact). Casual participants: total of < 18 hours	IGRA (QFT-G) 0.35 IU/ml positive response	TST 0.1 ml [PPD NIPPON (BCG Manufacturing Tokyo Japan)] Equivalent to 3 TU PPD-S	QFT-G positivity in close contacts 9.8% as compared with 1.8% in casual contacts ($p = 0.02$). TST (5 mm) positivity in close contacts 52.6% as compared with 67.2% ($p = 0.078$). TST (10 mm) 34.2% compared with 28.7% ($p = 0.488$)	Not recorded. No child with negative QFT result developed active TB after 3 years. 3 out of 298 QFT negatives had a positive after 1 year	Not recorded	Authors suggest that QFT has the same performance characteristics in 8–12 year olds as adults. Suggestion of testing contacts 3 months after the end of exposure as an appropriate and sensitive approach
Lighter 2009[163]	Observational prospective	253 children aged < 18 years (mean age 9 years). Age stratified as follows < 24 months, 24–59 months, 60 months. Recruited from the well child clinic, paediatric chest clinic and paediatric inpatient ward. 42% were female. 72 received a single vaccination, 59 had visible BCG scars	Level of exposure graded as minimal (No known risk), low/ moderate risk factors [(birth in or travel to a disease-endemic region and/or living with a household member with specific risks (emigrating from a disease-endemic region, having HIV, or having a history of imprisonment, homelessness, or intravenous drug use)]. High (known direct contact with TB index case)	QFT-G. Considered positive when > 0.35 IU/ml and > 25% than nil control value	TST (Mantoux technique). Considered positive with induration of > 10 mm	Proportion of QFT-G positive results for children with increasing gradients of M tuberculosis exposure Minimal –0% of TST +and –ve Low/ moderate 6% of TST –ve and 19% TST+ were QFT-G+. High 0% of TST –ve and 100% of TST+ case were QFT-G+	Not determined	Pott's memorial foundation and the Thrasher Research Fund	Cut off of 0.35 IU/ml not validated especially for very young children who produce on average less IFN-8 than school-aged children and adults

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Okada 2008[164]	Observational/ Japan	They used 161 index cases and 217 contacts aged ≤5 years	Contacts stratified by varying risk of infection as classified by smear and culture result of index cases. (A) Smear –ve with positive or negative culture. (B) Smear positive grade 1+ including scanty smear. (C) Smear positive grade 2+. (D) Smear positive grade 3+	IGRA (QFT-G) 0.35 IU/ml positive response	TST 0.1 ml [PPD NIPPON (BCG Manufacturing Tokyo Japan)] Equivalent to 2.5 TU PPD-S	Measured concordance rates and kappa values by smear positivity of index cases and by age of children. Concordance 0.87, 0.906, 0.837, 0.893 and 0.877 overall, kappa 0.308, 0.711, 0.536, 0.774 and 0.626 overall. Also measured multivariate ORs for positive results for both TST and QFT-G. The following covariates were analysed. Sex, age, BCG scar, period from final contact and smear positivity	Not determined	Japan International Cooperation Agency	Smear positivity of index cases was the most important factor for positivity of both TST and QFT-G
Tsiouris 2006[165]	Observational/ United States/ South Africa	1741. Mean age of 5–15 years	Participants grouped according to the status of contact they were living with. (A) Current case of active TB in the household. (B). Past case of active TB. (C) Current and past case of active TB	IGRA (QFT-G)	TST PPD RT23 (2 tuberculin units were used)	Univariate analysis showed the likelihood of having a positive IGRA increased with increasing age ($p = 0.011$) as did having a TST >10 mm. Overall agreement increased with increasing cut-off of TST 0.52, 0.56 and 0.62 for 5 mm, 10 mm and 15 mm, respectively	Not determined	Aeras Global TB vaccine foundation	IGRA performed well without indeterminate results. The inability to obtain adequate blood specimen from 16.7% of participants is a drawback which is likely to be true of any whole-blood based paediatric test

continued

TABLE 53 Studies in children included in CG117[10] (*continued*)

Bibliography reference (Ref ID)	Study type/ country of study/origin of participants/BCG vaccination	Number/age/ patient characteristics	Exposure status/ contact/gradient	Type of test	Reference standard	Sensitivity and specificity modified measure of effect	Positive and negative predictive values	Source of funding	Additional comments
Winje 2008[192]	Cross sectional study/Norway/ determined by presence of scar	14–15 year olds	Factors associated with latent TB investigated include. Origin, sex, exposure to TB, travel history. Children grouped into western born, second generation and first generation	IGRA (QFT-G) 0.35 IU/ml positive	TST PPD RT23 (2 tuberculin units were used)	9% of 511 TST positive children were IGRA positive. They determined adjusted ORs for a positive IGRA for origin of child and exposure. 0.9 (0.3–2.4) and 3.3 (1.6–6.2) for second generation and first generation, respectively, as compared with Western born. 2.9 (1.1–7.6) comparing exposure with non-exposure of TB	Not determined	Division of infectious disease control at the Norwegian Institute of Public Health	The authors conclude that factors other than TB infection are widely contributing to positive TST results in this group and indicate the improved IGRA specificity for latent TB

ID, identification; PPD-S, purified protein derivatives; RR, relative risk; TU, tuberculin unit.

Immunocompromised people

TABLE 54 Studies in immunocompromised people included in CG117[10]

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Balcells 2008[167]	Observational study of individuals from Chile. HIV positive patients. Mean CD4 count 393/µl (range 100–977 µl) 116 mean age 38.8 years (range 21–71 years). Older age, history of previous TB disease, previous known exposure to a case of active pulmonary TB, health-care workers or individuals working with homeless people, residence in prison	TST (Mantoux method. 2 TU) dose of PPD RT23)	IGRA (QFT)	Correlation between TST and IGRA results in HIV-positive individuals IGRA+ / IGRA– / Total TST+ 9 2 11 TST– 8 90 98 Total 17 92 109 They also performed univariate analysis for a positive LTBI test depending on several factors TB risk factors	Not determined	Supported by a grant from the Department of the Pontificia, University of Chile. IGRA were supplied at reduced price by Cellestis	Authors observed that, multivariate analysis confirmed that past TB was independently associated with a positive TST ($p = 0.016$) as well as a higher CD4 count ($p = 0.044$). For IGRA past TB was the only factors significantly associated with a positive result. ($p = 0.041$)

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

<table>
<tr><th>Bibliography (Ref ID)</th><th>Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics</th><th>Reference test</th><th>Index test</th><th>Specificity and sensitivity or modified measure of effect/measures of agreement</th><th>Positive and negative predictive values</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td>Bartalesi 2009[168]</td><td>398 participants with rheumatic diseases requiring the use of biological drugs in Italy. Participants were treated with systemic corticosteroids, conventional DMARDs, and TNF-α inhibitors. Risk factors associated with LTBI included birth or residence in high prevalence area, close contact to patients with sputum-positive TB</td><td>TST (5 units PPD)</td><td>IGRA (QFT)</td><td>Overall results
<table><tr><th></th><th>IGRA+</th><th>IGRA–</th><th>Total</th></tr><tr><td>TST+</td><td>39</td><td>35</td><td>74</td></tr><tr><td>TST–</td><td>13</td><td>306</td><td>319</td></tr><tr><td>Total</td><td>52</td><td>341</td><td>393</td></tr></table>Also presented ORs adjusting for the association of risk factors for TB infection and IGRA and TST positivity
<table><tr><th rowspan="2">Number of risks</th><th colspan="2">IGRA+</th><th colspan="2">TST+</th></tr><tr><th>OR</th><th>p-value</th><th>OR</th><th>p-value</th></tr><tr><td>0</td><td>1</td><td></td><td>1</td><td></td></tr><tr><td>1</td><td>3.3</td><td><0.05</td><td>2.57</td><td><0.05</td></tr><tr><td>>2</td><td>5.71</td><td><0.05</td><td>5.35</td><td><0.05</td></tr></table></td><td>Not determined</td><td>Not recorded</td><td>Until further data are available on the implication of discordant TST/IGRA results, a strategy of simultaneous TST and IGRA testing in populations with low prevalence of BCG vaccination should maximise the sensitivity of LTBI diagnosis</td></tr>
</table>

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Cobanoglu 2007[169]	106 divided into groups 1 and 2. Group 1 (38 healthy individuals), group 2 (68 patients with chronic inflammatory diseases). 87% of these patients were on immunosuppressive medications such as methotrexate, methylprednisolone, prednisolone. The study was conducted in the University Faculty of Medicine in Ankara, Turkey	TST 0.1 ml (5TU) of PPD	IGRA (QFT)	Results stratified by age to adjust for supposed BCG effect < 25 years (57 participants) Group 1 9/25 discordant results All TST+ IGRA– Group 2 17/32 discordant results 16 (TST+ IGRA–) 1 (TST– IGRA+) > 25 years (40 participants) Group 1 4/11 discordant results 3 (TST+ IGRA–) 1 (TST– IGRA+) Group 2 13/29 discordant results All 13 (TST+ IGRA–) 9 had IGRA indeterminate results of whom 7 were immunocompromised	Not determined	Not recorded	Authors say study should be accepted as a basis for the design of future studies that will be helpful for physicians to decide whether or not the IGRA is more sensitive than TST to detect LTBI before the use of TNF-α blockers
Jones 2007[170]	207 HIV-infected individuals with a mean age of 47 years. 52% were male. They were also stratified according to CD4 count < 100, 19; 101–199, 24; 200–499, 88; > 500, 70. Study conducted in Mount Sinai Medical Centre in New York, New York, NY, USA	TST 0.1 ml (5 TU PPD)	IGRA (QFT)	Overall concordance between IGRA and TST results Ind, IGRA–, IGRA+, Total TST– 10 172 6 188 TST+ 0 8 5 13 Total 10 180 11 201 Ind, indeterminate.	Not determined	QuantiFERON kits donated by Cellestis	IGRA is able to distinguish between indeterminate tests and those that are truly negative. In contrast, a negative TST does not differentiate between individuals who are anergic and those who might have a truly negative TST

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

<table>
<tr><th>Bibliography (Ref ID)</th><th>Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics</th><th>Reference test</th><th>Index test</th><th>Specificity and sensitivity or modified measure of effect/measures of agreement</th><th>Positive and negative predictive values</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td>Luetkemeyer 2007[171]</td><td>294 HIV-infected patients sampled from two cohorts based in the United States. 55% of participants had lived or worked in homeless shelter, prison, hospital, or a drug rehabilitation unit or were born in a country with high TB incidence, or had had contact with an active TB case</td><td>TST (5TU PPD)</td><td>IGRA (QFT)</td><td>196 participants with both TST and IGRA results valid had the following overall result
<table><tr><th></th><th>TST+</th><th>TST–</th><th>Total</th></tr><tr><td>IG+</td><td>8</td><td>11</td><td>19</td></tr><tr><td>IG–</td><td>10</td><td>167</td><td>177</td></tr><tr><td>Total</td><td>18</td><td>178</td><td>196</td></tr></table>Results were also stratified by CD4 count
<table><tr><th colspan="5">CD4+ STRATA (cells/mm^3)</th></tr><tr><th></th><th>< 100</th><th>100–350</th><th>> 350</th><th>Total</th></tr><tr><td>IG+</td><td>0</td><td>6</td><td>19</td><td>25</td></tr><tr><td>IG–</td><td>26</td><td>101</td><td>127</td><td>254</td></tr><tr><td>IG(I)</td><td>5</td><td>4</td><td>6</td><td>15</td></tr><tr><td>Total</td><td>31</td><td>111</td><td>152</td><td>294</td></tr><tr><td>TST+</td><td>0</td><td>7</td><td>12</td><td>19</td></tr><tr><td>TST–</td><td>21</td><td>76</td><td>89</td><td>186</td></tr><tr><td>Total</td><td>21</td><td>83</td><td>101</td><td>205</td></tr></table></td><td>Not determined</td><td>Not recorded</td><td>Authors noted that until further data are available on the implication of discordant TST and IGRA results, a strategy of simultaneous TST and QFT testing where feasible would maximize potential LTBI diagnoses in HIV-infected patients</td></tr>
</table>

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Mandalakas 2008[172]	43 HIV-infected participants were enrolled in this study. 23 children and 20 adults. The mean age of adults was 18.7 years, the mean for children was 4.4 years. Study was conducted in South Africa	TST (2 TU 0.1 ml PPD RT23)	IGRA (QFT and T.SPOT.*TB*)	Discordant results for TST and IGRAs TSPOT+ TST– / TSPOT– TST+ All 29.7 / 10.8 Children 39.1 / 13.0 Adults 14.3 / 7.1 QFT+ TST– / QFT– TST+ All 0 / 26.9 Children 0 / 25.0 Adults 0 / 28.6	Not determined	Funded by Bill and Melinda Gates Foundation	Authors commented that no indeterminate results were observed in children with a CD4 count higher than adults. Adults with indeterminate results tended to have low CD4 counts and negative TST results

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Manuel 2006[173]	153 patients with chronic liver disease who were candidates for liver transplant. Patients had various risk factors such as contact with active TB patient, born or stay in country with high prevalence of TB. Study was conducted in a preliver transplant clinic in Canada	TST	IGRA (QFT)	Overall results 5 mm cut-off TST+ / TST– / Total IGRA+ 25 9 34 IGRA– 12 95 107 Total 37 104 141 10 mm cut-off TST+ / TST– / Total IGRA+ 18 16 34 IGRA– 9 98 107 Total 27 114 141 Indeterminate IGRA result 12/153 = 7.8%	Not determined	Test kits provided by Cellestis Ltd	Authors conclude that study demonstrates that IGRA and TST performed similarly for the diagnosis of LTBI in a population with end-stage liver disease

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Matulis 2008[174]	142 participants of which 126 received immunosuppressive therapy. 50% were female. AntiTNF, DMARDS and corticosteroids were the medicines they received. The mean age was 48 years. Study was conducted in a University Hospital in Berne Switzerland	TST (2 TU 0.1 ml PPD RT23)	IGRA (QFT)	Overall results TST+ TST– Un Total IG+ 10 5 2 17 IG– 34 60 23 117 Indeterminate 2 4 2 8 Total 46 69 27 142 Multivariate analysis were presented as ORs Corticosteroid treatment (yes, no) OR IGRA = 1.11 (0.30–4.14) OR TST = 0.74 (0.32–1.72) DMARDs treatment (yes, no) OR IGRA = 2.34 (0.52–10.6) OR TST = 0.75 (0.32–1.77) TNF-α inhibitors OR IGRA = 0.19 (0.05–0.76)	Not determined	Study funded by Swiss commission for Rheumatic Disease and the Swiss National Science Foundation	They did a multivariate analysis which did not include analysis for the participants which had two or more immunosuppressant medications

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Piana 2007[175]	138 immunosuppressed haematology patients in Italy. All patients were identified as nosocomial contacts of a case of smear positive TB. No information on graded exposure. Study was conducted in a chemotherapy unit in Italy	TST 0.1 ml (5 TU) of Siebert PPD	IGRA (T-SPOT.*TB*)	Overall result IGRA+ / IGRA– / Ind / Ins T cell / Total TST+ 21 3 0 0 24 TST– 34 57 5 2 98 No res 6 8 1 1 16 Total 61 68 6 3 138 Ind, indeterminate; Ins, insufficient; No res, no result. Results also stratified by pathological WBC count Pathological ($< 4.3 \times 10^3$ or $> 10.8 \times 10^3$ WBC/mm^{-3}) IGRA 44.3% +ve TST 14.5% +ve Non-pathological IGRA 44.6% +ve TST 25.9+ve	Not determined	T-SPOT.*TB* kits provided by Oxford Immunotech	It was important to determine whether or not the higher apparent prevalence of infection found with IGRA was due to the TST being falsely negative due to anergy, or to the IGRA being falsely positive in a number of patients

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Ponce de Leon 2008[176]	Cross sectional study conducted in Peru. 106 rheumatoid arthritis patients, of whom 73% were receiving methotrexate and 91% were receiving prednisolone at a dose of < 10 mg daily. They also recruited 97 controls	TST (Mantoux method. 2 TU dose of PPD RT23)	IGRA (QFT)	Overall results showing TST and IGRA results of immunosuppressed patients and controls	Not determined	Not recorded	Authors concede that a limitation of the study was the lack of a gold standard method for diagnosing LTBI. They attempted to compensate for this by evaluating both diagnostic tests in RA patients and matched controls. Data indicate that IGRA is more accurate than the TST in RA patients but cannot determine absolute sensitivity of both tests

RA patients

	TST+	TST–	Total
IG+	21	24	45
IG–	6	50	56
Total	27	74	101

RA, rheumatoid arthritis.

Control

	TST+	TST–	Total
IG+	50	5	55
IG–	11	27	38
Total	61	32	93

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

<table>
<tr><th>Bibliography (Ref ID)</th><th>Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics</th><th>Reference test</th><th>Index test</th><th>Specificity and sensitivity or modified measure of effect/measures of agreement</th><th>Positive and negative predictive values</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td>Richeldi 2009[177]</td><td>369 participants who were prospectively enrolled into the following immunosuppressed groups. Liver transplantation candidates, chronically HIV-infected patients and patients with haematological malignancies. Study participants were evaluated in a referral centre in Italy. Only about 3.6% patients were BCG vaccinated</td><td>TST (5 IU PPD)</td><td>IGRA (T-SPOT.TB) and (QFT)</td><td>Overall results
<table><tr><th></th><th>LTC</th><th>HIV</th><th>HM</th></tr><tr><td></td><td>120</td><td>116</td><td>95</td></tr><tr><td>TST+</td><td>20</td><td>6</td><td>10</td></tr><tr><td>TST–</td><td>100</td><td>110</td><td>85</td></tr><tr><td>TSP+</td><td>32</td><td>4</td><td>25</td></tr><tr><td>TSP–</td><td>87</td><td>112</td><td>69</td></tr><tr><td>TSP.I</td><td>1</td><td>0</td><td>1</td></tr><tr><td>QFT+</td><td>28</td><td>5</td><td>17</td></tr><tr><td>QFT–</td><td>80</td><td>104</td><td>73</td></tr><tr><td>QFT.I</td><td>12</td><td>7</td><td>5</td></tr></table>HM, haematologic ,malignancies;
LTC, liver transplantation candidates;
QFT.I, indeterminate result;
TSP.I indeterminate result.</td><td>Not determined</td><td>Not recorded</td><td>Study shows that the performance of IGRA, both in terms of rates of positive results and in diagnostic agreement varies greatly across different categories of patients who are at increased risk of TB reactivation. Because of the importance of targeting such high-risk groups, for effective TB control, we advise caution when interpreting the results of IGRA among immunosuppressed patients</td></tr>
<tr><td>Schoepfer 2008[178]</td><td>212 participants consisting of 114 Crohn's disease, 44 ulcerative colitis 10 indeterminate colitis and 44 controls. Study was conducted in Switzerland</td><td>TST (2 TU 0.1 ml PPD RT23)</td><td>IGRA (QFT)</td><td>Overall results
<table><tr><th>Diagnosis</th><th>n</th><th>BCG</th><th>IGRA+</th><th>TST+</th></tr><tr><td>IBD</td><td>168</td><td>+ve</td><td>12/118</td><td>27/118</td></tr><tr><td></td><td></td><td>–ve</td><td>2/50</td><td>3/50</td></tr><tr><td>Control</td><td>44</td><td>+ve</td><td>3/33</td><td>17/33</td></tr><tr><td></td><td></td><td>–ve</td><td>1/11</td><td>2/11</td></tr></table>IBD, inflammatory bowel disease.</td><td>Not determined</td><td>Not recorded</td><td>Authors concluded that the application of TST for detecting LTBI is limited in RA patients by the frequent presence of anergy. Combined IGRA assay and TST can aid in detecting LTBI in RA patients receiving adalimumab therapy</td></tr>
</table>

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Shovman 2009[179]	Study performed in Israel. 35 rheumatoid arthritis patients and 15 controls	TST (2 TU 0.1 ml PPD RT23)	IGRA (QFT)	Overall results **TST results as percentage** RA: +ve 45, –ve 17, Anergy 37 Control: +ve 15, –ve 7, Anergy 78 RA, rheumatoid arthritis. **IGRA results by percentage** RA: +ve 11.4, –ve 60, Indeterminate 28.6 Control: +ve 13, –ve 87, Indeterminate 0 RA, rheumatoid arthritis.	Not determined	Not recorded	The authors commented that the high rate of indeterminate results reduces the clinical utility of IGRA and questions its use in the diagnosis of LTBI in rheumatoid arthritis patients

continued

TABLE 54 Studies in immunocompromised people included in CG117[10] (*continued*)

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Soborg 2009[180]	302 patients with inflammatory disease were included. 153 had rheumatoid arthritis, 40 spondyloarthropathies, 51 sarcoidosis and 58 participants presenting with other conditions such as psoriatic arthritis. Patients either received DMARDs or corticosteroid treatment. The study was conducted in the rheumatology department of the Heart centre in Copenhagen, Denmark	TST (2 TU 0.1 ml PPD RT23)	IGRA (QFT)	Results presented as risk ratios which determined the associations between factors relevant to TB infection and test reactivity to either IGRA or TST Corticosteroid treatment (yes, no) RR IGRA = 0.5 (0.1–1.6) RR TST = 0.4 (0.1–1.0) DMARDs treatment (yes, no) RR IGRA = 0.7 (0.3–1.7) RR TST = 1.3 (0.7–2.3) CD4 count (< 500 > 500) RR IGRA = 1 (0.2–3.2) RR TST = 1.5 (0.7–3.3) **Danish Guideline** TST– / TST+ IGRA– 180 / 36 IGRA + 9 / 9 **US Guideline** TST– / TST+ IGRA– 159 / 57 IGRA+ 9 / 9	Not recorded	Not recorded	Interesting that authors stated that study was not designed to address the question of disease progression, as protocol recommended prophylactic treatment to test-positive patients

Bibliography (Ref ID)	Number of participants. Type of study/country of origin. Immunocompromised condition/medicines. Risk factors. Characteristics	Reference test	Index test	Specificity and sensitivity or modified measure of effect/measures of agreement	Positive and negative predictive values	Source of funding	Comments
Talati 2009[181]	336 HIV-positive patients of mean age of 42 years. Patients had a past medication history of LTBI, diabetes mellitus, chronic renal insufficiency, history of malignancy, anytime smoker and intravenous drug use. Study done in the USA	TST 0.1 ml (5 TU) of Siebert PPD	IGRA (TSPOT.*TB* AND QFT)	Reported a CD4 count of < 200 as associated with an indeterminate result for both IGRAs OR = 3.6 (1.9,6.8)	Not determined	Partly supported by Centers for Disease Control and Prevention (CDC)	Authors commented that given the results of the study and the limited data currently available it was unclear if IGRAs can be used alone for the diagnosis of LTBI in HIV-infected individuals
Vassilopoulos 2008[182]	Observational study Some were on DMARD and various other immunosuppressive medicines such as steroids 70 participants with various rheumatic diseases with a mean age of 60 years. The study was conducted in an outpatients rheumatology clinic in Athens, Greece	TST (Mantoux method 2 TU dose of PPD RT23)	IGRA (T-SPOT.*TB*)	Overall results showing discordant and concordant results between tests TST+ / TST– / Total IG+: 12 / 4 / 16 IG–: 15 / 39 / 54 Total: 27 / 43 / 70	Not determined	Not recorded	Authors concluded that at this point based on the available data, replacement of the TST by the TSPOT cannot definitely be recommended. More data examining the tests cost, feasibility and reproducibility as well as the outcome of antiTNF treated rheumatic patients with discordant TST/ TSPOT results are needed before recommendations can be made

–ve, negative; +ve, positive; DMARD, disease-modifying antirheumatic drug; ID, identification; IG, interferon gamma; RA, rheumatoid arthritis; TU, tuberculin unit; Un, unavailable.

Recent arrivals from countries with a high incidence of tuberculosis

TABLE 55 Studies in recent arrivals from countries with a high incidence of TB included in CG117[10]

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Brodie 2008[183]	Prospective	123	Not specifically recorded	United States/ does not mention countries of origin of immigrants	Patients > 5 years. Study group were those who had had contact with active TB patients and controls were those who had not had any contact. A lot of the patients were recent immigrants with a high rate of BCG vaccination	IGRA (ESAT-6 and CFP-10)	TST	Overall agreement between TSPOT.*TB* and TST was 64% and the kappa value was 0.33 (0.19–0.48). For BCG-vaccinated people it was 56% (43–68%) and 0.22 (0.06–0.37) respectively. In non-vaccinated people it was 82% (68–96%) and 0.64 (0.38–0.91)	Yes	Oxford Immunotech	Does not mention how they determined either those with ATB or LTBI. Used contact status as surrogate for LTBI and used that as gold standard. Does not give indication of prevalence or incidence of countries of origin of immigrants
Carvalho 2007[184]	Observational cross-sectional/ retrospective	130	Immigrants from countries with at least an incidence of 50 per 100,000	Italy/sub-Saharan Africa, Northern Africa, Eastern Europe, Asia, Latin America	32 female 98 male. Median age 28 years (range 19–50 years). Immigrants from high-incidence countries within the last 5 years	IGRA (QFTBG) threshold level 0.35 IU/ml	TST (threshold 10 mm)	Association of discordance/ concordance between two tests and BCG scar, sex, age, race, previous TB contact. Overall agreement was 71% k coefficient = 0.37. 100% agreement between TST and IGRA for induration below 10 mm	No data	Lombardia Region grant no 286/98	BCG vaccination independently negatively associated with discordance between tests. 0.28 (0.1–0.77) $p = 0.01$. BCG scar not always good indicator of BCG vaccination. Overall k coefficient = 0.37. 100% agreement between TST and IGRA for induration below 10 mm

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Diel 2008[186]	Observational prospective study	1794	Incidence of TB in Hamburg, Germany reported to be 10.8 per 100,000	Germany/noted as 'foreign born' but cases progressing to TB documented as from Turkey, Angola	Close contacts of sputum-smear positive cases with at least 40 hours exposure in a closed room. Age range between 0 and 60 years, with most (87.5%) falling between the 16–50 range. 28% were migrants from 29 different countries	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST (threshold 5 mm and 10 mm)	Overall kappa statistics 0.276 and 0.119 and 0.616 for BCG vaccinated and non BCG, respectively. For the concordance the values were 69.2%, 44.2% and 90.7% respectively. OR for a positive test if foreign born adjusted for BCG vaccination, age and exposure time were determined as follows. TST 5 mm 5.81 (3.6–9.1), 10 mm 5.2 (3.2–8.4), QFT 2.28 (1.3–3.9)	Not determined	No declared sponsor	Specific countries of origin of migrants not mentioned
Diel 2006[185]	Observational prospective study	311	TB incidence rate in Hamburg 12 per 100,000. Immigrants from countries with incidence of at least 20 per 100,000	Germany/25 different countries including former Soviet Union and Turkey	Close contacts of sputum-smear positive cases. Contacts with <40 hours contact time were excluded. Mean age 28.5 years Previous BCG vaccination 157 (50.8%), foreign/ German (27.1%/ 72.9)	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST 5 mm = 137/309 TST (28/137 positive by IGRA) 10 mm = 64/309 15 mm = 25/309	Overall kappa statistics 0.2, 95% CI 0.14 to 0.23. Concordant results 197/309 (63.8%). Positive result 169/172 (98.2%). Negative result 28/137 (20.4%). Concordance for 5 mm between BCG vaccination 38.9% k = 0.08 (0.026–0.08). Not vaccinated 89.5% k = 0.58 (0.4–0.68) for 10 mm, 77.1% k = 0.35 (0.24–0.35) for no BCG, and 94.1% k = 0.68 (0.46–0.81) for BCG. For TST (5 mm) OR = 5.4, TST (10 mm) 7.3 and 4.7 QFT	No data	No sponsor	For QFT-only origin is an independent predictor of a positive test result. For TST BCG vaccination also acts an independent predictor. Study does not mention how the specific countries or how recent migrants had been in the country
Franken 2007[187]	Prospective cross-sectional study	909	Range from < 10, 10–49, 50–99, 100–199 > 200) per 100,000	Netherlands/ Bosnia Kyrgystan Iraq and Afghanistan	Army personnel who had returned from mission (738) in high-incidence countries compared with new recruits (171) who had not been on mission	IGRA QFGinTube (ESAT-6 CFP-10, TB7.7)	TST (threshold 10 mm and 15 mm)	Discordance and concordance between tests. Overall concordance and kappa values were determined to be 82% and 0.19 respectively for 10 mm cut-off and 92.3% and 0.24 respectively for 15 mm TST cut-off	No data		Study not clear with regard to the definition of LTBI

continued

TABLE 55 Studies in recent arrivals from countries with a high incidence of TB included in CG117[10] (*continued*)

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Janssens 2008[188]	Observational prospective study	295	TB incidence 20 per 100,000 in Geneva. Incidence in countries from which immigrants originated between (50–>100) per 100,000	Switzerland/ countries not specified but categorised by incidence	Mean age 40 years (range 16–83 years). Foreign born 73.9% (218). Contacts were exposed to cavitary TB 105 (35.6%), non-cavitary TB 168 (56.9%) and pulmonary TB 22 (7.5%)	IGRA (ESAT-6, CFP-10) (T-SPOT.*TB*)	TST induration 5 mm 173 (58.6%), 10 mm 148 (50.2%), 61 mm (20.7%)	Overall concordant results showed 60.7% TST 5 mm, 63.6% 10 mm, 63.9% 15 mm. Kappa values were 0.24, 0.27 and 0.19 respectively. BCG Non-vaccinated subjects concordant results were 78.4%, 76.5% and 78.4% respectively while kappa values were 0.47, 0.41 and 0.28 for 5 mm, 10 mm and 15 mm respectively when comparing with IGRA. aOR for sex, BCG and incidence in country of origin (< 50 per 100,000 is used as baseline) showed these variables were independent predictors of a positive result 2.07 (1.22–3.51), 2.98 (1.39–6.41) 3.67 (1.40–1.90) respectively for TST 5 mm. Only incidence in country of origin showed the significant association with a positive result for TST 10 mm 2.22 (1.15–4.27) and 3.84 (1.61–9.20) for 50–99 per 100,000 and > 100 per 100,000 respectively. < 50 per 100,000 was baseline. For IGRA, age by 10-year increments and incidence in country of origin were the independent predictors of a positive result. 1.30 (1.06–1.6) for age and 2.17 (1.13–4.15) and 2.62 (1.18–5.82), respectively, for two categories of incidence	Not determined	Ligue Pulmonaire Genevoise	Countries of origin of foreign-born nationals not listed. Not very specific of exclusion of positive results if any of chest radiography. In the analysis they did not mention if they adjusted for immunocompromised individuals. They were only 6%. The TB incidence of Geneva from where they recruited was 20 per 100,000. They did not use that as the baseline value in calculations

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Kik 2009[189]	Observational retrospective study	821	Not specifically recorded	Netherlands/ South America, Asia, sub-Saharan Africa	Participants aged > 16 years. Close contacts of sputum smear positive TB patients. Foreign born and second generation immigrants	IGRA (QET-GIT, TSPOT.*TB*) (ESAT-6, CFP-10, TB7.7)	TST (threshold 5 mm 10 mm and 15 mm)	Associations between test results and remote exposure, defined as birth outside Europe and North America. Attributable fraction to particular risk factors calculated. Overall kappa values TST 15 mm 0.418 for QFT and 0.379 for TSPOT.*TB*. For 10 mm they were 0.198 and 0.190 respectively. Agreement values were 71.3% and 69.9% for QFT and TSPOT.*TB* respectively for 15 mm. For 10 mm they were 62.1% and 64.9% respectively. The continent of birth was the only variable which was independently associated with a positive result for TST 10 mm, *p*-value for trend 0.031. Both QFT and TSPOT.*TB* also showed a positive result independently associated with continent of birth and age	No data	Netherlands Organisation for Health Research and Development	Partial verification was performed on those with TST > 5 mm. Possibility of inclusion of patients with past active TB infections. Vague about the level of contact. Does not indicate duration of contact with infected individuals. Does not mention what they did with positive or negative CXRs. They do not mention how deduced LTBI

continued

TABLE 55 Studies in recent arrivals from countries with a high incidence of TB included in CG117[10] (*continued*)

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Nienhaus 2008[190]	Observational cross-sectional/ retrospective	1040	Incidence of TB in Germany reported to be < 6 per 100,000 and > 20 per 100,000 in countries from where the immigrants originated	Germany/ Germany Turkey, Eastern Europe and Africa	Study population 1040 healthy individuals. Mean age of 31.6 years 61.8% female, 25.4% foreign born, 43.4% had previous BCG vaccination. 41.8% HCW	IGRA (QFTBG) threshold level 0.35 IU/ml positive result 100/1033	TST (threshold 5 mm 311/ 1033 (30.1%) 10 mm = 191/ 1033 (18.5%) 15 mm = 69/ 1033 (6.7%)	Agreement 5 mm 74.8%, 10 mm 84.2%, 15 mm 89.8%. Kappa statistics 5 mm (0.26) 10 mm (0.37) 15 mm (0.33.) BCG vaccinated 5 mm (0.12) 10 mm (0.28) 15 mm (0.34). No vaccination 5 mm (0.5) 10 mm (0.54) 15 mm (0.3) aOR for positive TST (10 mm) for foreign birthplace was 4.6 (3.21–6.53) as compared with German birth, for QFT it was 2.6 (1.71–4.09)	No data	No sponsor reported	Although study states the population consisted of health persons they have said nothing to rule out symptomless TB by chest radiography. TST at 10 mm could possibly be confounded by sex, foreign birthplace and BCG vaccination. QFT could be confounded by age and foreign birthplace. TST +/QFT- discordance is associated with foreign birthplace. Authors explain that such discordance might be explained by resolved or old TB infections that are detected by TST and not QFT
Porsa 2006[191]	Cross-sectional/ observational	474	TB prevalence in United States < 10 per 100,000 of foreign born the prevalence reported 25–300 per 100,000	United States/ Mexico, Jamaica, Nicaragua, Ecuador, El Salvador, Honduras, the Philippines and Brazil	Adult inmates > 18 years. 114 female, 295 male. 370 born in the United States, 39 foreign born. 344 patients had prior incarceration. There was a mix of Caucasian African-American and Hispanic ethnicities	IGRA (ESAT-6 and CFP-10) (QFG-In-Tube)	TST induration 10 mm	Kappa statistics for discordance and concordance between TST and QFGT. Adjusted ORs calculated to determine which factors including ethnicity, old age, foreign birth and prior incarceration were more associated with discordance	Not determined	Health Resources and Services Administration Bureau of health professions Grant. Kits provided by Cellestis	On logistic regression African-American ethnicity only variable associated with positive results for both assays. Mentioned that positive IGRA indicates more recent and ongoing infection while positive TST indicates a remote infection in the past. Hence sensitivity appeared better in TSTs than IGRAs

Bibliographic reference (Ref ID)	Study type	Number of participants	Prevalence/ incidence	Country of study/origin of participants	Participant characteristics	Type of test	Reference standard	Sensitivity and specificity/modified measure of effect	Positive/negative predictive values or modified	Source of funding	Additional comments
Winje 2008[166]	Observational cross-sectional/ retrospective	1000	TB incidence rate in Norway 6.3 per 100,000	Norway/Iraq, Somalia, Russia, Iran, Eritrea, Afghanistan, sub-Saharan Africa	Asylum seekers. At least 18 years of age. 75.1% male and 24.9% female	IGRA (ESAT-6 and CFP-10) (QFG-In-Tube)	TST (threshold 6 mm) 460/ 912 (50.4%) 10 mm 311/ 921 (34.1%) 15 mm (15.5%)	Agreement 72% for 6 mm, 79% 10 mm, 78% 15 mm. Kappa 6 mm 0.43 (0.37–0.49), 10 mm 0.51 (0.45–0.57), 15 mm 0.39 (0.32–0.47), statistics 0.43 (0.37–0.49). aOR continent of origin with Asia as baseline for TST 15 mm 3.8 and 3.3 for QFT	Not determined		Definite prevalence or incidence not recorded for countries of origin. For QFT, BCG vaccination and sex were not independent predictors of a positive result while country of origin, age group and level of exposure independently predicted a positive test. For TST 15 mm the variables which independently predicted a positive result were sex, country of origin and level of exposure

aOR, adjusted odds ratio; CXR, chest radiography; HCW, health-care worker; ID, identification.

Appendix 6 List of studies excluded from the clinical effectiveness review with reasons for exclusion ($n = 424$)

MEDLINE

Number	Author ID	Details	Reason(s) for exclusion
1	Abud-Mendoza C	Should tuberculin skin test be positive to give latent tuberculosis treatment before tumor necrosis factor-alpha inhibitors in selected patients in developing countries? *J Rheumatol* 2010;**37**:672–3; author reply 673	Letter
2	Abu-Taleb AM	Interferon-gamma release assay for detection of latent tuberculosis infection in casual and close contacts of tuberculosis cases. *East Mediterr Health J* 2011;**17**:749–53	Mixed population and/or no subgroup of interest
3	Ahmadinejad Z	Diagnosis of latent tuberculosis infection in candidates for kidney transplantation (comparison of two tests). *Acta Med Iran* 2012;**50**:305–10	No construct validity
4	Altet-Gomez N	Diagnosing TB infection in children: analysis of discordances using in vitro tests and the tuberculin skin test. *Eur Respir J* 2011;**37**:1166–74	Results for TST and IGRA were combined
5	American College Health Association	Tuberculosis screening and targeted testing of college and university students. *J Am Coll Health* 2011;**59**:670–7	Guideline
6	Andrisani G	Comparison of Quantiferon-TB Gold versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease patients. *J Gastrointestin Liver Dis* 2013;**22**:21–5	No construct validity
7	Anibarro L	Tuberculin skin test and interferon-γ release assay show better correlation after the tuberculin 'window period' in tuberculosis contacts. *Scand J Infect Dis* 2011;**43**:424–9	Mixed population and/or no subgroup of interest
8	Anonymous	Proceedings of the Second Global Symposium on Interferon-Gamma Release Assays. Dubrovnik, Croatia, May 30–1 June 2009. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):3–70	Abstract
9	Baboolal S	Comparison of the QuantiFERON-TB Gold assay and tuberculin skin test to detect latent tuberculosis infection among target groups in Trinidad and Tobago. *Pan Am J Public Health* 2010;**28**:36–42	Inappropriate proxy for LTBI
10	Basu Roy R	Identifying predictors of interferon-γ release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette–Guérin?: a pTB-NET collaborative study. *Am J Respir Crit Care Med* 2012;**186**:378–84	No construct validity
11	Belard E	Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. *Inflamm Bowel Dis* 2011;**17**:2340–9	No construct validity

Number	Author ID	Details	Reason(s) for exclusion
12	Bergot E	Observational study of QuantiFERON-TB gold in-tube assay in tuberculosis contacts in a low incidence area. *PLOS ONE* 2012;**7**:e43520	Mixed population and/or no subgroup of interest
13	Bienek DR	Evaluation of an interferon-gamma release assay, T-SPOT.*TB*, in a population with a low prevalence of tuberculosis. *Int J Tuberc Lung Dis* 2009;**13**:1416–21	Mixed population and/or no subgroup of interest
14	Bottger EC	Interferon-γ release assays and the risk of developing active tuberculosis. *Am J Respir Crit Care Med* 2012;**185**:786–7; author reply 787	Letter
15	Bua A	Tuberculin skin test and QuantiFERON in children. *New Microbiol* 2013;**36**:153–6	No construct validity
16	Camlar SA	Performance of tuberculin skin test and interferon gamma assay for the diagnosis of latent tuberculosis infection in juvenile idiopathic arthritis. *Clin Rheumatol* 2011;**30**:1189–93	No construct validity
17	Campainha S	Negative predictive value of TST and IGRA in anti-TNF treated patients. *Eur Respir J* 2012;**40**:790–1	Letter
18	Carvalho AC	Contact investigation based on serial interferon-gamma release assays (IGRA) in children from the hematology-oncology ward after exposure to a patient with pulmonary tuberculosis. *Infection* 2013;**41**:827–31	IGRA vs. IGRA only (no TST)
19	Cassone A	High rate of Quantiferon positive and tuberculin negative tests in infants born at a large Italian university hospital in 2011: a cautionary hypothesis. *Pathog Glob Health* 2012;**106**:8–11	Review
20	Cheallaigh CN	Interferon gamma release assays for the diagnosis of latent TB infection in HIV-infected individuals in a low TB burden country. *PLOS ONE* 2013;**8**:e53330	No construct validity
21	Chou CH	Comparison of 2 interferon-gamma assays and Roche Cobas Amplicor *Mycobacterium tuberculosis* assay for rapid diagnosis of tuberculosis among patients with suspected tuberculosis in Taiwan. *J Microbiol Immunol Infect* 2009;**42**:251–7	IGRA vs. IGRA only (no TST)
22	Chung WK	Serial testing of interferon-gamma-release assays for the diagnosis of latent tuberculosis in hemodialysis patients. *J Infect* 2010;**61**:144–9	Serial testing, conversion and reversion rates
23	Connell DW	A comparison between interferon gamma release assays and the tuberculin skin test in the contact tracing of patients with chronic kidney disease. *Thorax* 2011;**66**:729–30; author reply 730	Letter
24	Connell TG	Indeterminate interferon-gamma release assay results in children. *Pediatr Infect Dis J* 2010;**29**:285–6	Letter
25	Critselis E	The effect of age on whole blood interferon-gamma release assay response among children investigated for latent tuberculosis infection. *J Pediatr* 2012;**161**:632–8	No construct validity
26	Dagnew AF	Diagnosis of latent tuberculosis infection in healthy young adults in a country with high tuberculosis burden and BCG vaccination at birth. *BMC Res Notes* 2012;**5**:415	Mixed population and/or no subgroup of interest
27	Davies MA	Detection of tuberculosis in HIV-infected children using an enzyme-linked immunospot assay. *AIDS* 2009;**23**:961–9	Active TB

Number	Author ID	Details	Reason(s) for exclusion
28	de Andrade Lima E	Evaluation of an IFN-gamma assay in the diagnosis of latent tuberculosis in patients with psoriasis in a highly endemic setting. *Acta Derm Venereol* 2011;**91**:694–7	No construct validity
29	de Kantor IN	Diagnosis of latent tuberculosis infection in BCG-vaccinated subjects in China. *Int J Tuberc Lung Dis* 2011;**15**:1560–1; author reply 1561	Letter
30	Del Tedesco E	Does anti-TNF therapy influence the performance of *Mycobacterium tuberculosis* antigen-specific interferon-gamma assays? A French multicenter experience. *Inflamm Bowel Dis* 2011;**17**:1824	Letter
31	Denholm JT	Immigration screening for latent tuberculosis infection. *Med J Aus* 2013;**198**:524	Letter
32	Denholm JT	Immigration screening for latent tuberculosis infection. *Med J Aus* 2013;**199**:654	Letter
33	Deuffic-Burban S	Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. *Int J Tuberc Lung Dis* 2010;**14**:471–81	Economic study
34	Diel R	Enhanced cost–benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany. *Respir Med* 2009;**103**:1838–53	Economic study
35	Dilektasli AG	Is the T-cell-based interferon-gamma releasing assay feasible for diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country? *Jpn J Infect Dis* 2010;**63**:433–6	Mixed population and/or no subgroup of interest
36	Doberne D	Preanalytical delay reduces sensitivity of QuantiFERON-TB gold in-tube assay for detection of latent tuberculosis infection. *J Clin Microbiol* 2011;**49**:3061–4	No relevant outcomes; population ineligible
37	Dowdy DW	Tests for latent tuberculosis infection and isoniazid preventive therapy. *Lancet Infect Dis* 2012;**12**:827–8	Letter
38	Dyrhol-Riise AM	Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantiFERON-TB Gold In-tube assay in outpatients from a tuberculosis low-endemic country. *BMC Infect Dis* 2010;**10**:57	Mixed population and/or no subgroup of interest
39	Garcia-Elorriaga G	Interferon in patients with HIV/AIDS and suspicion or latent tuberculosis infection. *Asian Pac J Trop Med* 2013;**6**:135–8	No construct validity
40	Garcia-Gasalla M	Use of Quantiferon-TB-Gold in Tube test for detecting latent tuberculosis in patients considered as candidates for anti-TNF therapy in routine clinical practice. *Enferm Infecc Microbiol Clin* 2013;**31**:76–81	No construct validity
41	Garcovich S	Clinical applicability of Quantiferon-TB-Gold testing in psoriasis patients during long-term anti-TNF-alpha treatment: a prospective, observational study. *J Eur Acad Dermatol Venereol* 2012;**26**:1572–6	No construct validity
42	Gautam M	Tuberculosis infection in the indigenous elderly white UK population: a study of IGRAs. *Int J Tuberc Lung Dis* 2012;**16**:564	Letter
43	Gilham L	Tuberculosis screening before biologics – T-SPOT for all? *J Rheumatol* 2011;**38**:179	Letter

Number	Author ID	Details	Reason(s) for exclusion
44	Girlanda S	ELISPOT-IFN-gamma assay instead of tuberculin skin test for detecting latent *Mycobacterium tuberculosis* infection in rheumatic patients candidate to anti-TNF-alpha treatment. *Clin Rheumatol* 2010;**29**:1135–41	Non-standard or in-house IGRA
45	Gogus F	Comparison of tuberculin skin test and QuantiFERON-TB gold in tube test in patients with chronic inflammatory diseases living in a tuberculosis endemic population. *Clin Exp Med* 2010;**10**:173–7	No construct validity
46	Gonzalez-Salazar F	Snapshot of Quantiferon TB gold testing in Northern Mexico. *Tuberculosis* 2011;**91**(Suppl. 1):34–7	Mixed population and/or no subgroup of interest
47	Goujon C	Diagnosis of latent tuberculosis infection (LTBI) before anti-TNF-alpha treatment – the tuberculin skin test is useful. *Eur J Dermatol* 2012;**22**:701–2	Case report
48	Grare M	QuantiFERON-TB Gold In-Tube as help for the diagnosis of tuberculosis in a French pediatric hospital. *Diagn Microbiol Infect Dis* 2010;**66**:366–72	No construct validity
49	Greveson K	Yield and cost effectiveness of mycobacterial infection detection using a simple IGRA-based protocol in UK subjects with inflammatory bowel disease suitable for anti-TNFalpha therapy. *J Crohns Colitis* 2013;**7**:412–18	IGRA only (no TST)
50	Griffin DW	Immigration screening for latent tuberculosis infection. *Med J Aus* 2013;**199**:654	Editorial
51	Grinsdale JA	Programmatic impact of using QuantiFERON-TB Gold in routine contact investigation activities. *Int J Tuberc Lung Dis* 2011;**15**:1614–20	Mixed population and/or no subgroup of interest
52	Gupta D	Interferon gamma release assay (QuantiFERON-TB Gold In Tube) in patients of sarcoidosis from a population with high prevalence of tuberculosis infection. *Sarcoidosis Vasc Diffuse Lung Dis* 2011;**28**:95–101	Active TB
53	Hanta I	Detection of latent tuberculosis infection in rheumatologic diseases before anti-TNFalpha therapy: tuberculin skin test versus IFN-γ assay. *Rheumatol Int* 2012;**32**:3599–603	No construct validity
54	Hardy AB	Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries. *Thorax* 2010;**65**:178–80	Economic study
55	Hatemi G	Quantiferon-TB Gold in tube assay for the screening of tuberculosis before and during treatment with tumor necrosis factor alpha antagonists. *Arthritis Res Ther* 2012;**14**:R147	No construct validity
56	He D	High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. *Clin Vaccine Immunol* 2013;**20**:842–7	IGRA only (no TST)
57	Helwig U	Corticosteroids and immunosuppressive therapy influence the result of QuantiFERON TB Gold testing in inflammatory bowel disease patients. *J Crohns Colitis* 2012;**6**:419–24	IGRA only (no TST)

Number	Author ID	Details	Reason(s) for exclusion
58	Hernandez-Garduno E	The positive predictive value of T-SPOT.*TB* and tuberculin skin test in patients with silicosis. *Am J Respir Crit Care Med* 2011;**183**:277; author reply 277–8	Letter
59	Hernandez-Garduno E	An update: the predictive value of QuantiFERON-TB-Gold In-Tube assay and the tuberculin skin test. *Am J Respir Crit Care Med* 2011;**183**:414; author reply 414–15	Letter
60	Hernandez-Garduno E	The predictive value of interferon-γ release assays and tuberculin skin test: what about those not vaccinated with Bacillus Calmette–Guérin? *Chest* 2013;**143**:1514–15	Letter
61	Higuchi K	Comparison of specificities between two interferon-gamma release assays in Japan. *Int J Tuberc Lung Dis* 2012;**16**:1190–2	IGRA vs. IGRA only (no TST)
62	Hill PC	Surprisingly high specificity of the PPD skin test for *M. tuberculosis* infection from recent exposure in the Gambia. *PLOS ONE* 2006;**1**:e68	Old pre-2009 study
63	Hoffmann M	Assessment of an Interferon-gamma release assay for the diagnosis of latent tuberculosis infection in haemodialysis patient. *Swiss Med Wkly* 2010;**140**:286–92	No construct validity
64	Huang YW	Latent tuberculosis infection among close contacts of multidrug-resistant tuberculosis patients in central Taiwan. *Int J Tuberc Lung Dis* 2010;**14**:1430–5	Mixed population and/or no subgroup of interest
65	Inanc N	Agreement between Quantiferon-TB gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 2009;**36**:2675–81	Included in CG117[10] and hence excluded from our search
66	Ingram PR	Latent tuberculosis infection in travelers: is there a role for screening using interferon-gamma release assays? *J Travel Med* 2009;**16**:352–6	Review
67	Jacobs S	The tuberculin skin test is unreliable in school children BCG-vaccinated in infancy and at low risk of tuberculosis infection. *Pediatr Infect Dis J* 2011;**30**:754–8	No relevant outcomes of interest; only children with positive TST result were given QFT-GIT
68	Jeong YJ	Positive tuberculin skin test or interferon-gamma release assay in patients with radiographic lesion suggesting old healed tuberculosis. *J Korean Med Sci* 2012;**27**:761–6	Mixed population and/or no subgroup of interest
69	Jo KW	Poor correlation between tuberculin skin tests and interferon-γ assays in close contacts of patients with multidrug-resistant tuberculosis. *Respirology* 2012;**17**:1125–30	Mixed population and/or no subgroup of interest
70	Katsenos S	Use of interferon-gamma release assay for latent tuberculosis infection screening in older adults exposed to tuberculosis in a nursing home. *J Am Geriatr Soc* 2011;**59**:858–62	Mixed population and/or no subgroup of interest
71	Kawamura LM	Interferon-γ release assays for prediction of tuberculosis. *Lancet Infect Dis* 2012;**12**:584	Letter
72	Kim EY	Performance of the tuberculin skin test and interferon-gamma release assay for detection of tuberculosis infection in immunocompromised patients in a BCG-vaccinated population. *BMC Infect Dis* 2009;**9**:207	No construct validity

Number	Author ID	Details	Reason(s) for exclusion
73	Kim JH	Factors influencing discrepancies between the QuantiFERON-TB gold in tube test and the tuberculin skin test in Korean patients with rheumatic diseases. *Semin Arthritis Rheum* 2013;**42**:424–32	No construct validity
74	Klein M	Quantiferon TB Gold and tuberculin skin tests for the detection of latent tuberculosis infection in patients treated with tumour necrosis factor alpha blocking agents. *Clin Exp Rheumatol* 2013;**31**:111–17	No construct validity
75	Kleinert S	Comparison of two interferon-gamma release assays and tuberculin skin test for detecting latent tuberculosis in patients with immune-mediated inflammatory diseases. *Ann Rheumatic Dis* 2010;**69**:782–4	Letter
76	Kowada A	Cost effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumor necrosis factor-alpha antagonist therapy. *Mol Diagn Ther* 2010;**14**:367–73	Economic study
77	Kowada A	Cost effectiveness of interferon-gamma release assay for school-based tuberculosis screening. *Mol Diagn Ther* 2012;**16**:181–90	Economic study
78	Kowada A	Cost effectiveness of the interferon-γ release assay for tuberculosis screening of hemodialysis patients. *Nephrol Dial Transplant* 2013;**28**:682–8	Economic study
79	Kwakernaak AJ	A comparison of an interferon-gamma release assay and tuberculin skin test in refractory inflammatory disease patients screened for latent tuberculosis prior to the initiation of a first tumor necrosis factor alpha inhibitor. *Clin Rheumatol* 2011;**30**:505–10	No construct validity
80	Lange B	Indeterminate results of a tuberculosis-specific interferon-gamma release assay in immunocompromised patients. *Eur Respir J* 2010;**35**:1179–82	Letter
81	Laskin BL	Cost-effectiveness of latent tuberculosis screening before steroid therapy for idiopathic nephrotic syndrome in children. *Am J Kidney Dis* 2013;**61**:22–32	Economic study
82	Latorre I	IFN-γ response on T-cell based assays in HIV-infected patients for detection of tuberculosis infection. *BMC Infect Dis* 2010;**10**:348	No construct validity
83	Lee SS	High prevalence of latent tuberculosis infection in dialysis patients using the interferon-gamma release assay and tuberculin skin test. *Clin J Am Soc Nephrol* 2010;**5**:1451–7	No construct validity
84	Legesse M	Community–based cross-sectional survey of latent tuberculosis infection in Afar pastoralists, Ethiopia, using QuantiFERON-TB Gold In-Tube and tuberculin skin test. *BMC Infect Dis* 2011;**11**:89	Mixed population and/or no subgroup of interest
85	Legesse M	Association of the level of IFN-γ produced by T cells in response to *Mycobacterium tuberculosis*-specific antigens with the size of skin test indurations among individuals with latent tuberculosis in a highly tuberculosis-endemic setting. *Int Immunol* 2012;**24**:71–8	Mixed population and/or no subgroup of interest

Number	Author ID	Details	Reason(s) for exclusion
86	Leung CC	Tests for prediction of active tuberculosis. *Lancet Infect Dis* 2012;**12**:6–8	Editorial
87	Lienhardt C	Evaluation of the prognostic value of IFN-gamma release assay and tuberculin skin test in household contacts of infectious tuberculosis cases in Senegal. *PLOS ONE* 2010;**5**:e10508. [Erratum published in *PLOS ONE* 2010;**5**(12)]	Mixed population and/or no subgroup of interest
88	Lighter-Fisher J	Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol* 2012;**119**:1088–95. [Erratum published in *Obstet Gynecol* 2012;**120**:399]	Mixed population and/or no subgroup of interest
89	Linas BP	Priorities for screening and treatment of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med* 2011;**184**:590–601	Economic study
90	Losi M	Tuberculosis infection in foreign-born children: a screening survey based on skin and blood testing. *Int J Tuberc Lung Dis* 2011;**15**:1182–4	No construct validity
91	Maden E	Evaluation of performance of quantiferon assay and tuberculin skin test in end stage renal disease patients receiving hemodialysis. *New Microbiol* 2011;**34**:351–6	No construct validity
92	Maeda T	Usefulness and limitations of QuantiFERON-TB Gold in Japanese rheumatoid arthritis patients: proposal to decrease the lower cutoff level for assessing latent tuberculosis infection. *Mod Rheumatol* 2010;**20**:18–23	Inappropriate proxy for LTBI; definition includes previous active TB
93	Maeda T	Comparison of QuantiFERON-TB Gold and the tuberculin skin test for detecting previous tuberculosis infection evaluated by chest CT findings in Japanese rheumatoid arthritis patients. *J Infect Chemother* 2011;**17**:842–8	No construct validity
94	Mahan CS	Concordance of a positive tuberculin skin test and an interferon gamma release assay in bacille Calmette–Guérin vaccinated persons. *Int J Tuberc Lung Dis* 2011;**15**:174–8	Mixed population and/or no subgroup of interest
95	Mancuso JD	Cost-effectiveness analysis of targeted and sequential screening strategies for latent tuberculosis. *Int J Tuberc Lung Dis* 2011;**15**:1223–30	Economic study
96	Mandalakas AM	Can we accurately diagnose tuberculosis infection in children? *Pediatr Infect Dis J* 2011;**30**:817–18	Letter
97	Mandalakas AM	Is screening immigrants for latent tuberculosis cost-effective? *Lancet Infect Dis* 2011;**11**:418–19	Editorial
98	Mandalakas AM	Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax* 2013;**68**:247–55	Economic study
99	Mandalakas AM	Detecting tuberculosis infection in HIV-infected children: a study of diagnostic accuracy, confounding and interaction. *Pediatr Infect Dis J* 2013;**32**:e111–18	No construct validity; two samples on exposure (HIV positive and HIV negative) were included together
100	Mariette X	Influence of replacing tuberculin skin test with ex vivo interferon release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy. *Ann Rheum Dis* 2012;**71**:1783–90	No construct validity

Number	Author ID	Details	Reason(s) for exclusion
101	Marques CD	Evaluation of an interferon gamma assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis. *Rheumatol Int* 2009;**30**:57–62	Inappropriate proxy for LTBI
102	Martin J	Comparison of interferon-γ release assays and conventional screening tests before tumour necrosis factor-α blockade in patients with inflammatory arthritis. *Ann Rheum Dis* 2010;**69**:181–5	IGRA vs. IGRA only (no TST)
103	Martyn-Simmons CL	Evaluating the use of the interferon-γ response to *Mycobacterium tuberculosis*-specific antigens in patients with psoriasis prior to antitumour necrosis factor-α therapy: a prospective head-to-head cross-sectional study. *Br J Dermatol* 2013;**168**:1012–18	No construct validity
104	Mendez-Echevarria A	Interferon-γ release assay for the diagnosis of tuberculosis in children. *Arch Dis Childhood* 2012;**97**:514–16	No construct validity; only for IGRA
105	Milman N	Quantiferon test for tuberculosis screening in sarcoidosis patients. *Scand J Infect Dis* 2011;**43**:728–35	IGRA only (no TST)
106	Minguez S	Interferon-gamma release assays in the detection of latent tuberculosis infection in patients with inflammatory arthritis scheduled for anti-tumour necrosis factor treatment. *Clin Rheumatol* 2012;**31**:785–94	No construct validity
107	Molicotti P	Performance of QuantiFERON TB in a student population at low risk of tuberculosis. *J Infect Develop Countries* 2012;**6**:100–1	Letter
108	Moran Mendoza O	Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection. *Eur Respir J* 2011;**38**:1237–8; author reply 1238–9	Letter
109	Moyo S	Tuberculin skin test and QuantiFERON assay in young children investigated for tuberculosis in South Africa. *Int J Tuberc Lung Dis* 2011;**15**:1176–81	Active TB
110	Mrozek N	Tuberculosis screening before biologic therapy. Comment about the article entitled 'role for interferon-gamma release assays in latent tuberculosis screening before TNF-alpha antagonist therapy' by Liote H *et al*. *Joint Bone Spine* 2011;**78**:655–6; author reply 656–7	Letter
111	Murakami S	Screening of tuberculosis by interferon-gamma assay before biologic therapy for rheumatoid arthritis. *Tuberculosis* 2009;**89**:136–41	Case–control study of test results
112	Nellore A	Screening strategies for tuberculosis in children with kidney disease: what is cost-effective? *Am J Kidney Dis* 2013;**61**:3–5	Letter
113	Nguyen MQ	What are the differences between the tuberculin skin test and the QuantiFERON-TB Gold test? *J Occupational Environ Med* 2012;**54**:1177–8	Editorial
114	Nkurununngi G	Determining *Mycobacterium tuberculosis* infection among BCG-immunised Ugandan children by T-SPOT.*TB* and tuberculin skin testing. *PLOS ONE* 2012;**7**:e47340	No construct validity
115	Ohnishi T	Comparison of QuantiFERON-TB Gold and the tuberculin skin test for the detection of previous tuberculosis infection evaluated by chest CT findings in Japanese rheumatoid arthritis patients. *J Infect Chemother* 2011;**17**:849–50	Letter

Number	Author ID	Details	Reason(s) for exclusion
116	Oni T	Smoking, BCG and employment and the risk of tuberculosis infection in HIV-infected persons in South Africa. *PLOS ONE* 2012;**7**:e47072	Non-standard or in-house IGRA
117	Onur H	Comparison of quantiferon test with tuberculin skin test for the detection of tuberculosis infection in children. *Inflammation* 2012;**35**:1518–24	Inappropriate proxy for LTBI
118	Ormerod LP	Further evidence supporting programmatic screening for, and treatment of latent TB Infection (LTBI) in new entrants to the UK from high TB prevalence countries. *Thorax* 2013;**68**:201	Letter
119	Pareek M	Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011;**11**:435–44	Economic study
120	Pareek M	Community-based evaluation of immigrant tuberculosis screening using interferon release assays and tuberculin skin testing: observational study and economic analysis. *Thorax* 2013;**68**:230–9	Economic study
121	Pattnaik S	Agreement between skin testing and QuantiFERON-TB Gold In-Tube assay (QFT-TB) in detecting latent tuberculosis infection among household contacts in India. *Indian J Tuberc* 2012;**59**:214–18	No construct validity
122	Petrescu L	Tuberculin skin test, interferon-gamma assay, and T cells subpopulations in hemodialysis patients. *J Ren Nutr* 2010;**20**(Suppl. 5):109–17	No construct validity
123	Pooran A	Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. *BMC Pulm Med* 2010;**10**:7	Economic study
124	Qumseya BJ	QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. *Inflamm Bowel Dis* 2011;**17**:77–83	No construct validity
125	Ramos JM	Contribution of interferon gamma release assays testing to the diagnosis of latent tuberculosis infection in HIV-infected patients: a comparison of QuantiFERON-TB Gold In Tube, T-SPOT.*TB* and tuberculin skin test. *BMC Infect Dis* 2012;**12**:169	Inappropriate proxy for LTBI
126	Riazi S	Rapid diagnosis of *Mycobacterium tuberculosis* infection in children using interferon-gamma release assays (IGRAs). *Allergy Asthma Proc* 2012;**33**:217–26	Active TB
127	Ringrose JS	Detecting latent tuberculosis infection during anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2011;**29**:790–4	No relevant outcomes
128	Santin M	Detection of latent tuberculosis by the tuberculin skin test and a whole-blood interferon-γ release assay, and the development of active tuberculosis in HIV-seropositive persons. *Diagn Microbiol Infect Dis* 2011;**69**:59–65	Mixed population and/or no subgroup of interest for construct validity
129	Sattah MV	Interferon-gamma release assay T-SPOT.*TB* and HIV-related tuberculosis. *Int J Tuberc Lung Dis* 2012;**16**:281–2	Letter
130	Sayarlioglu H	QuantiFERON-TB Gold test for screening latent tuberculosis infection in hemodialysis patients. *Tuberkuloz ve Toraks* 2011;**59**:105–10	No construct validity

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131	Schneider WJ	QuantiFERON-TB testing for latent tuberculosis infection in low-prevalence countries: making the most of an imperfect process. *Infect Control Hosp Epidemiol* 2011;**32**:1055	Letter
132	Serrano-Escobedo CJ	Performance of tuberculin skin test compared to QFT-IT to detect latent TB among high-risk contacts in Mexico. *Arch Med Res* 2013;**44**:242–8	Mixed population and/or no subgroup of interest
133	Seshadri C	Low sensitivity of T-cell based detection of tuberculosis among HIV co-infected Tanzanian in-patients. *East Afr Med J* 2008;**85**:442–9	Old pre-2009 study
134	Setiawati L	Effect of BCG vaccination and non-tuberculous *Mycobacterium* infection on interferon gamma specific assay and a tuberculin skin test among children with a tuberculosis contact in Surabaya, Indonesia. *Southeast Asian J Trop Med Public Health* 2011;**42**:1460–8	No construct validity
135	Shah M	Programmatic impact of QuantiFERON-TB Gold In-Tube implementation on latent tuberculosis diagnosis and treatment in a public health clinic. *PLOS ONE* 2012;**7**:e36551	Mixed population and/or no subgroup of interest
136	Shah M	QuantiFERON-TB gold in-tube implementation for latent tuberculosis diagnosis in a public health clinic: a cost-effectiveness analysis. *BMC Infect Dis* 2012;**12**:360	Economic study
137	Shanaube K	Risk factors associated with positive QuantiFERON-TB Gold In-Tube and tuberculin skin tests results in Zambia and South Africa. *PLOS ONE* 2011;**6**:e18206	Mixed population and/or no subgroup of interest
138	Shovman O	QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. *Int J Tuberc Lung Dis* 2009;**13**:1427–32	Included in CG117[10] and hence excluded from our search
139	Simsek H	Comparison of tuberculin skin testing and T-SPOT.*TB* for diagnosis of latent and active tuberculosis. *Jpn J Infect Dis* 2010;**63**:99–102	Mixed population and/or no subgroup of interest
140	Singanayagam A	Evaluation of screening methods for identification of patients with chronic rheumatological disease requiring tuberculosis chemoprophylaxis prior to commencement of TNF-alpha antagonist therapy. *Thorax* 2013;**68**:955–61	Inappropriate proxy for LTBI
141	Song Q	Evaluation of a new interferon-gamma release assay and comparison to tuberculin skin test during a tuberculosis outbreak. *Int J Infect Dis* 2012;**16**:e522–6	Non-standard or in-house IGRA
142	Song S	Performance of confirmatory interferon-γ release assays in school TB outbreaks. *Chest* 2012;**141**:983–8	QFT used as confirmatory test on subgroup of TST-positive patients
143	Soysal A	Diagnosing latent tuberculosis infection in haemodialysis patients: T-cell based assay (T-SPOT.*TB*) or tuberculin skin test? *Nephrol Dial Transplant* 2012;**27**:1645–50	No construct validity
144	Starke JR	Interferon-γ release assays for the diagnosis of tuberculosis infection in children. *J Pediatr* 2012;**161**:581–2	Letter
145	Stefan DC	Interferon-gamma release assays for the detection of *Mycobacterium tuberculosis* infection in children with cancer. *Int J Tuberc Lung Dis* 2010;**14**:689–94	No construct validity

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146	Steffen RE	Cost-effectiveness of Quantiferon-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. *PLOS ONE* 2013;**8**:e59546	Economic study
147	Sultan B	Comparison of two interferon-gamma release assays (QuantiFERON-TB Gold In-Tube and T-SPOT.*TB*) in testing for latent tuberculosis infection among HIV-infected adults. *Int J STD AIDS* 2013;**24**:775–9	IGRA vs. IGRA only (no TST)
148	Talati NJ	Diagnosis of latent tuberculosis infection among HIV discordant partners using interferon gamma release assays. *BMC Infect Dis* 2011;**11**:264.	No construct validity
149	Tannus Silva DG	Latent tuberculosis in rheumatoid arthritis: evaluating cellular response and high-resolution computed tomography. *Arch Bronconeumol* 2012;**48**:144–9	No construct validity
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151	Theodoropoulos N	Use of the QuantiFERON-TB Gold interferon-gamma release assay for screening transplant candidates: a single-center retrospective study. *Transplant Infect Dis* 2012;**14**:1–8	IGRA only (historical TST)
152	Thomas B	Concordance between tuberculin skin test and interferon-γ assay and interferon-γ response to mitogen in pediatric tuberculosis contacts. *Pediatr Pulmonol* 2011;**46**:1225–32	No construct validity
153	Thomas TA	Malnutrition and helminth infection affect performance of an interferon gamma-release assay. *Pediatrics* 2010;**126**:e1522–9	No construct validity
154	Uluk T	Evaluation of an interferon-gamma release assay in children with suspected tuberculosis in Papua New Guinea. *Pediatr Infect Dis J* 2013;**32**:187–9	No construct validity
155	Wassie L	Parasitic infection may be associated with discordant responses to QuantiFERON and tuberculin skin test in apparently healthy children and adolescents in a tuberculosis endemic setting, Ethiopia. *BMC Infect Dis* 2013;**13**:265	No construct validity
156	Weinfurter P	Predictors of discordant tuberculin skin test and QuantiFERON-TB Gold In-Tube results in various high-risk groups. *Int J Tuberc Lung Dis* 2011;**15**:1056–61	No construct validity
157	Wolf T	Tuberculosis skin test, but not interferon-γ-releasing assays is affected by BCG vaccination in HIV patients. *J Infect* 2013;**66**:376–80	No construct validity
158	Xie X	A T-cell-based enzyme-linked immunospot assay for tuberculosis screening in Chinese patients with rheumatic diseases receiving infliximab therapy. *Clin Exp Med* 2011;**11**:155–61	No construct validity
159	Yilmaz N	Comparison of QuantiFERON-TB Gold test and tuberculin skin test for the identification of latent *Mycobacterium tuberculosis* infection in lupus patients. *Lupus* 2012;**21**:491–5	No construct validity
160	Zhao J	Low agreement between the T-SPOT.*TB* assay and the tuberculin skin test among college students in China. *Int J Tuberc Lung Dis* 2011;**15**:134–6	No construct validity

ID, identification.

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161	No authors listed	Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders: erratum. *Curr Opin Rheumatol* 2011;**23**:504	Letter
162	No authors listed	Society for Adolescent Health and Medicine Annual Meeting: Impact of Trauma on Teens: Building the Safety Net Conference Proceedings. *J Adolesc Health* 2012;**50**(Suppl. 2)	Irrelevant
163	No authors listed	40th Annual Conference Abstracts, APIC 2013. *Am J Infect Control* 2013;**41**(Suppl. 6)	Abstract
164	No authors listed	World Tuberculosis Day Symposium 2012. *Tuberculosis* 2013;**93**(1)	Abstract
165	Abdel-Nabi EA	QuantiFERON vs. tuberculin testing in detection of latent tuberculous infection among chronic renal failure patients. *Egypt J Chest Dis Tuberc* 2014;**63**:161–5	No construct validity
166	Abdel-Samea SA	Comparative study between using QuantiFERON and tuberculin skin test in diagnosis of *Mycobacterium tuberculosis* infection. *Egypt J Chest Dis Tuberc* 2013;**62**:137–43	Mixed population and/or no subgroup of interest
167	Abraham B	Monitoring and management of latent tuberculosis in IBD patients on antiTNF therapy: a case series. *Am J Gastroenterol* 2013;**108**:S521–2	Abstract
168	Aggarwal P	Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol* 2012;**120**:398; author reply 398	Letter
169	Ahmad M	False-positive QuantiFERON Gold tests. *Chest* 2010;**138**:84A	Abstract
170	Ahmadinejad Z	Evaluation of QuantiFERON-gold (tuberculin skin test) for the identification of latent tuberculosis infection in would-be transplant recipient patients referring to an Iranian transplant clinic from September 2007 to December 2008. *Clin Microbiol Infect* 2010;**16**:S542	Abstract
171	Akpaka PE	Evaluation of cost and methods for detecting latent tuberculosis infection among target individual groups in Trinidad and Tobago. *Int J Infect Dis* 2010;**14**:e148	Abstract
172	Alberte-Castineiras A	Discordant QuantiFERON-TB Gold In-Tube and tuberculin skin test results in various high-risk groups. *Clin Microbiol Infect* 2012;**18**:548	Abstract
173	Andrisani G	Tubercolosis screening in Italian patients affected by inflammatory bowel disease: comparison of QuantiFERON-TB Gold versus tuberculin skin test. *Digest Liver Dis* 2010;**42**:S181–2	Abstract
174	Arias M	Performance of two interferon-gamma release assays (T-SPOT.*TB* and QuantiFERON-TB Gold in Tube) increase diagnostic yield of tuberculin skin testing for detection of latent tuberculosis in patients with inflammatory bowel disease. *Gastroenterology* 2011;**1**:S691	Abstract

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176	Awan S	Can Quanti-FERON-TB replace TST (Mantoux) as a screening tool prior to (biologics) anti-TNF therapy. *Irish J Med Sci* 2012;**181**:S75	Abstract
177	Bakir M	Use of T cell-based diagnosis of tuberculosis infection to optimize interpretation of tuberculin skin testing for child tuberculosis contacts. *Clin Infect Dis* 2009;**48**:302–12	Inappropriate proxy for LTBI
178	Behar SM	Use of the T-SPOT.*TB* assay to detect latent tuberculosis infection among rheumatic disease patients on immunosuppressive therapy. *J Rheumatol* 2009;**36**:546–51	Inclusion of TST-positive patients
179	Belard E	Effects of corticosteroid treatment on the performance of QuantiFERON Gold in-Tube test in the screening of latent tuberculosis infection. *Gastroenterology* 2010;**1**:S523	Abstract
180	Bergamini BM	Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. *Pediatrics* 2009;**123**:e419–24	IGRA vs. IGRA only (no TST)
181	Berry MPR	Systems biology approaches characterise the host response to tuberculosis. *Thorax* 2009;**64**:A10	Abstract
182	Bianchi L	Interferon-gamma release assay improves the diagnosis of tuberculosis in children. *Pediatr Infect Dis J* 2009;**28**:510–14	No construct validity
183	Blandinieres A	Deficient IFN-gamma response to *Mycobacterium tuberculosis* antigens in infants improved since 1 year of age. *Immunology* 2012;**137**:727–8	Abstract
184	Blandinieres A	QuantiFERON to diagnose infection by *Mycobacterium tuberculosis*: performance in infants and older children. *J Infect* 2013;**67**:391–8	No construct validity
185	Borkowska D	Interferon-gamma assays T-SPOT.*TB* for the diagnosis of latent tuberculosis infection. *Pneumonol Alergol Pol* 2011;**79**:264–71	Mixed population and/or no subgroup of interest
186	Borra H	Reliability of tuberculosis screening tests in patients receiving tumor necrosis factor antagonist therapy in a United States rheumatology clinic. *Arthritis Rheum* 2009;**60**:137	Abstract
187	Bortlik M	Usefulness of the QuantiFERON TB Gold test in assessing the necessity for TB prophylaxis in IBD patients treated with biologicals. *Gastroenterology* 2009;**1**:A197	Abstract
188	Bottger EC	Interferon-gamma release assays and the risk of developing active tuberculosis. *Am J Resp Crit Care Med* 2012;**185**:786–7	Abstract
189	Brebner J	Questionable utility of T-SPOT testing in a TB exposure incident on a clinical haematology unit. *Thorax* 2010;**65**:A103	Abstract
190	Bruzzese E	Gamma interferon release assays for diagnosis of tuberculosis infection in immune-compromised children in a country in which the prevalence of tuberculosis is low. *J Clin Microbiol* 2009;**47**:2355–7	Letter
191	Bua A	Epidemic of tuberculosis in a high school in Northern Sardinia. *Int J Mycobacteriol* 2012;**1**:161–3	No relevant outcomes

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193	Buonsenso D	Evaluation of a mathematical model proposed to predict the diagnosis of tuberculosis in children with cervical lymph node enlargement. *Int J Pediatr Otorhinolaryngol* 2012;**76**:1068–70	Letter
194	Buonsenso D	Pediatric tuberculosis in two tertiary hospitals in Rome: a 20-year retrospective study. *Arch Dis Childhood* 2012;**97**:A11–12	Abstract
195	Burgos JL	Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *Int J Tuberc Lung Dis* 2009;**13**:962–8	Economic study
196	Cagan Appak Y	Comparison of tuberculin skin testing and in vitro interferon-gamma release assay test for diagnosis of latent tuberculosis in children. *J Med Sci* 2013;**33**:1402–7	Foreign language (Turkish)
197	Cagatay T	The role of IGRA tests and tuberculin test for determination of latent tuberculosis in TNF-alpha antagonist users (candidates) [TNF-alpha antagonisti kullanacak hastalarda latent tuberkulozun belirlenmesinde IGRA testleri (quantiFERON-elispot) ve ppd'nin yeri]. *Turk Dermatoloji Dergisi* 2012;**6**:62–4	Foreign language (Turkish)
198	Capocci S	Screening for latent TB in HIV: are NICE and BHIVA guidance effective? *Thorax* 2011;**66**:A21–2	Abstract
199	Capocci S	Is testing for latent tuberculosis infection in an UK HIV clinic cost effective? *HIV Med* 2012;**13**:44	Abstract
200	Casas S	Diagnosis of tuberculosis infection in patients awaiting transplantation. *Clin Microbiol Infect* 2010;**16**:S73	Abstract
201	Castaneda-Hernandez DM	Importance of the use of interferon-gamma release assays in the epidemiological surveillance of tuberculosis *Rev Med Chile* 2012;**140**:128–9	Abstract
202	Cetin EA	QuantiFERON-TB gold test may be more advantageous than tuberculin skin test for screening latent tuberculosis infection in psychiatry clinics. *Balkan Med J* 2012;**29**:115–16	Abstract
203	Chang B	Interferon-gamma assay in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists in Korea. *Am J Resp Crit Care Med* 2010;**181**:A4773	Abstract
204	Chawla H	Use of the interferon-gamma release assay blood test to confirm latent tuberculosis infection in tuberculin skin test-positive immIGRAnts: Our experience at a Connecticut pulmonary clinic. *Am J Resp Crit Care Med* 2010;**181**:A4774	Abstract
205	Chen JW	Evaluation of a T-cell-based enzyme-linked immunospot assay for monitoring tuberculosis in patients with rheumatic diseases receiving Infliximab therapy. *Int J Rheum Dis* 2010;**13**:87	Abstract
206	Chen QF	Interferon-γ release assays screening for latent tuberculosis screening: a cost-effectiveness analysis. *Chinese J Evid Based Med* 2011;**11**:768–74	Foreign language (Chinese)

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207	Chun JK	The role of a whole blood interferon-γ releasing assay for the tracing of tuberculosis infection in bacilli Calmette Guérin vaccinated children. *Int J Infect Dis* 2010;**14**:e312	Abstract
208	Clark BJ	Detection of latent tuberculosis infection in patients with end stage renal disease: interferon-gamma release assays versus tuberculin skin test. *Am J Resp Crit Care Med* 2009;**179**:A5926	Abstract
209	Connell DW	Comparison between interferon-gamma release assays and the tuberculin skin test in the diagnosis of tuberculosis in patients with renal disease. *Thorax* 2009;**64**:A108	Abstract
210	Connell T	Interferon-γ release assays for the diagnosis of tuberculosis. *Pediatr Infect Dis J* 2009;**28**:758–9	Abstract
211	Costantino F	High level of disease activity in chronic inflammatory rheumatisms increases the rate of indeterminate interferon-gamma-release assay results for latent tuberculosis infection detection. *Arthritis Rheum* 2010;**62**:768	Abstract
212	Davarpanah MA	Association between PPD and QuantiFERON Gold TB test in TB infection and disease among HIV-infected individuals in Southern Iran. *Iran Red Crescent Med J* 2009;**11**:71–5	Included/excluded in CG117[10]
213	De Francisco R	Interferon-gamma release assays (T-SPOT.*TB* and QuantiFERON-TB GOLD in Tube) versus tuberculin skin testing for detection of latent tuberculosis in patients with inflammatory bowel disease. *J Crohns Colitis* 2011;**5**:S52–3	Abstract
214	De Leon DP	Comparison of IGRAs with TST for the detection of LTBI in RA patients in a TB endemic population. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):40–1	Abstract
215	Delgado Naranjo J	Comparative performance of QuantiFERON®-TB Gold IT versus tuberculin skin test among contact investigations for latent tuberculosis infection. *Med Clin* 2011;**137**:289–96	Foreign language (Spanish)
216	Del Tedesco E	Interferon gamma release assay (IGRA) and/or tuberculin skin test (TST) in inflammatory bowel disease population: discordance and performance. Best strategy for detecting tuberculosis. *Gastroenterology* 2010;**1**:S672–3	Abstract
217	Demkow U	Interferon gamma based tests as a new tool in diagnosis of latent tuberculosis. *Pneumonol Alergol Pol* 2011;**79**:261–3	Editorial
218	Denholm JT	Diagnosis and management of latent tuberculosis infection. *Med Today* 2010;**11**:72–6	Review
219	Diel R	The predictive value of interferon-gamma release assays and tuberculin skin test: what about those not vaccinated with bacillus Calmette–Guérin? Response. *Chest* 2013;**143**:1515–16	Abstract
220	Dominguez J	Role of the T-cell interferon-gamma release assays in preventing reactivation of latent tuberculosis infection in immunosuppressed patients in treatment with anti-TNF agents. *J Crohns Colitis* 2008;**2**:250–4	Old pre-2009 study
221	Eather G	Comparison of tuberculin skin test with an interferon-gamma release assay (IGRA) in screening for latent tuberculosis infection in a low prevalence population. *Respirology* 2012;**17**:17	Abstract

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223	Elzi L	Low sensitivity of an Interferon-gamma releasing assay (Elispot-TB™) for the diagnosis of latent tuberculosis in HIV-infected individuals. *Swiss Med Wkly* 2009;**139**:39S	Abstract
224	Erkens CG	Added value of interferon-gamma release assays in screening for tuberculous infection in the Netherlands. *Int J Tuberc Lung Dis* 2014;**18**:413–20	Mixed population and/or no subgroup of interest
225	Evans LC	IFN-gamma release assays improve detection of latent tuberculosis infection in tuberculin-anergic candidates for anti-TNF-alpha blockade. *Am J Resp Crit Care Med* 2009;**179**:A5927	Non-standard or in-house IGRA
226	Fernandez S	Use of interferon-gamma release assay (IGRA) and tuberculin skin test (TST) for tuberculosis screening in patients candidates for anti-TNF terapy in inflammatory bowel disease (IBD). *J Crohns Colitis* 2013;**7**:S58	Abstract
227	Ferrara G	Interferon-gamma-release assays detect recent tuberculosis re-infection in elderly contacts. *Int J Immunopathol Pharmacol* 2009;**22**:669–77	Mixed population and/or no subgroup of interest
228	Fontana R	Diagnosis and management of latent tuberculosis identified by the QuantiFERON assay in liver transplant patients. *Am J Transpl* 2010;**10**:97	Abstract
229	Francois C	Cost effectiveness analysis of strategies using new immunological diagnostic tests of latent tuberculosis infection before anti-TNF therapy. *Ann Rheum Dis* 2013;**72**:A538	Abstract
230	Gao KK	Comparison of detection performances between two kits for mycobacterium tuberculosis infection. *J Shanghai Jiaotong Uni Med Sci* 2011;**31**:1440–3	Foreign language (Chinese)
231	Gao Y	Evaluation of latent *Mycobacterium tuberculosis* infection screening using TSPOT.*TB* assay and TST in IMID patients prior to initiation of anti-TNF alpha therapy. *Int J Infect Dis* 2011;**15**:S103	Abstract
232	Garcia-Garcia JM	Comparison of tuberculin skin test and QuantiFERON-TB-Gold in Tube in the diagnosis of latent tuberculosis infection (LTBI) in a prospective community study of contacts. *Am J Resp Crit Care Med* 2010;**181**:A1789	Abstract
233	Garcia-Pedrazuela M	Evaluation of the use of QuantiFERON TB-Gold in the routine setting at a university hospital, 2007–2011. *Clin Microbiol Infect* 2012;**18**:544	Abstract
234	Garfein RS	Latent tuberculosis among persons at risk for infection with HIV, Tijuana, Mexico. *Emerg Infect Dis* 2010;**16**:757–63	IGRA only (no TST)
235	Gomes CMF	Clinical performance of 4 methods for detecting latent tuberculosis infection (LTbI) in patients with active chronic inflammatory arthritis taking TNFalpha blockers. *Arthritis Rheum* 2013;**65**:S1063	Abstract
236	Gonzalez-Diaz V	Efficiency of interferon-γ release assay for screening for latent tuberculosis in patients with systemic lupus erythematosus. *Lupus* 2013;**22**:48	Abstract

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238	Gray JM	Improvement in latent tuberculosis testing of HIV patients after switching from the tuberculin skin test to QuantiFERON-TB Gold-In-Tube. *Am J Resp Crit Care Med* 2010;**183**:A1197	Abstract
239	Greveson K	Comparative cost-effectiveness of IGRA to detect latent TB infection in UK inflammatory bowel disease patients initiating anti-TNFalpha agents. *Thorax* 2012;**67**:A87–8	Abstract
240	Guidi L	Screening inflammatory bowel disease patients for latent tubercolosis in Italy: comparison of QuantiFERON-TB Gold versus tuberculin skin test. *Gastroenterology* 2010;**1**:S526	Abstract
241	Hadaya K	Contribution of interferon gamma release assays to the diagnosis of latent tuberculosis infection after renal transplantation. *Respiration* 2013;**85**:590	Abstract
242	Hanjiu W	Application of the T-SPOT.*TB* assay to identify tuberculosis infection in children. *Acta Med Mediterr* 2013;**29**:443–6	No relevant outcomes
243	Hashemi Shahri M	To compare the performance of Quanti-FERON with the tuberculin skin test for identifying latent tuberculosis infection. *Iran J Epidemiol* 2012;**7**:57–65	Foreign language (Persian)
244	Hasunuma T	New tools for old diseases comparison of positive reaction of tuberculin skin test and QuantiFERON among healthy adult males in Japan. *Basic Clin Pharmacol Toxicol* 2010;**107**:321–2.	Abstract
245	Hayes, Inc.	*Interferon-Gamma Release Assays for Tuberculosis*. Lansdale, PA: Hayes, Inc.; 2012	Abstract
246	Hesseling AC	The predictive value of the ELIspot-based interferon-γ-release assay for tuberculosis disease. *Ann Intern Med* 2009;**150**:428–9	Letter
247	Hesseling AC	Highly discordant T cell responses in individuals with recent exposure to household tuberculosis. *Thorax* 2009;**64**:840–6	No construct validity
248	Higuchi K	Comparison of performance in two diagnostic methods for tuberculosis infection. *Med Microbiol Immunol* 2009;**198**:33–7	IGRA vs. IGRA only (no TST)
249	Hofland R	Should screening for latent tuberculosis infection be repeated after travel to tuberculosis endemic areas in patients treated with TNF-alpha inhibitor therapy? *Gastroenterology* 2012;**1**:S249	Abstract
250	Horsburgh CR	Latent tuberculosis infection in the United States. *N Engl J Med* 2011;**364**:1441–8	Editorial
251	Horvat RT	From the arm to the test tube: laboratory's new role in tuberculosis testing. *Clin Microbiol News* 2012;**34**:117–25	Review
252	Hosker HSR	How useful are interferon-gamma release assays in cases of suspected tuberculosis? *Thorax* 2009;**64**:A108	Abstract

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253	Hsia EC	QuantiFERON-TB Gold In-Tube test versus tuberculin skin test across RA, PsA, and AS patients prior to treatment with golimumab, a human anti-TNF antibody. *Arthritis Rheum* 2010;**62**:908	Abstract
254	Iqbal AZ	Cost-effectiveness of Using QuantiFERON Gold (QFT-G)® versus tuberculin skin test (TST) among US and foreign born populations at a public health department clinic with a low prevalence of tuberculosis. *Public Health Nurs* 2014;**31**:144–52	Economic study
255	Jackson C	Diabetes and latent tuberculosis infection: nested case–control study within the PREDICT cohort. *Thorax* 2013;**68**:A31–2	Abstract
256	James PM	The performance of QuantiFERON-TB Gold in-Tube (QFT-IT) test compared to tuberculin skin test (TST) in detecting latent tuberculosis infection (LTBI) in the presence of HIV coinfection in a high TB-burden area with BCG-vaccinated population. *J Int Assoc Provid AIDS Care* 2014;**13**:47–55	No construct validity
257	Jan Wu YJ	Different cut off of tuberculin skin test in latent tuberculosis screening in systemic lupus erythematosus, rheumatoid arthritis and ankylosing spondylitis with an intermediate tuberculosis burden population. *Ann Rheum Dis* 2013;**72**:A963–4	Abstract
258	Jegal Y	The significance of whole blood interferon-gamma assay in patients with history of pulmonary tuberculosis. *Am J Resp Crit Care Med* 2009;**179**:A4098	Abstract
259	Jeong JC	Utility of QuantiFERON-TB assay for prediction of tuberculosis development in kidney transplant patients in an intermediate-tuberculosis-burden country: lack of evidence for enhanced prediction for short-term tuberculosis development. *Transplant Proc* 2014;**46**:583–7	IGRA only (no TST) for construct validity
260	Jeong Y	Prevalence of latent tuberculosis infection in patients with radiographic lesions suggesting old healed tuberculosis. *Am J Resp Crit Care Med* 2011;**183**:A1190	Abstract
261	Jordan N	QuantiFERON Gold screening for latent tuberculosis: cost comparison with mantoux testing. *Rheumatology* 2009;**48**:i70	Abstract
262	Jung YJ	The 'either test positive' strategy for latent tuberculous infection before anti-tumour necrosis factor treatment. *Int J Tuberc Lung Dis* 2014;**18**:428–34	No construct validity
263	Kadavath S	Effectiveness of combining tuberculin skin test and interferon gamma release assays as a screening strategy for detecting latent tuberculosis infection in high risk patients with systemic lupus erythematosus. *Ann Rheum Dis* 2013;**72**:478	Abstract
264	Kalyoncu U	Comparison of QuantiFERON-TB test and TST in routine practice during anti-TNF treatment. *Ann Rheum Dis* 2013;**72**:231	Abstract
265	Karabela S	QuantiFERON TB Gold assay in tuberculosis diagnosis in patients from areas with high and low TB incidence. *Clin Microbiol Infect* 2009;**15**:S669–70	Abstract
266	Karabela S	QuantiFERON TB Gold in Tube assay for TB diagnosis: a two-year experience. *Clin Microbiol Infect* 2009;**15**:S392–3	Abstract

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267	Karimi A	Discrepancy between whole blood interferon gamma assay and tuberculin skin test for diagnosis of latent TB infection in BCG vaccinated children. *IUBMB Life* 2009;**61**:314	Abstract
268	Kariminia A	Comparison of QuantiFERON TB-G-test to TST for detecting latent tuberculosis infection in a high-incidence area containing BCG-vaccinated population. *J Eval Clin Pract* 2009;**15**:148–51	Mixed population and/or no subgroup of interest
269	Kashyap RS	Latent TB infection diagnosis in population exposed to TB subjects in close and poor ventilated high TB endemic zone in India. *PLOS ONE* 2014;**9**:e89524	Abstract
270	Kawamura LM	IGRAs in public health practice: economic issues. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):60–3	Economic study
271	Kenney A	Physicians inconsistently perform tuberculosis screening in inflammatory bowel disease patients managed with anti-TNF agents. *Inflamm Bowel Dis* 2011;**17**:S45	Abstract
272	Ketenci A	Comparison of whole blood gamma interferon assay and tuberculin skin testing in tuberculosis contacts. *Respirology* 2013;**18**:71	Abstract
273	Khalilzadeh S	Role of QuantiFERON-TB test in detection of children infected with mycobacterium tuberculosis. *Tanaffos* 2010;**9**:22–7	No construct validity
274	Kiet G	Comparing T-SPOT and tuberculosis skin testing screening methods for treatment acceptance and cost efficacy. *J Adolesc Health* 2012;**1**:S68	Abstract
275	Kik S	Predictive value of IGRAs. *Enfermedades Emergentes* 2009;**11**:178–9	Abstract
276	Kim C	Comparison of QuantiFERON-TB gold with tuberculin skin test for detecting latent tuberculosis infection before kidney transplantation. *Am J Transpl* 2013;**13**:341	Abstract
277	Kim EY	Performance of tuberculosis skin test and inferferon-γ release assay for detection of tuberculosis infection in immunocompromised patients in an intermediate burden country. *Respirology* 2009;**14**:A188	Abstract
278	Kim H	Clinical usefulness of ELISPOT assay for diagnosis of tuberculosis in a Korean population. *Clin Microbiol Infect* 2010;**16**:S545	Abstract
279	Kim JH	Evaluation of the usefulness of interferon-gamma release assays and tuberculin skin test for detection of latent mycobacterium tuberculosis infection in Korean rheumatic patients with biologic agents. *Arthritis Rheum* 2013;**65**:S560	Abstract
280	Kleinert S	Screening for latent tuberculosis infection (LTBI) performance of tuberculous skin test and interferon-gamma release assays (IGRA) under real life conditions. *Arthritis Rheum* 2010;**62**:782	Abstract
281	Kowada A	Cost effectiveness of IGRAs assays in Japan. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):59–60	Abstract
282	Kowada A	Cost effectiveness of interferon-gamma release assay for TB screening of HIV positive pregnant women in low TB incidence countries. *J Infect* 2014;**68**:32–42	Abstract

Number	Author ID	Details	Reason(s) for exclusion
283	Kruczak K	QuantiFERON-TBGIT (QFT) vs TST in diagnosis of latent tuberculosis (TB) infection (LTBI) in vaccinated population in Poland. *Am J Resp Crit Care Med* 2009;**179**:A5925	Abstract
284	Kruczak K	QuantiFERON-TBGIT (QFT) vs tuberculosis skin test (TST) in diagnosis of latent tuberculosis (Tb) infection (LTBI) in patients treated by oral glucocorticosteroids. *Am J Resp Crit Care Med* 2010;**181**:A4779	Abstract
285	Kumar P	Basic and clinical immunology – 3019. Gamma interferon release assay for diagnosis of latent tuberculosis – comparison with TB skin test. *World Allergy Organ J* 2013;**6**(Suppl. 1):P195	Abstract
286	Lagrange PH	A toolbox for tuberculosis (TB) diagnosis: an Indian multicentric study (2006–2008). Evaluation of QuantiFERON-TB Gold in Tube for TB diagnosis. *PLOS ONE* 2013;**8**:e73579.	Active TB
287	Lee J	Comparison of quantiferon-TB gold assay with tuberculin skin test in Korean children. *J Allergy Clin Immunol* 2010;**1**:AB152	Abstract
288	Lee JH	Poor agreement between QuantiFERON-TB Gold test and tuberculin skin test results for the diagnosis of latent tuberculosis infection in rheumatoid arthritis patients and healthy controls. *Korean J Intern Med* 2014;**29**:76–84	No construct validity
289	Lee SJ	Risk factors for latent tuberculosis infection in close contacts of active tuberculosis patients in South Korea. *Respirology* 2012;**17**:130	Abstract
290	Lee SSJ	Positive predictive value of interferon-gamma release assay for incident active tuberculosis in HIV-infected persons. *Retrovirology* 2012;**9**(Suppl. 1):P133	Abstract
291	Lee SSJ	Prediction of the risk of active tuberculosis in HIV-infection with an interferon-gamma release assay. *Lancet* 2013;**382**:16	Abstract
292	Lee T	Diagnosis of latent tuberculosis infection by using the QuantiFERON-TB Gold in-Tube test in children whose household contact has contagious pulmonary tuberculosis disease. *Int J Infect Dis* 2010;**14**:e307	Abstract
293	Leung CC	Evaluation of the T SPOT-*TB* test in the targeted screening of close contacts of smear-positive tuberculosis patients. *Am J Resp Crit Care Med* 2011;**183**:A1186	Abstract
294	Lim S	Risk of latent tuberculosis infection following exposure to active tuberculosis in at-risk children with rheumatic diseases. *Intern Med J* 2011;**41**:32	Abstract
295	Lim SC	Risk of latent tuberculosis in at-risk children with rheumatic diseases. *Pediatr Rheumatol* 2011;**9**(Suppl. 1):P218	Abstract
296	Linas BP	The cost effectiveness of tuberculin skin test and interferon gamma release assay screening for latent tuberculosis infection in the US. *Am J Resp Crit Care Med* 2011;**183**:A6337	Abstract
297	Lindemann M	Diagnosis of tuberculosis infection in patients awaiting liver transplantation. *Hum Immunol* 2009;**70**:24–8	No relevant outcomes

Number	Author ID	Details	Reason(s) for exclusion
298	Ling DI	Interferon-gamma release assay for pediatric tuberculosis: does it impact diagnostic and treatment decisions? *Am J Resp Crit Care Med* 2010;**181**:A4776	Abstract
299	Liza MI	Anti-TNFa therapy and tuberculosis risk: a two-centre experience. *Int J Rheum Dis* 2010;**13**:90	Abstract
300	Lombardi G	Tuberculosis infection in young children: a screening based on skin and blood testing. *Clin Microbiol Infect* 2012;**18**:548	Abstract
301	Lopez Y	Correlation between the response to *Mycobacterium tuberculosis* antigens and the tuberculin skin test in patients with rheumatoid arthritis in Colombia. *Biomedica* 2013;**33**:226–32	No construct validity
302	Losi M	Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in patients with rheumatic diseases. *Clin Microbiol Infect* 2010;**16**:S543	Abstract
303	Losi M	Role of the QFT-IT assay for the diagnosis of latent tuberculosis infection among adult immigrants. *Am J Resp Crit Care Med* 2011;**183**:A1194	Abstract
304	Machado A Jr	Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. *Int J Tuberc Lung Dis* 2009;**13**:446–53	Mixed population and/or no subgroup of interest
305	Machado J	Diagnosis of latent tuberculosis in patients with inflammatory bowel disease: prospective comparison between tuberculin skin test and IGRA test QuantiFERON TB-Gold. *J Crohns Colitis* 2011;**5**:S64	Abstract
306	Mahomed H	Predictive value of the TST vs. QuantiFERON-TB Gold in-Tube in adolescents in a high-burden setting. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):48–9	Presentation
307	Manosa M	Current incidence of active tuberculosis in IBD patients treated with anti-TNF agents: still room for improvement. *J Crohns Colitis* 2013;**7**:e499–500	Letter
308	Mardani M	Performance of QuantiFERON TB Gold test compared with the tuberculin skin test for detecting latent tuberculosis infection in lung and heart transplant candidates. *Exp Clin Transpl* 2014;**12**:129–32	No construct validity
309	Mardani M	Accuracy of QuantiFERON-TB Gold test versus tuberculin skin test to detect latent tuberculosis infection in HIV-positive individuals in Iran. *Clin Microbiol Infect* 2009;**15**:S391–2	Abstract
310	Mardani M	Performance of QuantiFERON-TB Gold test compared to tuberculin skin test in detecting latent tuberculosis infection in HIV-positive individuals in Iran. *Ann Thorac Med* 2010;**5**:43–6	No construct validity
311	Mariette X	Before beginning anti-TNF, a better targeted screening and a twice decrease frequency of latent tuberculosis (TB) with IFN gamma release assays (IGRA) compared with tuberculin skin test. Results in 396 patients from the ETAT study. *Arthritis Rheum* 2010;**62**:376	Abstract
312	Maritsi D	Assessment of quantiferon as a screening tool prior to initiation of infliximab: a single centre's perspective. *Clin Exp Rheumatol* 2011;**29**:402–3	Abstract

Number	Author ID	Details	Reason(s) for exclusion
313	Marra F	Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts. *Int J Tuberc Lung Dis* 2008;**12**:1414–24	Economic study
314	Martinez-Morillo M	Interferon-γ release assays in rheumatic patients: baseline study and in the course of anti-tumor necrosis factor-α agents. *Arthritis Rheum* 2011;**63**(Suppl. 10):1941	Abstract
315	Martinez-Morillo M	Interferon-gamma release assays in rheumatic patients: baseline study and in the course of anti-tumor necrosis factor-alpha agents. *Ann Rheum Dis* 2014;**71**(Suppl. 3):277	Abstract
316	Mateo L	Usefulness of in vitro interferon-release assays (IGRAS) for diagnosis of latent tuberculosis infection in rheumatic patients scheduled for anti-TNF-treatment. *Arthritis Rheum* 2009;**60**:996	Abstract
317	Matsubara J	Indeterminate and positivity rates of a commercially available enzyme-linked immunospot (ELISPOT) blood test in at-risk groups for tuberculosis infection. *Am J Infect Control* 2010;**38**:e48–9	Abstract
318	Matsubara J	Indeterminate and positivity rates of the T-SPOT.*TB* test in at-risk individuals screened for tuberculosis infection. *Am J Resp Crit Care Med* 2010;**181**:A6831	Abstract
319	Mehta B	Combining tuberculin skin test and interferon gamma release assays for latent tuberculosis infection screening may be necessary for the exclusion of latent tuberculosis in a high risk individuals with rheumatoid arthritis. *Arthritis Rheum* 2011;**63**(Suppl. 10):1190	Abstract
320	Mehta B	A proposed effective strategy to screening latent TB infection in RA patients. *Ann Rheum Dis* 2013;**71**(Suppl. 3):169	Abstract
321	Melath S	Screening for latent TB in patients with rheumatic disorders prior to biologic agents in a 'high-risk' TB population: comparison of two interferon gamma release assays. *Rheumatol Int* 2014;**34**:149–50	Abstract
322	Mendes MA	Contact screening in tuberculosis: can we identify those with higher risk? *Eur Respir J* 2013;**41**:758–60	Mixed population and/or no subgroup of interest
323	Mendoza OM	Interferon-gamma release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection. *Eur Respir J* 2011;**38**:1237–8	Letter
324	Meyssonnier V	Performance of Quantiferon® for the diagnosis of TB. *Med Mal Infect* 2012;**42**:579–84	Active TB
325	Milburn H	A comparison between interferon gamma release assays and the tuberculin skin test in the contact tracing of patients with chronic kidney disease response. *Thorax* 2011;**66**:730	Letter
326	Miller RF	Comparison of two interferon-gamma release assays (Quantiferon-TB Gold in-Tube and T-SPOT.*TB*) in screening for latent tuberculosis infection (LTBI) among HIV-infected adults attending an inner London HIV clinic. *Thorax* 2011;**66**:A72–3	Abstract

Number	Author ID	Details	Reason(s) for exclusion
327	Ministro P	Diagnosis of latent tuberculosis in patients with inflammatory bowel disease: prospective comparison between tuberculin skin test and interferon gamma release assay (IGRA) test. *Gastroenterology* 2011;**140**:S776	Abstract
328	Mittal C	QuantiFERON TB gold testing for latent tuberculosis is more frequently indeterminate in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:S62	Abstract
329	Mount C	Mantoux or gamma interferon (IGRA) – which test is best in children? *Thorax* 2011;**66**:A138–9	Abstract
330	Mulder C	Predictive value of the tuberculin skin test among newly arriving immigrants. *PLOS ONE* 2013;**8** e60130	IGRA only (no TST)
331	Munoz L	Prevention of tuberculosis associated with tumour necrosis factor antagonists. An 8-year observational cohort study. *Clin Microbiol Infect* 2012;**18**:33	Abstract
332	Neira-Munoz E	Extensive transmission of mycobacterium tuberculosis among children on a school bus. *Pediatr Infect Dis J* 2008;**27**:836–7	Abstract
333	Ni Cheallaigh C	Sensitivity, specificity and inter-test agreement of interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals with advanced immunodeficiency. *Clin Microbiol Infect* 2010;**16**:S72	Abstract
334	Nicol MP	Comparison of T-SPOT.*TB* assay and tuberculin skin test for the evaluation of young children at high risk for tuberculosis in a community setting. *Pediatrics* 2009;**123**:38–43	Inappropriate proxy for LTBI
335	Noorbakhsh S	Evaluation of the agreement between Quantiferon-TB assay and tuberculin skin test in TB infected cases: Tehran, Iran. *Int J Infect Dis* 2012;**16**:e288	Abstract
336	Novak S	Tuberculosis among patients treated with anti TNF inhibitors prior and after the use of Quantiferon test. *Clin Exp Rheumatol* 2009;**27**:710	Abstract
337	O'Flynn E	Quantiferon testing in mantoux negative patients commencing anti-TNF therapy identifies additional at risk patients. *Irish J Med Sci* 2012;**181**:S58	Abstract
338	Ong SY	How good are we at screening for infections prior to anti-TNF-alpha therapy? *J Gastroenterol Hepatol* 2012;**27**:113–14	Abstract
339	Oon H	The interferon-gamma release assay: experience from a tertiary dermatology center in the tropics. *J Am Acad Dermatol* 2013;**68**:AB135	Abstract
340	Ortakayla M	Concordance of the interferon-γ release assay (IGRA) and the tuberculin skin test (TST) for the screening of tuberculosis infection in the inflammatory rheumatic disease (IRD) population. *Chest* 2012;**142**(Suppl. 4):211A	Abstract
341	Ozbek S	Detection of latent tuberculosis infection in rheumatologic diseases before anti-TNFalpha therapy: tuberculin skin test versus IFN-γ assay. *Arthritis Rheum* 2013;**65**:S577	Abstract
342	Ozen Alahdab Y	Interferon-gamma release assay or tuberculin skin test in inflammatory bowel disease patients – which is reliable. *J Crohns Colitis* 2011;**5**:S53	Abstract

Number	Author ID	Details	Reason(s) for exclusion
343	Painter JA	Tuberculosis screening by tuberculosis skin test or QuantiFERON-TB Gold In-Tube assay among an immigrant population with a high prevalence of tuberculosis and BCG vaccination. *PLOS ONE* 2013;**8**:e82727	Active TB
344	Paluch-Oles J	Identification of latent tuberculosis infection in rheumatic patients under consideration for treatment with anti-TNF-alpha agents. *Arch Med Sci* 2013;**9**:112–17	No construct validity
345	Papay P	Immunosuppressive (IS) therapy impacts the results of QuantiFERON and tuberculin skin test in routine screening for latent tuberculosis (LTB) in patients with inflamm bowel diseases (IBD). *Gastroenterol* 2009;**1**:A195.	Abstract
346	Pareek M	Modelling the health impact and cost-effectiveness of screening new entrants to the UK for latent tuberculosis infection. *J Infect* 2009;**59**:S442	Abstract
347	Pareek M	Community-based evaluation of immigrant TB screening using interferon gamma release assays and tuberculin skin testing: yields and cost-effectiveness. *Thorax* 2011;**66**:A20	Abstract
348	Patel D	Screening for latent tuberculosis in patients starting anti-TNF therapy. *Rheumatol* 2012;**51**:iii175	Abstract
349	Pease E	Does the dual-testing strategy under-diagnose latent TB infection in HIV-infected individuals? A 1-year experience in a TB high-incidence area in the UK. *HIV Med* 2013;**14**:69	Abstract
350	Perez-Escolano E	Comparison of an interferon-gamma release assay with tuberculin skin test for the diagnosis of tuberculosis infection in a contact investigation. *Clin Microbiol Infect* 2009;**15**:S392	Abstract
351	Perez-Escolano E	Comparison of QuantiFERON TB Gold with tuberculin skin test for the diagnosis of tuberculosis infection in risk groups. *Clin Microbiol Infect* 2010;**16**:S542–3	Abstract
352	Pesola GR	Quantiferon gold in tube latent tuberculosis testing in low risk healthy adults. *Am J Resp Crit Care Med* 2011;**183**:A4884	Abstract
353	Pullar ND	Low prevalence of positive interferon-gamma tests in HIV-positive long-term immigrants in Norway. *Int J Tuberc Lung Dis* 2014;**18**:180–7	No construct validity
354	Punal Rioboo J	*Interferon-Gamma Release Assays (IGRAs) for Diagnosis of Latent Tuberculosis Infection and Active Tuberculosis*. Santiago de Compostela: Galician Agency for Health Technology Assessment (AVALIA-T); 2010	Abstract
355	Qin LL	T-SPOT.*TB* for detection of tuberculosis infection among hematological malignancy patients and hematopoietic stem cell transplant recipients. *Asian Pac J Cancer Prev* 2013;**14**:7415–19	No construct validity
356	Richeldi L	Prior tuberculin skin testing does not boost QuantiFERON-TB results in paediatric contacts. *Eur Respir J* 2008;**32**:524–5	Letter

Number	Author ID	Details	Reason(s) for exclusion
357	Rotar Z	Performance of a two-step latent tuberculosis screening algorithm in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis prior to treatment with tumor necrosis alpha inhibitors: prospective observational data from the Biorx.Si registry. *Arthritis Rheum* 2013;**65**:S578	Abstract
358	Sauzullo I	Detection of *M. tuberculosis* infection by interferon-gamma release assays: a comparative study in HIV-infected patients and in immunosuppressed candidates for anti-TNF-alpha therapy. *HIV Med* 2009;**10**:155–6	Abstract
359	Sauzullo I	Usefulness of interferon-gamma release assays for latent tuberculosis screening in patients candidate for TNF-α therapy. *Clin Microbiol Infect* 2010;**16**:S72	Abstract
360	Schichter-Konfino V	Interferon-γ-release assay prevents unnecessary tuberculosis therapy in individuals with positive tuberculin skin test. *J Allergy Clin Immunol* 2014;**133**:AB244	Abstract
361	Seagar AL	Assessment of the use of the Quantiferon-TB gold in-tube assay for the diagnosis of TB infection in Lothian, Scotland. *Clin Microbiol Infect* 2010;**16**:S544	Abstract
362	Sester M	Head-to-head analysis of *M. tuberculosis* interferon-γ release assays (IGRAs) and skin-testing in immunocompromised patients: interim analysis of a European multicenter TBNET study. *Am J Transpl* 2011;**11**:115	Abstract
363	Shakak AO	Latent tuberculosis infections (LTBI): tuberculin skin test and whole blood IFN-gamma as surrogate markers in developing countries. *Clin Chem Lab Med* 2011;**49**:S541	Abstract
364	Sharma N	ELISPOT as a predictor for development of TB in children with TB contact. *Thorax* 2009;**64**:320	Abstract
365	Soborg B	Comparison of screening procedures for LTBI among patients with inflammatory diseases. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):38–40	Included/excluded in CG117[10]
366	Stavri HR	Prospective comparison of two brands of tuberculin skin tests and Quantiferon-TB Gold in-Tube assay performances for tuberculosis infection in hospitalized children. *Medica* 2010;**5**:271–6	Active TB
367	Swaminath A	Quantiferon testing is superior to tuberculosis skin test (TST) in identifying latent TB in immunosuppressed patients with inflammatory bowel disease: a decision analysis. *Am J Gastroenterol* 2012;**107**:S688	Abstract
368	Swaminath A	Cost-effectiveness of QuantiFERON testing before initiation of biological therapy in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:2444–9	Economic study
369	Tavast E	IGRA tests perform similarly to TST but cause no adverse reactions: pediatric experience in Finland. *BMC Res Notes* 2009;**2**:9	Active TB
370	Tavast E	Immunosuppression adversely affects TST but not IGRAs in patients with psoriasis or inflammatory musculoskeletal diseases. *Int J Rheumatol* 2012;**2012**:381929	Non-standard or in-house IGRA

Number	Author ID	Details	Reason(s) for exclusion
371	Triverio PA	Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. *Nephrol Dial Transpl* 2009;**24**:1952–6	Included/excluded in CG117[10]
372	Van Zyl-Smit RN	Immunodiagnosis of latent TB in HIV-infected persons in a high burden setting. *Am J Resp Crit Care Med* 2011;**183**:A4885	Abstract
373	Vassilopoulos D	Comparison of two interferon-gamma release assays to tuberculin skin testing for latent tuberculosis screening in rheumatic patients starting anti-TNF treatment. *Arthritis Rheum* 2009;**60**:1907	Abstract
374	Velizarova SA	To what extent T-SPOT.*TB* could be used in the diagnosis of tuberculosis in children exposed to TB infection? *Eur J Immunol* 2009;**39**:S217	Abstract
375	Vortia E	Use of the QuantiFERON-TB Gold in-Tube test for latent tuberculosis screening in children with inflammatory bowel disease treated with infliximab. *Gastroenterology* 2013;**144**:S887	Abstract
376	Wang H	Clinical value of a whole blood interferon-γ release assay for the diagnosis of *Mycobacterium tuberculosis* infection during antitubercular treatment. *Exp Ther Med* 2013;**6**:455–8	Active TB
377	Wiwanitkit V	QuantiFERON-TB Gold test versus tuberculin skin test. *Ann Thorac Med* 2010;**5**:119	Abstract
378	Wollman J	The effect of the severity of psoriasis on screening for latent tuberculosis: a comparison study between psoriasis and rheumatoid arthritis patients. *Ann Rheum Dis* 2013;**71**(Suppl. 3):692	Abstract
379	Wong SH	Tuberculosis screening with interferon-gamma release assay in inflammatory bowel disease in a tuberculosis-endemic population. *Gastroenterology* 2013;**144**:S418	Abstract
380	Yilmaz N	Comparison of QuantiFERON-TB Gold test and tuberculin skin test for identification of latent *Mycobacterium tuberculosis* infection in lupus patients. *Arthritis Rheum* 2009;**60**:286	Abstract
381	Zapantis E	What is the optimal screening test to detect latent tuberculosis infection in high risk patients with systemic lupus erythematosus? Findings from a US inner city high-risk SLE cohort. *Lupus* 2013;**22**:61	Abstract
382	Zelinkova Z	Effectiveness of the screening for latent tuberculosis in inflammatory bowel disease patients with previous BCG vaccination. *Gastroenterology* 2013;**144**:S413–14	Abstract
383	Zlnay M	The risk of tuberculosis in patients with ankylosing spondylitis during anti-TNF therapy: data from national database in Slovakia. *Ann Rheum Dis* 2013;**72**(Suppl. 3):513	Abstract

ID, identification.

December 2014 update

Number	Author ID	Details	Reason(s) for exclusion
384	Al-Taweel T	A pilot study of optimal screening for latent tuberculosis in patients with inflammatory bowel disease. *Gastroenterology* 2014;**1**:S–582	Abstract
385	Al Wakeel JS	The use of QuantiFERON TB Gold in-Tube test in screening latent and active tuberculosis among saudi dialysis patients. *Nephrol Dial Transpl* 2014;**29**:iii477–8	Abstract
386	Arenas Miras MDM	Diagnosis of latent tuberculosis in patients with systemic lupus erythematosus: T.SPOT.*TB* versus tuberculin skin test. *Biomed Res Int* 2014;**2014**:291031	No construct validity; immunocompromised: concordance information
387	Arstikyte I	The value of the Quantiferon TB Gold In-Tube test in the identification of latent tuberculosis in rheumatic patients before treatment with TNF-alpha blockers in Vilnius University Hospital Santariskiu Clinics. *Scand J Rheumatol* 2014;**43**:44–5	Abstract
388	Belknap R	Interferon-gamma release assays. *Clin Lab Med* 2014;**34**:337–49	Review
389	Bennett A	Does the tuberculin skin test increase the detection of TB infection when screening HIV positive patients? Three years' experience in a district general hospital. *Thorax* 2014;**69**:A209	Abstract
390	Calzada-Hernandez J	PReS-FINAL-2265: tuberculosis in pediatric patients who are receiving anti-TNF agents. *Pediatr Rheumat* 2013;**11**(Suppl. 2):P255	Abstract
391	Chuke SO	Tuberculin skin tests versus interferon-gamma release assays in tuberculosis screening among immigrant visa applicants. *Tuberc Res Treat Print* 2014;**2014**:217969	No construct validity; recently arrived: concordance information
392	Cruz AT	Relationship between tuberculin skin test (TST) size and interferon gamma release assay (IGRA) result: when should clinicians obtain IGRAs in children with positive TSTs? *Clin Pediatr* 2014;**53**:1196–9	No construct validity for LTBI (prior TB is not a construct of LTBI); study aim was to compare the tests in predicting chest radiography result suggesting the presence of MTB
393	Duman N	Screening for latent tuberculosis infection in psoriasis and psoriatic arthritis patients in a tuberculosis-endemic country: a comparison of the Quantiferon-TB Gold In-Tube test and tuberculin skin test. *Int J Dermatol* 2014;**53**:1286–292	No construct validity
394	Elfrink F	Screening travellers to high-endemic countries for infection with *Mycobacterium tuberculosis* using interferon gamma release assay; a prospective study. *BMC Infect Dis* 2014;**14**:515	Repeat testing
395	Elmahdy MMGF	Tuberculin skin test and QuantiFERON test for detection of latent *Mycobacterium tuberculosis*. *Int J Infect Dis* 2014;**21**:349	Abstract
396	Golovics PA	Is the tuberculin skin test alone accurate in moderate-to-severe BCG vaccinated patients with inflammatory bowel disease to test for latent tuberculosis? *J Crohns Colitis* 2014;**8**:S144	Abstract

Number	Author ID	Details	Reason(s) for exclusion
397	Islam S	Tuberculin skin test and QuantiFERON performance, and testing of populations at low risk for tuberculosis infection. *Clin Infect Dis* 2014;**59**: 1187–8	Letter to the editor
398	Jenum S	The frequencies of IFNγ+IL2+TNFα+ PPD-specific CD4+CD45RO+ T-cells correlate with the magnitude of the QuantiFERON Gold In-Tube response in a prospective study of healthy Indian adolescents. *PLOS ONE* 2014;**9**:e101224	Comparing antigens
399	Julian AN	Diagnosis of tuberculosis infection in pediatric patients treated with inhibitors of the tumour necrosis factor alpha. A multicenter national study comparing tuberculin skin test and igra tests. *Pediatr Rheumatol* 2014;**12**:P282	Abstract
400	Marquez C	Tuberculosis infection in early childhood in Uganda and the influence of HIV exposure. *Topics Antiviral Med* 2014;**22**:47–8	Abstract
401	Mathad JS	Effect of HIV on latent TB screening of pregnant women in Pune, India. *Topics Antiviral Med* 2014;**22**:425–6	Abstract
402	McMullen SE	Performance of QuantiFERON-TB Gold and tuberculin skin test relative to subjects' risk of exposure to tuberculosis. *Clin Infect Dis* 2014;**58**:1260–6	Population aged > 18 years
403	Mendy A	Higher specificity of tuberculin skin test compared with QuantiFERON-TB Gold for detection of exposure to *Mycobacterium tuberculosis*. *Clin Infect Dis* 2014;**59**:1188–9	Letter to editor
404	Nassiri AA	Re: Interferon-gamma release assay agreement with tuberculin skin test in pretransplant screening for latent tuberculosis in a high-prevalence country. *Iran J Kidney Dis* 2014;**8**:432–3	Letter
405	O'Flynn E	Performance and benefits of replacing Mantoux test with QuantiFERON in screening for latent TB in patients prior to anti-TNF therapy. *Ann Rheum Dis* 2014;**73**(Suppl. 2):2–1247	Abstract
406	O'Flynn E	Performance and benefits of replacing Mantoux test with QuantiFERON in screening for latent TB in patients prior to anti TNF therapy. *Irish J Med Sci* 2014;**183**:S105	Abstract
407	Opris D	Is tuberculosis screening sufficient for preventing TB reactivation in biologic treated patients? *Ann Rheum Dis* 2014;**73**:497	Abstract
408	O'Shea MK	Tuberculin skin testing and treatment modulates interferon-gamma release assay results for latent tuberculosis in migrants. *PLOS ONE* 2014;**9**:e97366	Military recruits
409	Panchal RK	The effectiveness of primary care based risk stratification for targeted latent tuberculosis infection screening in recent immigrants to the UK: a retrospective cohort study. *Thorax* 2014;**69**:354–62	No comparison between IGRA and TST
410	Pease E	Does the dual testing strategy under-diagnose latent tuberculosis infection in UK HIV-infected individuals?: a one year experience in a tuberculosis high incidence area. *Int J STD AIDS* 2013;**24**:56	Poster

Number	Author ID	Details	Reason(s) for exclusion
411	Prignano F	Latent tuberculosis infection in psoriasis and other dermatological immunomediated diseases: a combined approach by QuantiFERON-TB Gold and tuberculin skin tests. *Int J Dermatol* 2014;**53**:e372–4	Letter
412	Rose W	QuantiFERON Gold-in-Tube assay for TB screening in HIV infected children: influence of quantitative values. *BMC Infect Dis* 2014;**14**:516	Repeat testing, proportion of people had self-read TST results
413	Sanchez Riera L	QuantiFERON-TB more useful than tuberculin skin test for latent tuberculosis screening: a hospital experience. *Ann Rheum Dis* 2014;**73**:950–1	Abstract
414	Santoro-Lopes G	Screening for latent tuberculosis infection in low-incidence areas. *Am J Transpl* 2014;**14**:1709	Letter to the editor
415	Savaj S	Interferon-gamma release assay agreement with tuberculin skin test in pretransplant screening for latent tuberculosis in a high-prevalence country. *Iranian J Kidney Dis* 2014;**8**:329–32	No construct validity
416	Scholman T	Analysis of agreement between IGRAs and tuberculin skin-testing by the use of PPD as the same antigen. *Transplantation* 2014;**90**:540	Abstract
417	Senturk T	Comparison of diagnostic test for latent tuberculosis infection. *Int J Rheum Dis* 2014;**17**:103	Abstract
418	Shokrollahi MR	Diagnosis of latent tuberculosis in individuals with recent exposure: tuberculin skin test versus interferon-gamma release assay. *Br J Biomed Sci* 2014;**71**:125–6	Not population of interest
419	Soare A	Preventing active tuberculosis in rheumatoid arthritis patients receiving TNF inhibitors: TB screening at baseline is not enough. *Ann Rheum Dis* 2014;**73**:325	Abstract
420	Sztajnbok F	PReS-FINAL-2054: latent tuberculosis infection in patients with juvenile idiopathic arthritis undergoing methotrexate therapy: a longitudinal study with TST and ELISPOT. *Pediatr Rheumatol Online J* 2013;**11**(Suppl. 2):P67	Repeat testing at 3 and 12 months
421	Sztajnbok F	Tuberculin skin test and ELISPOT/T.SPOT.*TB* in children and adolescents with juvenile idiopathic arthritis. *Pediatr Rheumatol* 2014;**12**:17	Repeat testing at 3 and 12 months
422	Verhagen LM	Agreement between QuantiFERON-TB Gold in-Tube and the tuberculin skin test and predictors of positive test results in Warao Amerindian pediatric tuberculosis contacts. *BMC Infect Dis* 2014;**14**:383	Repeat testing
423	Zelinkova Z	Screening for latent tuberculosis is effective but does not fully protect against tuberculosis reactivation during anti-TNF treatment in areas with high background incidence of tuberculosis. *J Crohns Colitis* 2014;**8**:S212	Abstract
424	Zelinkova Z	Screening for latent tuberculosis is effective but does not fully protect against tuberculosis reactivation during anti-TNF treatment in areas with high background incidence of tuberculosis. *Gastroenterology* 2014;**1**:S585	Abstract

ID, identification.

Appendix 7 ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform list of excluded ongoing studies ($n = 30$)

TABLE 56 ClinicalTrials.gov and WHO ICTRP list of excluded ongoing studies

Number	Study title	Recruitment status	URL[a]	Reason(s) for exclusion
1	Screening for latent tuberculosis infection (LTBI) in US army recruits	Active, not recruiting	http://ClinicalTrials.gov/show/NCT00804713	Army recruits
2	Diagnosis of tuberculosis infection in health care workers using ex-vivo interferon-gamma assay	Completed	http://ClinicalTrials.gov/show/NCT01007396	Health-care workers, active TB
3	Comparison of the Quantiferon®-TB GOLD (in Tube) assay with tuberculin skin testing for detecting latent tuberculosis infection in patients with chronic liver disease being evaluated for or awaiting liver transplantation	Withdrawn	http://ClinicalTrials.gov/show/NCT00424684	Withdrawn
4	Surveillance and follow-up for latent tuberculosis infection and risk of developing active tuberculosis in patients receiving long-term dialysis	Completed	http://ClinicalTrials.gov/show/NCT01311999	No comparison between IGRAs and TST
5	QuantiFERON®-TB Gold in-Tube for the diagnosis of tuberculosis infection in contact tracing study (OPTIMIST)	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01223534	No subgroup of interest
6	QuantiFERON for detection of latent tuberculosis in healthcare workers	Completed	http://ClinicalTrials.gov/show/NCT00797836	Health-care workers
7	Is tuberculin skin testing effective in screening for latent tuberculosis (TB) in elderly residents of nursing homes?	Completed	http://ClinicalTrials.gov/show/NCT00756808	No subgroup of interest
8	QuantiFERON Gold test for detecting tuberculosis (TB) infection in HIV/AIDS patients in South Africa	Recruiting	http://ClinicalTrials.gov/show/NCT02119130	Active TB
9	Diagnosis and treatment of co-infection with human immunodeficiency virus/latent tuberculosis infection (HIV/TBL)	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01875952	No comparison between IGRAs and TST
10	The role of IGRA in screening and monitoring for TB during anti TNF therapy in patients with IMID	Recruiting	http://ClinicalTrials.gov/show/NCT02135289	No comparison between IGRAs and TST
11	Immune response to *Mycobacterium tuberculosis* infection	Completed	http://ClinicalTrials.gov/show/NCT00257907	Active TB
12	Performance of IGRAs for TB infection diagnosis in elderly (IGRage)	Recruiting	http://ClinicalTrials.gov/show/NCT01895582	Active TB
13	Monthly follow up of interferon gamma releasing assay (IGRA) among health-care workers treating tuberculosis (TB) patients	Completed	http://ClinicalTrials.gov/show/NCT01121068	Health-care workers
14	Vitamin A supplementation for modulation of *Mycobacterium tuberculosis* immune responses in latent tuberculosis	Withdrawn	http://ClinicalTrials.gov/show/NCT00558480	Withdrawn

continued

TABLE 56 ClinicalTrials.gov and WHO ICTRP list of excluded ongoing studies (*continued*)

Number	Study title	Recruitment status	URL[a]	Reason(s) for exclusion
15	Diagnosis of latent tuberculosis (TB) infection in health care workers using TST and whole blood interferon-γ assay	Completed	http://ClinicalTrials.gov/show/NCT00962793	Health-care workers
16	Latent tuberculosis infection in bone marrow transplant recipients	Completed	http://ClinicalTrials.gov/show/NCT01021124	No comparison between IGRAs and TST
17	Conversion rate of (TST) tuberculin skin test and QuantiFERON-TB Gold in Tube assay in health care workers	Completed	http://ClinicalTrials.gov/show/NCT01376843	Health-care workers
18	Determining risk in latent tuberculosis	Terminated	http://ClinicalTrials.gov/show/NCT01571739	Study terminated
19	Treatment of latent tuberculosis infection with isoniazid	Completed	http://ClinicalTrials.gov/show/NCT00293228	Focus on the effect of treatment
20	Effects of vitamin D supplementation on antimycobacterial immunity	Completed	http://ClinicalTrials.gov/show/NCT00157066	Focus on the effect of treatment
21	A Phase I/IIa safety and immunogenicity of AERAS-456 in HIV-negative adults with and without latent tuberculosis infection (C-035–456)	Completed	http://ClinicalTrials.gov/show/NCT01865487	Comparing antigen and placebo
22	Isoniazid (INH) treatment based on ELISPOT assay	Completed	http://ClinicalTrials.gov/show/NCT01087190	Focus on the effect of treatment
23	A safety and immunogenicity trial with an adjuvanted TB subunit vaccine (Ag85B-ESAT-6 + IC31) (THYB-03)	Completed	http://ClinicalTrials.gov/show/NCT01049282	Comparing antigens
24	IFN-gamma-releasing assay based approach in patients with suspected tuberculous peritonitis	Recruiting	http://ClinicalTrials.gov/show/NCT02175134	Diagnosis of tuberculous peritonitis
25	A Phase III contact tracing trial comparing the diagnostic performance of C-Tb to QuantiFERON®-TB Gold in-Tube, in combination with a double blind randomized split body safety assessment of C-Tb versus 2 TU tuberculin PPD RT23 SSI	Authorised	www.clinicaltrialsregister.eu/ctr-search/trial/2011-005617-36/ES	Active TB
26	Ensayo clínico de dos estrategias para la toma de decisiones terapéuticas en el estudo de contactos de tuberculosis: estrategia estándar, basada en la prueba de la tuberculina (PT) sola frente a la combinación de PT y QuantiFERON-TB-Gold in-Tube	Authorised	www.clinicaltrialsregister.eu/ctr-search/trial/2009-017430-49/ES	Not English language
27	Interferon-gamma release assays in tuberculosis (TB) – HIV co-infected children	Recruiting	http://ClinicalTrials.gov/show/NCT00604617	Active TB
28	Screening for latent tuberculosis in healthcare workers with QuantiFERON-Gold assay: a cost-effectiveness analysis	Recruiting	http://ClinicalTrials.gov/show/NCT00449345	Health-care workers and economic analysis
29	Use TST and QFT-RD1 test to monitor the tuberculous infection in patients, close contact people and health care workers	Recruiting	http://ClinicalTrials.gov/show/NCT00311220	Health-care workers
30	Diagnosis of active tuberculosis by ELISPOT	Recruiting	http://ClinicalTrials.gov/show/NCT00174083	Active TB

a All accessed 13 January 2016.

Appendix 8 Included ongoing trials comparing interferon gamma release assays with the tuberculin skin test ($n = 20$)

TABLE 57 Included ongoing trials comparing IGRAs with the TST

Number	Study title	Recruitment status	URL
1	Interferon gamma release assays (IGRA) testing versus tuberculin skin test in renal transplant recipients	Completed	http://ClinicalTrials.gov/show/NCT01608685
2	Latent tuberculosis in second generation immigrants from high risk countries compare to low-risk young Israeli adults	Not yet recruiting	http://ClinicalTrials.gov/show/NCT02073669
3	Evaluation of 2 interferon γ assays in the diagnosis of latent tuberculosis in HIV-infected patients (ANRS EP 40 QUANTI SPOT)	Completed	http://ClinicalTrials.gov/show/NCT00647205
4	The usefulness of interferon-γ release assays and tuberculin skin test for detection of latent tuberculosis infection	Unknown	http://ClinicalTrials.gov/show/NCT01685905
5	Use of a gamma-IFN assay in contact tracing for tuberculosis in a low-incidence, high immigration area	Completed	http://ClinicalTrials.gov/show/NCT00557765
6	Detection of latent tuberculosis in haemodialysis patients	Completed	http://ClinicalTrials.gov/show/NCT00695734
7	Improving latent tuberculosis (TB) diagnosis in Thai children (TB Px)	Completed	http://ClinicalTrials.gov/show/NCT00947609
8	Is tuberculin skin testing effective in screening for latent tuberculosis in patients with HIV?	Completed	http://ClinicalTrials.gov/show/NCT00763295
9	Prevalence of latent tuberculosis (TB) infection diagnosed by interferon-gamma release assay and tuberculin skin tests in patients with old healed TB	Completed	http://ClinicalTrials.gov/show/NCT01099098
10	T cell interferon-gamma release assay (TIGRA) in immunocompromised individuals (TBNET-TIPS)	Completed	http://ClinicalTrials.gov/show/NCT00707317
11	A study on changes in IFN-gamma levels following anti-TNF treatment in patients undergoing serial QuantiFERON-TB Gold in-Tube	Completed	http://ClinicalTrials.gov/show/NCT01475409
12	Medical and economical impact of IGRAs diagnosis of latent tuberculosis in HIV-infected patients	Completed	http://ClinicalTrials.gov/show/NCT00805272
13	Comparison of Quantiferon-TB Gold assay with tuberculin skin testing in patients with chronic liver disease	Completed	http://ClinicalTrials.gov/show/NCT00402402
14	Tuberculosis (TB) screening for the diagnosis of latent TB in immunocompromised populations	Completed	http://ClinicalTrials.gov/show/NCT00134342
15	Impact of new immunological diagnosis tests of latent tuberculosis before anti TNF therapy	Completed	http://ClinicalTrials.gov/show/NCT00811343
16	Latent tuberculosis infection in cancer patients	Completed	http://ClinicalTrials.gov/show/NCT00507754
17	Latent tuberculosis infection in renal transplant recipients	Completed	http://ClinicalTrials.gov/show/NCT00682045

continued

TABLE 57 Included ongoing trials comparing IGRAs with the TST (*continued*)

Number	Study title	Recruitment status	URL
18	Prognostic value of interferon gamma release assays in predicting active tuberculosis among individuals with, or at risk of, latent tuberculosis infection (PREDICT)	Not yet recruiting	http://clinicaltrials.gov/show/NCT01162265
19	Comparison of the tuberculin skin test (TST) and QuantiFERON®-TB Gold Test (QFT-G) in patients with rheumatoid arthritis being considered for anti-TNF-alpha therapy	Unknown	http://clinicaltrials.gov/show/NCT00925249
20	Quantiferon-TB Gold in the assessment of latent TB in patients candidate to treatment or treated with TNFα antagonists	Unknown	http://clinicaltrials.gov/show/NCT00491933

Appendix 9 Data extraction tables for included clinical effectiveness studies

Children

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Adetifa 2010[105] **Country:** Gambia **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Community-based **Number of centres:** NR **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Medical Research Council (MRC) labs UK
Aim of the study
To compare TSPOT, QFT-GIT, and TST for diagnosis of LTBI in Gambian childhood contacts of TB patients
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Children
Participants
Recruitment dates: NR **Total N of recruited patients:** 285 **Inclusion criteria:** Household contacts (< 16 yrs) of newly diagnosed TB index cases **Exclusion criteria:** History of treatment for active TB, TB diagnosis within 1 month of recruitment **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** NR **Total N of patients with valid results for both IGRA and TST:** 215 (for TST) and 245 (for IGRAs) **Methods of active TB diagnosis (if applicable):** Sputum smears and mycobacterial cultures examined using standard methods **Outcomes (study-based) list:** Agreement; associations of test results with risk factors; combining two tests to explore gains in sensitivity and loss in specificity **Characteristics of participants (total study sample)** Mean (range or SD) Age (years): NR Women (n [%]): 145 [51] Race/ethnicity (n [%]):NR Geographic origin (n[%]): NR BCG vaccination (n [%]): 127/199 [59.1] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): NR Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): HIV positive (3 [1.1]) Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	NR	72	143	2	215
IGRA	NR	71	144	0	215

(TSPOT):					
TST (≥10mm):	NR	57	158	0	215
Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 215 for all three tests					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group – sleep proximity					
Non-exposed	Different house (reference group)				
Exposed 1 **(specify):**	Same house – different room				
Exposed 2 **(specify):**	Same house – same room				
Exposed 3 **(specify):**	NA				
Exposed 4 **(specify):**	NA				
Tests					
	Assay used, methodology, timing for test measurement, manufacturer		**Cut-off values/thresholds Definition of test+**		**Other information**
IGRA (TSPOT)	Carried out according to manufacturer's instructions. The spot unit counting performed using ELISPOT reader (AID GmbH, Strassburg, Germany)		Where the negative control had 0-5 spots, a positive result was defined as ≥6 spots in either the ESAT-6 or CFP-10 panel after subtracting the number of spots in the negative control panel In case of >6 spots in negative control panel, ESAT-6 or CFP-10 panel had to contain at least twice the number of spots in negative control panel to obtain a positive result		NA
IGRA (QFT-GIT)	Carried out according to manufacturer's instructions. IFN gamma levels measured using Dynex ELISA reader ver. 6.0 (Dynex Technologies, West Sussex, UK)		Positive result was defined as ≥0.35 IU/ml		NA
TST (≥10mm)	Carried out with 2 TU (PPD RT23, Statens Serum Institut, Copenhagen, Denmark) immediately after blood samples' completion. Indurations were recorded at 48-72 hours		≥10mm threshold for positivity		NA
Association between test results and incidence of active TB (if applicable)					

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST (≥10mm)**			
	Sleep proximity		Total		Sleep proximity		Total
	Same house – same room	Different house			Same house – same room	Different house	
IGRA +	14	19	33	TST +	15	10	25
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	215	Total	NR	NR	215

Test performance parameters	
IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
Same house same room vs. Different house OR (crude; for T^+ reported) = 3.20 (95% CI: 1.20, 9.10)	**Same house same room vs. Different house** OR (crude; for T^+ reported) = 10.10 (95% CI: 3.20, 32.10)
Same house same room vs. Different house OR (regression-based; reported) = 4.00 (95%	**Same house same room vs. Different house** OR (regression-based; reported) = 15.00 (95% CI: 4.70, 47.20)

CI: 1.40, 11.40) List of covariates: age, sex, ethnic group	List of covariates: age, sex, ethnic group
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 0.58 (0.28, 0.90)
Ratio of ORs (regression-based; reported) = 0.52 (0.29, 0.91)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥10mm)**			
	Sleep proximity		Total		Sleep proximity		Total
	Same house – different room	Different house			Same house – different room	Different house	
IGRA +	39	18	57	TST +	32	10	42
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	215	Total	NR	NR	215

Test performance parameters

IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
Same house different room vs. Different house OR (crude; for T^+ reported) = 2.00 (95% CI: 0.80, 5.10)	**Same house different room vs. Different house** OR (crude; for T^+ reported) = 2.40 (95% CI: 1.00, 5.80)
Same house different room vs. Different house OR (regression-based; reported) = 2.60 (95% CI: 0.90, 7.10) List of covariates: age, sex, ethnic group	**Same house different room vs. Different house** OR (regression-based; reported) = 2.90 (95% CI: 1.30, 6.70) List of covariates: age, sex, ethnic group
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 0.83(0.43, 1.60)
Ratio of ORs (regression-based; reported) = 0.90(0.46, 1.76)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥10mm)**			
	Sleep proximity		Total		Sleep proximity		Total
	Same house – same room	Different house			Same house – same room	Different house	
IGRA +	14	18	32	TST +	15	10	25
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeter	NR	NR	NR	Indetermina	NR	NR	NR

minate				te			
Total	NR	NR	215	Total	NR	NR	215
Test performance parameters							
IGRA				**TST**			
Sensitivity = NR				Sensitivity = NR			
Specificity = NR				Specificity = NR			
PPV = NR				PPV = NR			
NPV = NR				NPV = NR			
DOR (for T^+ calculated) = NR				DOR (for T^+ calculated) = NR			
Same house same room vs. Different house OR (crude; for T^+ reported) = 5.30 (95% CI: 1.50, 18.50)				**Same house same room vs. Different house** OR (crude; for T^+ reported) = 10.10 (95% CI: 3.20, 32.10)			
Same house same room vs. Different house OR (regression-based; reported) = 6.60 (95% CI: 1.70, 25.20) List of covariates: age, sex, ethnic group				**Same house same room vs. Different house** OR (regression-based; reported) = 15.00 (95% CI: 4.70, 47.20) List of covariates: age, sex, ethnic group			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = 0.52(0.22, 1.25)							
Ratio of ORs (regression-based; reported) = 0.44(0.18, 1.09)							
Other reported measure = NA							
Association between test results and levels of TB exposure (if applicable)							
IGRA (TSPOT)				**TST (≥10mm)**			
	Sleep proximity		Total		Sleep proximity		Total
	Same house – same room	Different house			Same house – same room	Different house	
IGRA +	14	18	32	TST +	15	10	25
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	215	Total	NR	NR	215
Test performance parameters							
IGRA				**TST**			
Sensitivity = NR				Sensitivity = NR			
Specificity = NR				Specificity = NR			
PPV = NR				PPV = NR			
NPV = NR				NPV = NR			
DOR (for T^+ calculated) = NR				DOR (for T^+ calculated) = NR			
Same house same room vs. Different house OR (crude; for T^+ reported) = 5.30 (95% CI: 1.50, 18.50)				**Same house same room vs. Different house** OR (crude; for T^+ reported) = 10.10 (95% CI: 3.20, 32.10)			
Same house same room vs. Different house OR (regression-based; reported) = 6.60 (95% CI: 1.70, 25.20) List of covariates: age, sex, ethnic group				**Same house same room vs. Different house** OR (regression-based; reported) = 15.00 (95% CI: 4.70, 47.20) List of covariates: age, sex, ethnic group			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							

Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = 0.52 (0.22, 1.25)							
Ratio of ORs (regression-based; reported) = 0.44 (0.18, 1.09)							
Other reported measure = NA							
Association between test results and BCG status (if applicable)							
IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = NR				DOR (for T+ calculated)$_{TST}$ = NR			
OR (crude; for T^+ reported)$_{QFT}$ = 1.10 (95% CI: 0.60, 2.00) OR (crude; for T^+ reported)$_{TSPOT}$ = 1.10 (95% CI: 0.61, 2.09)				OR (crude; for T+ reported) = 0.89 (95% CI: 0.50, 1.70)			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates:				OR (regression-based; reported) $_{TST}$ = NR List of covariates:			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample: **QFT-GIT**							
	TST (≥10mm) +			TST -			Total
IGRA (QFT-GIT) +	43			29			72
IGRA (QFT-GIT) -	14			129			143
Indeterminate	NR			NR			2
Total							217
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total – QFT-GIT							
TST + threshold: ≥10mm							
Parameters							
Kappa = 0.52 (95% CI: 0.39, 0.65)							
% concordance = 80.00% (95% CI: 74.15, 84.8)							
% discordance = 20.00% (95% CI: 15.2, 25.85)							
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample : TSPOT							
	TST (≥10mm) +			TST -			Total
IGRA (TSPOT) +	43			28			71
IGRA (TSPOT) -	14			130			144
Indeterminate	0			0			0

Total	57	158	215
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total -TSPOT			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.53 (95% CI: 0.40, 0.66)			
% concordance = 80.47% (95% CI: 74.65, 85.21)			
% discordance = 19.53% (95% CI: 14.79, 25.35)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
TST was most responsive of the 3 tests; none of the tests was affected by prior BCG vaccination
Reviewers:
Similar moderate agreement between TSPOT vs. TST and QFT vs. TST; TSPOT and TST were more strongly correlated with sleep proximity than QFT; none of the tests was influenced by BCG vaccination
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Cruz 2011[106] **Country:** US **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Pediatric tuberculosis clinics **Number of centres:** 3 **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Cellestis, Ltd, Oxford Immunotec, Inc
Aim of the study
To compare the performance of 1 IGRA, the T-SPOT.TB assay with the tuberculin skin test (TST) in children with different epidemiologic risk factors for tuberculosis
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Children
Participants
Recruitment dates: 2005 to 2006 **Total N of recruited patients:** NR **Inclusion criteria:** Children (aged 1 month to 18 years) with LTBI or tuberculosis disease and children uninfected with tuberculosis **Exclusion criteria:** Children on any tuberculosis medication for 2 or more months were not eligible for enrollment **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** 215 (22 did not have valid results) **Total N of patients with valid results for both IGRA and TST:** 193 (of these, 30 had diagnosis of TB) **Methods of active TB diagnosis (if applicable):** Children with tuberculosis disease was subcategorized as those with confirmed or clinically diagnosed tuberculosis. Children with confirmed tuberculosis had a positive culture or polymerase chain reaction result for Mycobacterium tuberculosis. Clinically diagnosed case subjects were defined as children without positive mycobacterial culture results who had radiographic or clinical findings consistent with tuberculosis and at least 1 or more of the following: (1) exposure to a known tuberculosis case; (2) a positive TST result (≥5 mm); or (3) histopathologic findings compatible with tuberculosis (eg, caseating granulomas) and the exclusion of reasonable alternative diagnoses **Outcomes (study-based) list:** Agreement, exposure-based **Characteristics of participants (total study sample)** Mean (range or SD) age (years): Median 8.6 (range: 1 mo to 18 yrs) Women (n [%]): 94 [51] Race/ethnicity (n [%]): Hispanic 115 [62.5], Non-Hispanic black 36 [19.6], Non-Hispanic white 19 [10.3], Asian 6 [3] Geographic origin (n[%]): Low prevalence regions (US/UK) (121 [65.7]) BCG vaccination (n [%]): 68 [37] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): None Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): NR Co-morbidity (n [%]): NA Type of during-study treatment (n [%]): NR
Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results**

					available)
IGRA (TSPOT):	185 (30 TB pts not counted)	94	69	22	163
TST (≥15mm):	185 (30 TB pts not counted)	94	69	22	163
Test 3 (specify)	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 163					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group					
Non-exposed	No contact with an identifiable source case				
Exposed 1 **(specify):**	contact with an identifiable source case				
Exposed 2 **(specify):**	NA				
Exposed 3 **(specify):**	NA				
Exposed 4 **(specify):**	NA				
Tests					
	Assay used, methodology, timing for test measurement, manufacturer		**Cut-off values/thresholds Definition of test+**		**Other information**
IGRA (TSPOT)	The commercially available T-SPOT.TB assay (Oxford Immunotec, Oxford, United Kingdom) was performed within 5 hours of specimen collection in the laboratory of 1 of the investigators (per manufacturer instructions. Briefly, this assay used 2 M tuberculosis–specific antigens, early secreted antigenic target 6-kDa protein (ESAT-6) and culture filtrate protein 10 (CFP10), to stimulate interferon-production in washed and enumerated peripheral blood mononuclear cells; 8 mL of blood was drawn from children 10 years old or older and 4 mL from children younger than 10 years. Peripheral blood mononuclear cells were counted to ensure that a standardized cell number was added in the assay to control for low T-cell volumes. General T-cell reactivity was confirmed by a positive mitogen control (phytohemagglutinin). A negative control was used to identify nonspecific cell activation		Spots were counted manually by using a microscope and confirmed by using an automated plate counter by the manufacturer. Assays with 8 or more spots were considered positive, and assays with less than 5 spots were considered negative. Borderline results (5–7 spots) were excluded from concordance analyses but were analyzed separately. A subgroup analysis was performed for specimens with 6 to 7 spots, because these specimens are sometimes considered positive internationally.		NA

TST (≥15mm)	Trained clinic or health department personnel placed and interpreted Mantoux tests. Transverse induration was measured at 48 to 72 hours and interpreted according to the American Thoracic Society criteria	TSTs were considered positive for all children who had results of 15 mm or more, 10 mm or more for children with chronic medical problems or exposure to people at high risk, and 5 mm or more for children with suspected disease or who were immunocompromised or children with identifiable source cases	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST≥15mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR

OR (regression-based; reported) = 4.41 [95% CI: 1.78, 10.94]) List of covariates: NR	OR (regression-based; reported) = 0.48 [95% CI: 0.26, 0.91] List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = 9.19 (95% CI: 5.23, 16.3)
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA				TST			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = 4.77 [95% CI: 2.29, 9.95]
OR (regression-based; reported) $_{IGRA}$ = 0.69 [95% CI: 0.37, 1.31] List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 4.32 [95% CI: 1.02, 18.35] List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total
TST + threshold: ≥15mm

Parameters

Kappa = NR
% concordance = NR
% discordance = NR

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR
TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
T-SPOT.TB was more specific than the TST for children who were immunized with BCG. Contact with a source case was associated with T-SPOT.TB result but not TST
Reviewers:
BCG influenced TST but not TSPOT in terms of false positives; TSPOT performed better than TST in terms of the association with exposure (contact with TB case)
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Kasambira 2011[107]
Country: South Africa
Study design: Retrospective cohort/cross-sectional study (with limited follow-up of 6 months)
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community based
Number of centres: 3
Total length of follow up (if applicable): 6 months
Funding (government/private/manufacturer/other - specify)**:** The United States Agency for International Development

Aim of the study

To determine and compare the prevalence of M. tuberculosis infection as assessed by TST and by QFT-GIT. Secondary objectives were to assess agreement between the two test methods and identify factors associated with various patterns of test results

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: October 2006 and December 2009
Total N of recruited patients: NR
Inclusion criteria: Children aged 6-16 years whose parents/guardians were TB index cases aged ⩾18 years, with diagnosis of pulmonary TB within the preceding 3 months, willingness to have the child undergo study testing and provision of informed consent
Exclusion criteria: Children's prior diagnosis or treatment of active or latent TB.
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 270
Total N of patients with valid results for both IGRA and TST: 254
Methods of active TB diagnosis (if applicable): Microbiological tests, histopathology, clinician diagnosis or a combination of these. Performance of diagnostic testing for adult TB suspects was not a component of this study, and diagnoses of pulmonary TB in the adult index cases were made by non-study clinicians. The study team reviewed medical records and interviewed adult index cases to corroborate the diagnosis
Outcomes (study-based) list: LTBI prevalence, agreement, association of test positivity with different index case- and child-related baseline factors
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median 6 [3–9]
Women (n [%]): 141 [52]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 257 [95]
History of anti-TB treatment (n [%]): None
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): NR
Clinical examination (yes/no): Yes
Morbidity (n [%]): HIV 14 [5]
Co-morbidity (n [%]): NA
Type of during-study treatment (n [%]): Active TB treatment 37 [19%] and LTBI treatment 19 [10%]

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (GIT):	270	79	172	19	251

TST (⩾5 mm):	270	71	183	16	254
Test 3 (specify)	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 254

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group –

	Adult index case type of TB diagnosis	**Adult index case smear grade**	**Exposure to index case during the day**
Non-exposed	Smear-positive TB	Negative	Minority of day (< 6 h)
Exposed 1 **(specify):**	Smear-negative, culture-positive TB	Scanty	Majority of day (> 7 h)
Exposed 2 **(specify):**	Clinical TB	1+	NA
Exposed 3 **(specify):**	NA	2+	NA
Exposed 4 **(specify):**	NA	3+	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	All children underwent QFT-GIT testing 5–30 min after TST placement. Blood was drawn from the right arm. QFT-GIT testing was performed according to the manufacturer's instructions, and included nil control, mitogen control and TB antigen tubes. Assays were conducted in a single laboratory at the study site by the same trained technician. Average interval between blood collection and initiation of incubation was 8.3 min (median 5, range 2–60, interquartile range 3–10). Following stimulation and centrifugation, harvested plasma specimens were stored at 4°C for up to 28 days prior to ELISA testing	Results were calculated and interpreted by the assay software as positive, negative or indeterminate	NA
TST⩾5 mm	the Mantoux method using Tuberculin purified protein derivative (PPD) RT-23 (2 units, Statens Serum Institut, Copenhagen, Denmark) was injected subcutaneously into the left forearm and the test was read 48–96 h later	An induration of ⩾5 mm was considered a positive test during the study	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA

PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA

Ratio of incidence density rate ratios = NA

Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥5mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	46	32	78	TST +	42	29	71
IGRA -	108	81	189	TST -	99	81	180
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	154	113	267	Total	141	110	251

Test performance parameters

IGRA	**TST**
Exposure to index case during the day (see 2 x 2 above) Sensitivity = 46/154 = 29.87% (95% CI: 23.2, 37.52)	**Exposure to index case during the day (see 2 x 2 above)** Sensitivity = 42/141 = 29.79% (95% CI: 22.86, 37.79)
Exposure to index case during the day (see 2 x 2 above) Specificity = 81/113 = 71.68% (95% CI: 62.77, 79.17)	**Exposure to index case during the day (see 2 x 2 above)** Specificity = 81/110 = 73.64% (95% CI: 64.71, 80.97)
Exposure to index case during the day (see 2 x 2 above) PPV = 46/78 = 58.97% (95% CI: 47.89, 69.22)	**Exposure to index case during the day (see 2 x 2 above)** PPV = 42/71 = 59.15% (95% CI: 47.54, 69.83)
Exposure to index case during the day (see 2 x 2 above) NPV = 81/189 = 42.86% (95% CI: 36.01, 49.99)	**Exposure to index case during the day (see 2 x 2 above)** NPV = 45.00% (95% CI: 37.91, 52.30)
DOR (for T^+ calculated) = not calculated	DOR (for T^+ calculated) = not calculated
OR (crude; for T^+ reported) = Adult index case type of TB diagnosis Smear-positive TB: 1.00 (reference group) Smear-negative, culture-positive TB: 0.18 (95% CI: 0.05, 0.70) Clinical TB: 0.81 (95% CI: 0.45, 1.50) Adult index case smear grade Negative: 1.00 (reference group) Scanty: 0.3 (95% CI: 0.05, 1.60) 1+: 1.50 (95% CI: 0.70, 3.60) 2+: 1.50 (95% CI: 0.50, 4.90) 3+: 3.20 (95% CI: 1.40, 7.40)	OR (crude; for T^+ reported) = Adult index case type of TB diagnosis Smear-positive TB: 1.00 (reference group) Smear-negative, culture-positive TB: 0.17 (95% CI: 0.05, 0.60) Clinical TB: 0.46 (95% CI: 0.24, 0.89) Adult index case smear grade Negative: 1.00 (reference group) Scanty: NR 1+: 2.81 (95% CI: 1.20, 6.70) 2+: 2.90 (95% CI: 0.80, 10.60) 3+: 4.10 (95% CI: 1.50, 11.10)

Exposure to index case during the day Minority of day (< 6 h) – 1.00 reference group Majority of day (> 7 h): 1.1 (95% CI: 0.63, 1.80)	Exposure to index case during the day Minority of day (< 6 h) – 1.00 reference group Majority of day (> 7 h): 1.20 (95% CI: 0.67, 2.10)
OR (regression-based; reported) = Adult index case type of TB diagnosis Smear-positive TB: 1.00 (reference group) Smear-negative, culture-positive TB: 0.84 (95% CI: 0.09, 7.80) Clinical TB: 3.90 (95% CI: 0.67, 23.5) Adult index case smear grade Negative: 1.00 (reference group) Scanty: NR 1+: 5.50 (95% CI: 0.89, 34.70) 2+: 8.70 (95% CI: 1.20, 62.00) 3+: 11.40 (95% CI: 1.80, 72.00) Exposure to index case during the day Minority of day (< 6 h) – 1.00 reference group Majority of day (> 7 h): 1.30 (95% CI: 0.69, 2.30) List of covariates: NR	OR (regression-based; reported) = Adult index case type of TB diagnosis Smear-positive TB: 1.00 (reference group) Smear-negative, culture-positive TB: 2.70 (95% CI: 0.56, 13.0) Clinical TB: NR Adult index case smear grade Negative: 1.00 (reference group) Scanty: NR 1+: 7.90 (95% CI: 1.50, 41.00) 2+: 15.70 (95% CI: 2.60, 92.0) 3+: 11.70 (95% CI: 2.20, 62.00) Exposure to index case during the day Minority of day (< 6 h) – 1.00 reference group Majority of day (> 7 h): 1.10 (95% CI: 0.58, 2.10) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NR
Ratio of OR (crude; for T^+ reported) = 0.78 (95% CI: 0.40, 1.52) [Adult index case smear grade: 3+ vs. negative]
Ratio of ORs (regression-based; reported) = 0.97 (95% CI: 0.27, 3.47) [Adult index case smear grade: 3+ vs. negative]
Ratio of OR (crude; for T^+ reported) = 0.92 (0.62, 1.36) [Exposure to index case during the day (>7 h)]
Ratio of ORs (regression-based; reported) = 1.18 (0.75, 1.85) [Exposure to index case during the day (>7 h)]
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (specify)				TST (specify)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	75	2	77	TST +	68	2	70
IGRA -	182	3	185	TST -	175	2	177
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	257	5	262	Total	243	4	247

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = 0.61 (95% CI: 0.10, 3.77)	DOR (for T+ calculated)$_{TST}$ = 0.38 (95% CI: 0.05, 2.81)
OR (crude; for T^+ reported) = 0.62 (95% CI: 0.08, 4.76) reference group flipped (yes vs. no)	OR (crude; for T+ reported) = 0.38 (95% CI: 0.05, 2.85) reference group flipped (yes vs. no)
OR (regression-based; reported)$_{IGRA}$ = 0.83 (95% CI: 0.08, 8.33) reference group flipped (yes vs. no)	OR (regression-based; reported)$_{TST}$ = 0.52 (95% CI: 0.06, 4.00) reference group flipped (yes vs. no)

List of covariates: NR		List of covariates:	
Other reported measure = NR		Other reported measure = NR	
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST + (≥5mm)	TST -	Total
IGRA (QFT-GIT) +	56	19	75
IGRA -	12	149	161
Indeterminate	3	15	18
Total	71	183	254
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥5mm			
Parameters			
Kappa = 0.68 (95% CI: 0.56, 0.81) indeterminate excluded			
% concordance = 205/236 = 86.86% (95% CI: 81.96, 90.59) ; indeterminate excluded			
% discordance = 31/236 = 13.14% (95% CI: 9.41, 18.04) indeterminate excluded			
Stratification (≥10mm)):			
	TST +(≥10mm)	TST -	Total
IGRA +	48	27	75
IGRA -	7	154	161
Indeterminate	2	16	18
Total	57	197	254
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.64 (95% CI: 0.51, 0.76)			
% concordance = 202/236 = 85.59% (95% CI: 80.54, 89.5)			
% discordance = 34/236 = 14.41% (95% CI: 10.5, 19.46)			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
Prevalence of M. tuberculosis infection in paediatric contacts was high regardless of the diagnostic			

method used. TST should not be excluded for the detection of paediatric M. tuberculosis infection in this setting, but QFT-GIT may be a feasible alternative in children aged ⩾2 years
Reviewers:
Similar performance of TST and IGRA for exposure DORs; BCG did not affect TST or IGRA positivity differentially; TST threshold did not influence the agreement between the two tests
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Data extraction sheet for included primary study reports

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Laniado-Laborin 2014[148]
Country: Mexico
Study design: Cross-sectional/retrospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify): Tuberculosis (TB) clinic
Number of centres: one
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To compare the prevalence of LTBI between paediatric contacts of drug-resistant cases and drug susceptible cases

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: From August 2011 to June 2013
Total N of recruited patients: NR
Inclusion criteria: Family contacts of culture–proven cases age ≤16 years
Exclusion criteria: Subjects with a history of TB, a previous diagnosis of LTBI or the administration of TST in the past year
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 173
Total N of patients with valid results for both IGRA and TST: 172
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: concordance between TST and QFT-GIT test, association between exposure and test results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): drug susceptible (7.79 SD4.28); drug resistant (7.36 SD4.46)
Women (n [%]): 86/173 [50.0%]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 164 [95%]
History of anti-TB treatment (n [%]): None
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NA
Co-morbidity (n [%]): NA
Type of during-study treatment (n [%]): 77/173 [44.5%] contacts of multidrug susceptible index cases were treated for LTBI with INH or rifampicin (RMP). 96/173 [55.5%] contacts of multidrug resistant cases did not receive treatment for LTBI

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	173	71	101	1	172
TST (≥5mm):	173	136	36	1	172

Total N of patients with valid results for both IGRA and TST: 172

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – various definitions (see below)	
Non-exposed	NR
Exposed 1 **(specify):**	Exposure to source
Exposed 2 **(specify):**	Hours/day exposure
Exposed 3 **(specify):**	Cohabitants, n
Exposed 4 **(specify):**	Rooms, n

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QuantiFERON Gold In-Tube assay (QFT-GIT) (QIAGEN Inc., Valencia, CA, USA) Each participant had 73 ml of blood drawn which was performed according to the manufacturer's instructions	QFT-GIT result was considered positive if the interferon-gamma response to TB antigens minus the negative control was ≥0.35 IU/ml and also >25% of the negative control, negative if these criteria were not met and indeterminate if either the negative control had a result of >8 IU/ml or the positive control had a result of <0.5 IU/ml	
TST(≥5mm)	TST (5 tuberculin units purified protein derivative [PPD]; Tubersol, Sanofi Pasteur Lt, Toronto, ON, Canada) was performed using the Mantoux method. An intradermal injection of 0.1 ml PPD was administered to the volar surface of the forearm. The transverse diameter of induration was recorded in mm 48 h after administration	An induration of ≥5 mm was considered positive, as every subject was a close contact of a culture-proven case	

Association between test results and incidence of active TB (if applicable)

IGRA				**TST (>5mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA
NPV= NA	NPV= NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = NA	
Ratio of incidence density rate ratios = NA	
Other reported measure = NA	
Association between test results and levels of TB exposure (if applicable)	

IGRA-GIT				**TST≥5mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = Exposure to source: 0.91 (95% CI 0.57, 1.45) Hours/day exposure: 1.03 (95% CI 0.96, 1.10) # of cohabitants: 0.91 (95% CI 0.79, 1.05) # of rooms: 1.12 (95% CI 0.77, 1.61) List of covariates: age, sex, history of BCG vaccination, intensity of exposure, exposure time of the contacts to a source case, exposure to a drug-susceptible case, and exposure to a drug-resistant case	OR (regression-based; reported) = Exposure to source: NR (p=NR; NS) Hours/day exposure: NR (p=NR; NS) # of cohabitants: NR (p=NR; NS) # of rooms: NR (p=NR; NS) List of covariates: age, sex, history of BCG vaccination, intensity of exposure, exposure time of the contacts to a source case, exposure to a drug-susceptible case, and exposure to a drug-resistant case
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Association between test results and BCG status (if applicable)							
IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA

OR (regression-based; reported) $_{IGRA}$ = NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +≥5mm	TST -	Total
IGRA +	69	2	71
IGRA -	67	34	101
indeterminate	NR	NR	1
Total	136	36	172
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥ 5mm			
Parameters			
Kappa = 0.27 (95% CI: 0.17, 0.38)			
% concordance = [69+34]/172 = 59.88% (95% CI: 52.42, 66.92)			
% discordance = 69/172 = 40.12% (95% CI: 33.08, 47.58)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Conclusions			
Authors:			
The only variables predictive of a positive QFT-GIT were older age and TST positivity. Logistic regression analysis with TST as a dependent variable had similar results, with a positive QFT-GIT test as the only predictor of a positive TST (results not shown). The main finding in our study is that overall prevalence of LTBI in paediatric contacts in our region is high, and not significantly different among contacts of drug-susceptible and those of drug resistant patients			

Reviewers:
There was no associations between exposure to TB and GIT test results; likewise for TST (but no results reported); inconclusive results; between test agreement was poor
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Mahomed 2011b[108]
Country: South Africa
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** High schools
Number of centres: 11
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** The Aeras Global TB Vaccine Foundation and the Gates Grand Challenge 6 and Gates Grand Challenge 12 grants for QuantiFERON testing

Aim of the study

To determine the prevalence of and predictive factors associated with latent TB infection in adolescents

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children (adolescents in a high TB burden area)

Participants

Recruitment dates: NA
Total N of recruited patients: 6363 enrolled, 5244 enrolled for analysis
Inclusion criteria: All adolescents aged 12-18 years
Exclusion criteria: Diagnosed with active TB
Total N of excluded patients: 13 (an indeterminate QFT results), 639 (TST was not performed with past TB), 22 (TST was not performed with current TB, 22 (diagnosed with active TB)
Total N of patients tested with both IGRA and TST: 5244
Total N of patients with valid results for both IGRA and TST: 5244
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: TST and QFT results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 12-18 years
Women (n [%]): 2842 [54.2]
Race/ethnicity (n [%]): Indian/White (410 [7.8]); Mixed race (3839 [73.2]); Black (995 [19.0])
Geographic origin (n[%]): NR
BCG vaccination (n [%]): No (46 [0.9]); yes (4917 [93.8]); unknown (281 [5.4])
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): No
Clinical examination (yes/no): No
Morbidity (n [%]): NR
Co-morbidity (n [%]): Chronic allergy related condition e.g. asthma, hay fever, eczema yes (53 [1.0]); No (5191 [99.0])
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	Unclear	2669	2562	13	5244
TST (≥5mm):	Unclear	2894	2350	0	5244
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 5244

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NR

Exposed 1 **(specify):**	Current or prior TB household contact
Exposed 2 **(specify):**	BCG scar
Exposed 3 **(specify):**	BCG reported as being given
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA	QuantiFERON- TB Gold In-Tube (QFT-GIT, Cellestis, Carnegie, Victoria, Australia)	A result was considered positive if the QFT-GIT was ≥ 0.35 IU	NA
TST	Mantoux method on either forearm, using 2 tuberculin units of RT23 (Statens Serum Institut, Copenhagen, Denmark). Induration at the TST site was read 48-96 hours later with a ruler or a caliper, by trained personnel	A result was considered positive if induration ≥ 5mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (current or prior TB household contact)

IGRA (QFT-GIT)				TST≥ 5mm			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	888	1781	2669	TST +	950	1944	2894
IGRA -	444	2118	2562	TST -	382	1968	2350
Indeterminate	0	13	13	Indeterminat	0	0	0

			(excluded)	e			
Total	1332	3912	5244	Total	1332	3912	5244
Test performance parameters							
IGRA				**TST**			
Sensitivity = 888/1332 = 66.67%, 95% CI (64.09, 69.15)				Sensitivity = 950/1332 = 71.32%, 95% CI (68.83, 73.69)			
Specificity = 2118/3899 = 54.32%, 95% CI (52.75, 55.88)				Specificity = 1968/3912 = 50.31%, 95% CI (48.74, 51.87)			
PPV = 888/2669 = 33.27%, 95% CI (31.51, 35.08)				PPV = 950/2894 = 32.83%, 95% CI (31.14, 34.56)			
NPV = 2118/2562 = 82.67%, 95% CI (81.16, 84.09)				NPV = 1968/2350 = 83.74%, 95% CI (82.2, 85.18)			
DOR (for T^+ calculated) = 2.38, 95% CI (2.09, 2.71)				DOR (for T^+ calculated) = 2.52, 95% CI (2.20, 2.88)			
OR (crude; for T^+ reported) = 2.40, 95% CI (2.11, 2.74)				OR (crude; for T^+ reported) = 2.52, 95% CI (2.20, 2.88)			
OR (regression-based; reported) = 1.90, 95% CI (1.70, 2.20) List of covariates: NR				OR (regression-based; reported) = 2.00 (1.70, 2.30) List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T+ calculated) = 0.94 (95% CI: 0.86, 1.04)							
Ratio of OR (crude; for T+ reported) = 0.94 (95% CI: 0.86, 1.04)							
Ratio of ORs (regression-based; reported) = 0.95 (95% CI: 0.86, 1.05)							
Other reported measure = NR							
Association between test results and BCG status (if applicable)							
IGRA (QFT-GIT)				**TST (≥ 5mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	2064	1490	3554	Total	2064	1490	3554
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = NA				DOR (for T+ calculated)$_{TST}$ = NA			
OR (crude; for T^+ reported) = 0.99, 95% CI (0.86, 1.12)				OR (crude; for T+ reported) = 1.16, 95% CI (1.0, 1.33)			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates:				OR (regression-based; reported) $_{TST}$ = NR List of covariates:			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample ≥ 5mm							
	TST +			TST -			Total
IGRA +	NR			NR			NR
IGRA -	NR			NR			NR
Indeterminate	NR			NR			NR
Total	NR			NR			NR
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total							
TST + threshold: ≥ 5mm							
Parameters							

Kappa = 0.70, 95% CI: 0.68, 0.71			
% concordance = 84.8% (95% CI NR)			
% discordance = NR			
Total sample (≥ 10mm)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥ 10mm			
Parameters			
Kappa = 0.63, 95% CI: 0.61, 0.65			
% concordance = 81.4% (95% CI NR)			
% discordance = NR			
Total sample (≥ 15mm)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify):			
TST + threshold: ≥ 15mm			
Parameters			
Kappa = 0.30, 95% CI: 0.27, 0.32			
% concordance = 64.3% (95% CI NR)			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
The predictive factor profile for both measures was similar
Reviewers:
TST was slightly influenced by BCG vaccination, but not IGRA; Both tests performed similarly in detection LTBI; 5mm threshold TST had better agreement than 10 and 15mm
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Metin Timur 2014[150]
Country: Turkey
Study design: prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify): community based contact study
Number of centres: NR
Total length of follow up (if applicable): 3 years as outpatients with 3 months intervals
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To compare QuantiFeron-TB gold in tube test (QFT-GIT) and tuberculin skin test (TST) as a diagnosis of latent tuberculosis infection in the children with Bacille Calmette-Guerin (BCG) vaccine

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: between 2008 and 2011
Total N of recruited patients: NR
Inclusion criteria: children with positive TST results, children without a history of contact with a TB case, active TB case in the household was not detected through the family screening, children having no medical reason for immunosuppression, children who had diagnosed TB disease without a contact with active TB case
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 81
Total N of patients with valid results for both IGRA and TST: 81
Methods of active TB diagnosis (if applicable): LTBI as defined both TST and QFT-GIT test positive in a children who had no abnormality on the chest x-ray. Active TB disease was defined both TST and QFT-GIT test positive in a child who had symptoms of TB disease and/or abnormal findings on chest radiograph, CT or proven M. tuberculosis culture, PCR or histo- pathological examination.
Outcomes (study-based) list: diagnosis of prevalent TB, incidence of active TB
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 94.8 ±51.9 months (range: 6-193)
Women (n [%]): 33 [40.7%]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): one BCG scar (69 [85.2%]; two BCG scars (12 [14.8%]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): None
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NA
Co-morbidity (n [%]): acute appendicitis (1 [1.2%])
Type of during-study treatment (n [%]): no treatment (n=69 children with TST^{+}/QFT^{-} results); isoniazid (n=8 children with TST^{+}/QFT^{+} results but no symptoms – assumed with LTBI); isoniazid, rifampicin and pyrazinamide (n=4 children with TST^{+}/QFT^{+} results with symptoms –with TB)

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	81	12	69	0	81

TST (≥15mm):	81	81	0	0	81
Total N of patients with valid results for both IGRA and TST: 81					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group					
Non-exposed	NA				
Exposed 1 **(specify)**:	NA				
Exposed 2 **(specify)**:	NA				
Exposed 3 **(specify)**:	NA				
Exposed 4 **(specify)**:	NA				

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Peripheral blood samples were taken in the laboratory, where they were processed by trained physicians and performed according to manufacturer's instructions. For each child, total 3 mL whole blood was taken, then blood was collected in three special tubes: gray- (negative control, ''nil''), red- (test tube), and purple-cap (positive control; mitogen-coated) tubes. Test tube is specially designed for blood collection which is coated with M. tuberculosis-specific antigens (ESAT-6, CFP-10, and a portion of TB 7.7). Once blood was collected it is essential to provide adequate shaking for antigens to dissolve. They were incubated at 37°C for 16 to 24 hours and centrifugation at 3000 g for 15 minutes, then plasma was separated. The amount of IFN-γ was measured by using the QFT ELISA	A positive result was defined if the difference in the IFN-γ levels between the test tube and negative control is greater than or equal to 0.35 IU/mL and is greater than 25% of the nil value. Also for determinate results, nil control must be < 8.0 IU/mL	
TST(≥15mm)	All children underwent a TST with 5 TU of purified protein derivative, according to intradermal Mantoux method	When interpreting a TST result, the widest diameter of induration, not erythema, was measured in millimetres after 72 hours by trained physician or nurses. TST was considered as positive if an induration was ≥ 15mm, regardless of BCG vaccination scar numbers	

Association between test results and incidence of active TB (if applicable)							
IGRA-GIT				**TST (≥15mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	0	0	0	TST +	0	69	69
IGRA -	0	69	69	TST -	0	0	0
indeterminate	0	0	0	indeterminate	0	0	0
Total	0	69	69	Total	0	69	69

Test performance parameters	
IGRA-GIT	**TST≥15mm**
Sensitivity = NA	Sensitivity = NA
Specificity = 69/69 = 100% (95% CI: NR)	Specificity = 0/69 = 0.0% (95% CI: NR)
PPV= NA	PPV = 0/69=0.0% (95% CI: NR)
NPV= 69/69 = 100% (95% CI: NR)	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = 0/69 = 0.0% (95% CI: NR)
Cumulative Incidence $_{IGRA-}$ = 0/69 = 0.0% (95% CI: NR)	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios= NA
Other reported measure= NA

Association between test results and levels of TB exposure (if applicable)							
IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA
NPV= NA	NPV= NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA				TST			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$= NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported) $_{IGRA}$= NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			

% concordance = NA
% discordance = NA
Conclusions
Authors:
Study suggests that confirmation of positive TST results with QFT- GIT test may enhance the accuracy of diagnosing both active TB and LTBI, particularly among BCG vaccinated children. The correct diagnosis of LTBI prevents unnecessary treatment and treatment complications
Reviewers:
None of the 69 children with TST positive results and QFT-GIT negative results developed active TB, indicating better specificity of QFT-GIT vs. TST (100% vs. 0%)
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Pavic 2011[109]
Country: Croatia
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Children hospital and general hospital
Number of centres: 2
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** None

Aim of the study

To evaluate an IGRA for diagnosis of LTBI in BCG –vaccinated children up to 5 years of age, with documented exposure to active TB

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Younger children with history of exposure to active TB

Participants

Recruitment dates: Between January 2008 and December 2009
Total N of recruited patients: 142
Inclusion criteria: Pediatric patients' ≤5 years of age and a documented exposure (close or distant contact) to a case of active TB. Close contact (household contact with aggregate exposure to a patient with active TB of not < 40 hours in closed room and distant contact (occasional or unclear exposure time of <40 hours during the presumed period of infectiousness)
Exclusion criteria: Children >5 years, immunocompromised children, inadequate blood sampling and diagnosis of active TB
Total N of excluded patients: 1 (diagnosed with pneumonia**:** data were not included in further statistical analysis)
Total N of patients tested with both IGRA and TST: 142
Total N of patients with valid results for both IGRA and TST: 141
Methods of active TB diagnosis (if applicable): Induration of ≥10mm
Outcomes (study-based) list: Test results, impact of age and on results of IGRA and level of agreement between IGRA and TST results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 29 ± 16 months
Women (n [%]): 57 [40.1]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 142 [100]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): NR
Co-morbidity (n [%]): Pneumonia 1 [0.7]
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	142	18	123	1	141
TST (≥10mm):	142	24	118	0	142
Test 3 (specify)	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 142					

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group	
Non-exposed	Distant contact was defined as occasional or unclear exposure time or < 40 hours during the presumed period of infectiousness.
Exposed 1 **(specify):**	Close contact was defined as household contact with aggregate exposure to a patient with active TB ≥40 hours in closed rooms
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT (Cellestis Limited, Chadstone, Australia)	≥ 0.35 IU/mL as recommended by the manufacturer.	Blood samples for QFT-GIT were drawn under standardized condition in our hospital at the same day as TST. The test was considered indeterminate if the value of the positive-control well was less than 0.5 IU/mL, and/or nil negative control was more than 8 IU/L
TST≥ 10 mm	Two tuberculin units of standardized purified protein derivative solution (Tuberculin PPD RT 23, Statens Serum Institute, Copenhagen, Denmark) injected into the volar aspect of the forearm and transverse induration and was measured by a trained healthcare worker 68 to 72 hours later	Induration ≥ 10 mm	NA

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (close contact)

IGRA (QFT-GIT)				TST≥ 10 mm			
	Exposure level		Total		Exposure level		Total
	Close	Distant			Close	Distant	
IGRA +	17	1	18	TST +	23	1	24
IGRA -	70	53	123	TST -	64	54	118
Indeterminate	0	1	1 (excluded)	Indeterminate	0	0	0
Total	87	54	141	Total	87	55	142

Test performance parameters

IGRA	TST
Sensitivity = 17/87 = 19.54%, 95% (12.57, 29.08)	Sensitivity = 23/87 = 26.44%, 95% (18.31, 36.56)
Specificity = 53/54 = 98.15%, 95% (90.23, 99.67)	Specificity = 54/55 = 98.18%, 95% (90.39, 99.68)
PPV = 17/18 = 94.44%, 95% (74.24, 99.01)	PPV = 23/24 = 95.83%, 95% CI (79.76, 99.26)
NPV = 53/123 = 43.09%, 95% (34.68, 51.92)	NPV = 54/118 = 45.76%, 95% CI (37.05, 54.74)
DOR (for T^+ calculated) = 12.87, 95% CI (1.66, 99.80)	DOR (for T^+ calculated) = 19.41, 95% CI (2.53, 148.40)
OR (crude; for T^+ reported) = 1.66, 95% CI (0.92, 3.35) error	OR (crude; for T^+ reported) = 1.75, 95% CI (0.92, 3.35) error
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 0.66 (95% CI: 0.15, 2.89)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT)				TST (>10 mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA (TSPOT/QFT)	TST (>5 mm)
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = NR OR (regression-based; reported)$_{TSPOT}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)

This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST +	TST -	Total
IGRA +	14	4	18
IGRA -	11	112	123
Indeterminate	0	1	1 (excluded)
Total	25	116	141
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total			
TST + threshold: ≥10 mm in duration			
Parameters			
Kappa = 0.59, 95% CI (0.42, 0.75)			
% concordance = 126/141 = 89.36%, 95% CI (83.19, 93.45)			
% discordance = 15/141 = 10.64%, 95% CI (6.554, 16.81)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
Authors concluded that in a high-risk population of children ≤ 5 years, both the TST and IGRA should be performed and a positive result on either test a suggestive of LTBI
Reviewers:
Tests performed similarly well in identifying LTBI by association with the active TB exposure

Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Perez-Porcuna 2014[151]
Country: Brazil
Study design: Cross-sectional/retrospective
Study setting (e.g., outbreak investigation, community-based - specify): community-based
Number of centres: 2
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify): the Brazilian National Counsel of Technological and Scientific Development (CNPq), the Foundation of Research Support of the State of Amazonas (FAPEAM), and the University of Barcelona. Cellestis Ltd. donated QuantiFERON test kits. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Aim of the study

To evaluate the response of the IGRA QuantiFERON-TB Gold In-Tube (QFT) and TST tests in young children with recent exposure to an index case

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: from March 2009 to February 2010
Total N of recruited patients: 140
Inclusion criteria: children from 0–6 years of age with recent contact with an adult symptomatic TB index case within the last 12 months
Exclusion criteria: Subjects receiving treatment or prophylaxis for TB
Total N of excluded patients: 3
Total N of patients tested with both IGRA and TST: 135
Total N of patients with valid results for both IGRA and TST: 116
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: between-test agreement, discordance, concordance, associations between different factors and test results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 46 (28.0; 64.5) months
Women (n [%]): 74 (54.8%)
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 118 (90.8%)
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NA
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	135	36	80	19	116
TST: ≥ 10mm	135	47	88	0	135

Total N of patients with valid results for both IGRA and TST: 116

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – Time of exposure to the index case

Non-exposed	NA		
Exposed **(specify)**:	# months measured as continuous covariate		
Definition of exposure group – mycobacterium tuberculosis contact (MTC) score: 0-15			
Non-exposed	NA		
Exposed **(specify)**:	MTC score measured as continuous covariate. The score is composed of infectivity of the index case (0–4), the duration of exposure hours per day (0–4), the relationship to the index case (0–4) and the type of exposure (0–3)		
Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA [QFT-GIT]	The QFT (Cellestis, Carnegie, Australia) was carried out and interpreted according to the manufacturer's instructions was considered indeterminate if there was excessive IFN-c production with the negative control tube $8.0 IU/mL	The result was positive (QFT+) if the net value of IFN-c to the TB antigens (after subtracting the negative control) was ≥0.35 U/mL and ≥25% of the value of the negative control, independently of the response of the mitogen. The result was negative if the net value of the IFN-c was <0.35 IU/mL and mitogen response was sufficient (≥0.50 IU/mL). The result was indeterminate if there was excessive IFN-c production with the negative control tube ≥8.0 IU/mL (indeterminate hypereactive) or with insufficient net mitogen response <0.50 IU/mL plus insufficient net response of the TB antigen < 0.35 IU/mL (indeterminate hyporeactive) When the QFT result was indeterminate the test was repeated to confirm the result	Experienced laboratory technicians who were unaware of the data of the study subjects
TST≥ 10mm	The TST was performed with an intradermic injection of 2 tuberculin units (TU) of PPD RT23 (Statens Serum Institut,	≥ 10mm positivity threshold according to the protocols of the WHO	Experienced laboratory technicians who were unaware of the data of the study subjects

	Copenhagen, Denmark) and read 72 hours thereafter	≥ 5-9 mm weak reaction ≥ 10mm strong reaction	

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST (≥10mm)**			
	Exposure level (# of months of exposure to the index case)		Total		Exposure level (# of months of exposure to the index case)		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated)= NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported)= NR (p=0.024) OR is associated with one unit increase in # of exposure months	OR (crude; for T^+ reported) = NR (p<0.001) OR is associated with one unit increase in # of exposure months
OR (regression-based; reported) = NR (p = 0.537); OR is associated with one unit increase in # of exposure months List of covariates: NR	OR (regression-based; reported) = 1.15 (95% CI 1.04, 1.27; p = 0.009) OR is associated with one unit increase in # of exposure months

				List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NA							
Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST (≥10mm)**			
	Exposure level (MTC score)		Total		Exposure level (MTC score)		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR
Test performance parameters							
IGRA				**TST**			
Sensitivity = NA				Sensitivity = NA			
Specificity = NA				Specificity = NA			
PPV= NA				PPV= NA			
NPV= NA				NPV= NA			
DOR (for T^+ calculated) = NA				DOR (for T^+ calculated) = NA			
OR (crude; for T^+ reported) = NR (p = 0.021) OR is associated with one unit increase in MTC score				OR (crude; for T^+ reported) = NR (p<0.001) OR is associated with one unit increase in # MTC score			
OR (regression-based; reported) = 1.16 (95% CI 1.01, 1.33; p = 0.035); OR is associated with one unit increase in MTC score List of covariates: NR				OR (regression-based; reported) = 1.29 (95% CI 1.08, 1.54; p = 0.005) OR is associated with one unit increase in MTC score List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = 0.90 (95% CI: 0.80, 1.01)							
Other reported measure= NA							
Association between test results and BCG status (if applicable)							
IGRA (GIT)				**TST (10mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	35	1	36	TST +	37	2	39
IGRA -	72	8	80	TST -	70	7	77
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	107	9	116	Total	107	9	116
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = 3.89 (95% CI: 0.46, 32.33)				DOR (for T+ calculated)$_{TST}$ = 1.85 (95% CI: 0.36, 9.36)			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates:				OR (regression-based; reported) $_{TST}$ = NR List of covariates:			
Other reported measure = NR				Other reported measure = NR			

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST + (≥10mm)	TST -	Total
IGRA +	21	15	36
IGRA -	18	62	80
indeterminate	8	11	19
Total	47	88	135
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.35 (95% CI: 0.16, 0.53) p<0.001			
% concordance = [21+62]/116=71.55 (95% CI: 62.75, 78.97)			
% discordance = [18+15]/116 = 28.44 (95% CI: 21.03, 37.25)			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Conclusions			
Authors:			
We observed that the results of both tests were related to the intensity of exposure, although, as previously reported, the TST was more strongly influenced by exposure than QFT. Another factor we observed was that TST+ results were related to a greater time of exposure while the same was not observed for QFT. Likewise, we did not observe any association between the TST results and the presence of a BCG scar. Analysis of our data supports the contention that QFT probably undergoes more rapid conversion (step from negative to positive) after primary infection than the TST and would explain most of the discordant test results in this group			
Reviewers:			
Both the TST and QFT were associated with the intensity of exposure (MTC score) with only the TST being significantly associated with the time of exposure (regression-based analyses). Concordance			

between the TST and QFT (excluding the indeterminate cases) was fair (Kappa = 0.35); presence of BCG scar did not significantly influence the odds of TST or IGRA
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Rutherford 2012a[110] and Rutherford 2012b[111] (same study but plus neighborhood contacts; agreement analysis)
Country: Indonesia
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Out-patient-based clinic
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** NR

Aim of the study

aimed to quantify M. tuberculosis infection in children living with a smear-positive adult TB case and identify risk factors for TST and QFT-GIT positivity

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: NR
Total N of recruited patients: 320
Inclusion criteria: Child contacts living for more than 3 months with newly diagnosed TB cases (index case) who were smear and chest X-ray (CXR) positive
Exclusion criteria: Child contacts who had received a diagnosis of TB disease within the past year or who were aged <6 months were excluded (the latter due to known poor parental acceptability of blood collection)
Total N of excluded patients: 16 (active TB)
Total N of patients tested with both IGRA and TST: 304
Total N of patients with valid results for both IGRA and TST: 288
Methods of active TB diagnosis (if applicable): Active TB was defined by CXR findings consistent with TB according to the consultants
Outcomes (study-based) list: Association of test positivity with exposure factors (Rutherford 2012a), agreement (Rutherford 2012b)
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median [IQR] 58 [31–81] months
Women (n [%]): 152 [50.7]
Race/ethnicity (n [%]): Sundanese (284 [93.7]), Other (19 [6.3])
Geographic origin (n[%]): NR
BCG vaccination (n [%]): With scar (221 [73.2]), unknown BCG status (30 [9.9])
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes (Children who were symptomatic and test-negative (on either IGRA or TST) were referred to the children's clinic for further assessment according to clinic policy
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	304	152	138	14	290
TST (≥10mm):	304	145	157	2	302
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 288

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group – Characteristics of TB case smear positivity	
Non-exposed	Scanty and 1+
Exposed 1 **(specify):**	2+
Exposed 2 **(specify):**	3+
Definition of exposure group – Relationship to child	
Non-exposed	Other
Exposed 1 **(specify):**	Aunt/uncle
Exposed 2 **(specify):**	Parent
Definition of exposure group – Sleeping proximity to child	
Non-exposed	Different room
Exposed 1 **(specify):**	Same room
Exposed 2 **(specify):**	Same bed
Definition of exposure group – Time spent with child (# hrs/day)	
Non-exposed	< 2
Exposed 1 **(specify):**	2 - 8
Exposed 2 **(specify):**	> 8

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA (QFT-GIT)	For QFT-GIT, 3 ml of venous blood was collected into a syringe; 1 ml was immediately transferred to each of the QFT-GIT tubes (nil, mitogen and antigen). The tubes were vigorously hand-shaken and placed in an incubator within 3 h. Incubated samples were centrifuged and stored at 4°C for up to 1 month. The QFT-GIT assay was conducted and interpreted according to the manufacturer's instructions using specific software	NR	NA
TST (≥10mm)	TST was performed by the study nurse following blood collection using two tuberculin units of purified protein derivative (PPD; RT23 Biofarma®, Bandung, Indonesia). Induration was measured 48–72 h after administration and confirmed by the study doctor	An induration of ⩾10 mm was considered positive	NA

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)					**TST (≥10mm)**				
	Exposure level characteristics of TB case Smear positivity			Total		Exposure level characteristics of TB case Smear positivity			Total
	3+	2+	Scanty/1+			3+	2+	Scanty/1+	
IGRA +	75	36	40	152	TST +	78	34	33	145
IGRA -	45	34	59	138	TST -	48	38	71	157
Indeterminate	NR	NR	NR	14 (excluded)	Indeterminate	NR	NR	NR	2 (excluded)
Total	120	70	99	290	Total	126	72	104	302

Test performance parameters

IGRA	**TST**
Trend in ORs across the gradient of exposure (p = 0.001) Scanty/1+: OR (crude; reported) = 1.00 (reference group) 2+: OR (crude; reported) = 1.56 (95% CI: 0.78, 3.11) 3+: OR (crude; reported) = 2.43 (95% CI: 1.21, 4.86) **3+ vs. scanty/1+** Sensitivity = 75/120 = 62.5% (95% CI: 53.58, 70.65) Specificity = 59/99 = 59.6% (95% CI: 49.75, 68.73) PPV = 75/115 = 65.22% (95% CI: 56.15, 73.3) NPV = 59/104 = 56.73% (95% CI: 47.14, 65.85) DOR (for T^+ calculated) = 2.46 (95% CI: 1.42, 4.24) OR (crude; for T^+ reported) = 2.43 (95% CI: 1.21, 4.86) OR (regression-based; reported) = 2.28 (95% CI: 1.06, 4.90) List of covariates: TB case's relationship to child, marital status of household head Other reported measure = NR	Trend in ORs across the gradient of exposure (p = 0.000) Scanty/1+: OR (crude; reported) = 1.00 (reference group) 2+: OR (crude; reported) = 1.80 (95% CI: 0.89, 3.63) 3+: OR (crude; reported) = 3.35 (95% CI: 1.81, 6.21) **3+ vs. scanty/1+** Sensitivity = 78/126 = 61.9% (95% CI: 53.19, 69.91) Specificity = 71/104 = 68.27% (95% CI: 58.81, 76.43) PPV = 78/111 = 70.27% (95% CI: 61.21, 77.98) NPV = 71/119 = 59.66% (95% CI: 50.68, 68.04) DOR (for T^+ calculated) = 3.50 (95% CI: 2.02, 6.04) OR (crude; for T^+ reported) = 3.35 (95% CI: 1.81, 6.21) OR (regression-based; reported) = 2.93 (95% CI: 1.59, 5.39) List of covariates: TB case's relationship to child Other reported measure = NR

Comparison between tests (IGRA vs. TST)

3+ vs. scanty/1+ Ratio of DORs (for T^+ calculated) = 0.70 (95% CI: 0.47, 1.04)
3+ vs. scanty/1+ Ratio of OR (crude; for T^+ reported) = 0.73 (95% CI: 0.45, 1.17)
3+ vs. scanty/1+ Ratio of ORs (regression-based; reported) = 0.78(95% CI: 0.47, 1.28)
Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)			**TST (≥10mm)**		
	Exposure level	Total		Exposure level	Total

	relationship to child					relationship to child			
	parent	Aunt or uncle	Other			parent	Aunt or uncle	Other	
IGRA +	134	8	10	152	TST +	128	9	8	145
IGRA -	85	19	34	138	TST -	101	19	37	157
Indeterminate	NR	NR	NR	14 (excluded)	Indeterminate	NR	NR	NR	2 (excluded)
Total	219	27	44	290	Total	229	28	45	302

Test performance parameters

IGRA	TST
Trend in ORs across the gradient of exposure (p = 0.000) Other: OR (crude; reported) = 1.00 (reference group) Aunt/uncle: OR (crude; reported) = 1.51 (95% CI: 0.44, 5.17) Parent: OR (crude; reported) = 5.61 (95% CI: 2.40, 13.12) **Parent vs. Other** Sensitivity = 134/219 = 61.19% (95% CI: 54.59, 67.4) Specificity = 34/44 = 77.27% (95% CI: 63.01, 87.16) PPV = 134/144 = 93.06% (95% CI: 87.69, 96.18) NPV = 34/119 = 28.57% (95% CI: 21.22, 37.26) DOR (for T^+ calculated) = 5.36 (95% CI: 2.52, 11.41) OR (crude; for T^+ reported) = 5.61 (95% CI: 2.40, 13.12) OR (regression-based; reported) = 4.30 (95% CI: 1.48, 12.45) List of covariates: marital status of household head, smear positivity of household head Other reported measure = NR	Trend in ORs across the gradient of exposure (p = 0.000) Other: OR (crude; reported) = 1.00 (reference group) Aunt/uncle: OR (crude; reported) = 2.31 (95% CI: 0.77, 6.79) Parent: OR (crude; reported) = 5.85 (95% CI: 2.56, 13.38) **Parent vs. Other** Sensitivity = 128/229 = 55.9% (95% CI: 49.42, 62.18) Specificity = 37/45 = 82.22% (95% CI: 68.67, 90.71) PPV = 128/136 = 94.12% (95% CI: 88.82, 96.99) NPV = 37/138 = 26.81% (95% CI: 20.12, 34.76) DOR (for T^+ calculated) = 5.86 (95% CI: 2.61, 13.14) OR (crude; for T^+ reported) = 5.85 (95% CI: 2.56, 13.38) OR (regression-based; reported) = 7.04 (95% CI: 2.23, 22.28) List of covariates: marital status and smear positivity of household head Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Parent vs. Other
Ratio of DORs (for T^+ calculated) = 0.91 (95% CI: 0.52, 1.61)

Parent vs. Other
Ratio of OR (crude; for T^+ reported) = 0.96 (95% CI: 0.52, 1.75)

Parent vs. Other
Ratio of ORs (regression-based; reported) = 0.61 (95% CI: 0.27, 1.36)

Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)					TST (≥10mm)				
	Exposure level Sleeping proximity to child			Total		Exposure level Sleeping proximity to child			Total
	Same bed	Same room	Different room			Same bed	Same room	Different room	
IGRA +	93	15	43	152	TST +	85	13	47	145
IGRA -	64	12	62	138	TST -	80	15	62	157

Indeterminate	NR	NR	NR	14 (excluded)	Indeterminate	NR	NR	NR	2 (excluded)
Total	157	27	105	290	Total	165	28	109	302

Test performance parameters	
IGRA	**TST**
Trend in ORs across the gradient of exposure (p = 0.006) Different room: OR (crude; reported) = 1.00 (reference group) Same room: OR (crude; reported) = 1.87 (95% CI: 0.70, 5.02) Same bed: OR (crude; reported) = 2.01 (95% CI: 1.12, 3.61) **Same bed vs. different room** Sensitivity = 93/157 = 59.24% (95% CI: 51.42, 66.61) Specificity = 62/105 = 59.05% (95% CI: 49.48, 67.97) PPV = 93/136 = 68.38% (95% CI: 60.15, 75.6) NPV = 62/126 = 49.21% (95% CI: 40.63, 57.83) DOR (for T^+ calculated) = 2.09 (95% CI: 1.26 , 3.46) OR (crude; for T^+ reported) = 2.01 (95% CI: 1.12, 3.61) OR (regression-based; reported) = 1.45 (95% CI: 0.70, 2.99) List of covariates: case's relationship to child, age of child, smear positivity Other reported measure = NR	Trend in ORs across the gradient of exposure (p = 0.186) Different room: OR (crude; reported) = 1.00 (reference group) Same room: OR (crude; reported) = 1.21 (95% CI: 0.41, 3.53) Same bed: OR (crude; reported) = 1.35 (95% CI: 0.79, 2.32) **Same bed vs. different room** Sensitivity = 85/165 = 51.52% (95% CI: 43.94, 59.02) Specificity = 62/109 = 56.88% (95% CI: 47.51, 65.79) PPV = 85/132 = 64.39% (95% CI: 55.92, 72.05) NPV = 62/142 = 43.66% (95% CI: 35.78, 51.88) DOR (for T^+ calculated) = 1.40 (95% CI: 0.86, 2.28) OR (crude; for T^+ reported) = 1.35 (95% CI: 0.79, 2.32) OR (regression-based; reported) = NR List of covariates: NA Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Same bed vs. different room Ratio of DORs (for T^+ calculated) = 1.49 (95% CI: 1.04, 2.14)	
Same bed vs. different room Ratio of OR (crude; for T^+ reported) = 1.47 (95% CI: 1.05, 2.16)	
Same bed vs. different room Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NR	

Association between test results and levels of TB exposure (if applicable)									
IGRA (QFT-GIT)					**TST (≥10mm)**				
	Exposure level Time spent with child h/day			Total		Exposure level Time spent with child h/day			Total
	>8	2-8	<2			>8	2-8	<2	
IGRA +	78	46	27	152	TST +	75	42	28	145
IGRA -	72	46	20	138	TST -	83	54	20	157
Indeterminate	NR	NR	NR	14 (excluded)	Indeterminate	NR	NR	NR	2 (excluded)
Total	150	92	47	290	Total	158	96	48	302

Test performance parameters	
IGRA	**TST**
Trend in ORs across the gradient of exposure (p = 0.948) <2 h: OR (crude; reported) = 1.00 (reference group) 2-8 h: OR (crude; reported) = 0.78 (95% CI: 0.33, 1.80) >8 h: OR (crude; reported) = 0.83 (95% CI: 0.38, 1.79)	Trend in ORs across the gradient of exposure (p = 0.494) <2 h: OR (crude; reported) = 1.00 (reference group) 2-8 h: OR (crude; reported) = 0.55 (95% CI: 0.24, 1.24)

>8 vs. <2 Sensitivity = 78/150 = 52.00% (95% CI: 44.06, 59.85) Specificity = 20/47 = 42.55% (95% CI: 29.51, 56.72) PPV = 78/105 = 74.29% (95% CI: 65.17, 81.68) NPV = 20/92 = 21.74% (95% CI: 14.54, 31.21) DOR (for T^+ calculated) = 0.80 (95% CI: 0.41, 1.55) OR (crude; for T^+ reported) = 0.83 (95% CI: 0.38, 1.79) OR (regression-based; reported) = NR List of covariates: NA Other reported measure = NR	>8 h: OR (crude; reported) = 0.64 (95% CI: 0.31, 1.36) **>8 vs. <2** Sensitivity = 75/158 = 47.47% (95% CI: 39.83, 55.22) Specificity = 20/48 = 41.67% (95% CI: 28.85, 55.72) PPV = 75/103 = 72.82% (95% CI: 63.52, 80.47) NPV = 20/103 = 19.42% (95% CI: 12.94, 28.1) DOR (for T^+ calculated) = 0.64 (95% CI: 0.33, 1.24) OR (crude; for T^+ reported) = 0.64 (95% CI: 0.31, 1.36) OR (regression-based; reported) = NR List of covariates: NA Other reported measure = NR

Comparison between tests (IGRA vs. TST)

>8 vs. <2
Ratio of DORs (for T^+ calculated) = 1.25 (95% CI: 0.77, 2.02)

>8 vs. <2
Ratio of OR (crude; for T^+ reported) = 1.30 (95% CI: 0.75, 2.24)

>8 vs. <2
Ratio of ORs (regression-based; reported) = NA

Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	104	34	138	TST +	105	29	134
IGRA -	105	17	122	TST -	116	22	138
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	209	51	260	Total	221	51	272

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = 0.49 (95% CI: 0.26, 0.94)	DOR (for T+ calculated)$_{TST}$ = 0.68 (95% CI: 0.37, 1.27)
OR (crude; for T^+ reported) = 0.51 (95% CI: 0.26, 1.00)	OR (crude; for T+ reported) = 0.68 (95% CI: 0.35, 1.35)
OR (regression-based; reported) $_{IGRA}$ = 0.60 (95% CI: 0.26, 1.38) List of covariates: TB case's relationship to child, marital status of household head	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

From Rutherford 2012b	TST +	TST -	Total
IGRA +	121	35	156
IGRA -	22	114	136
Indeterminate	1 (excluded)	6 (excluded)	7 (excluded)
Total	143	149	292

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total (household contacts of TB cases)

TST + threshold: ≥10mm

Parameters

Kappa = 0.61 (95% CI: 0.49, 0.72)			
% concordance = 235/292 = 80.48% (95% CI: 75.55, 84.62)			
% discordance = 57/292 = 19.52% (95% CI: 15.38, 24.45)			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			

% concordance = NR		
% discordance = NR		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
In this setting, M. tuberculosis infection by either test was high in children living with a smear-positive TB case. Test positivity was driven by high index case infectivity levels and intimacy of exposure (if the index case was the child contact's parent). Child contacts whose parent was the index case were over four times as likely to be positive by both or either tests. High increased risk of M. tuberculosis infection when the index case is the parent, particularly the mother, has been reported elsewhere. Both the TST and QFT-GIT responded as expected to most hypothesised risk factors, and neither test performed significantly better than the other along any of the gradients		
Reviewers:		
IGRA and TST performed well showing similar strong associations with a) characteristics of TB case smear positivity and b) relationship to child. IGRA did better than TST for sleeping proximity. Neither test showed association with time spent with child. None of the tests was influenced by BCG status		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details					
First author surname year of publication: Talbot 2012[112] **Country:** US **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** College health setting **Number of centres:** 1 **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Oxford Immunotec					
Aim of the study					
To test the specificity of the tuberculin skin test and the T-SPOT.TB assay among students at low risk for TB exposure					
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)					
Children (student at low risk for TB exposure)					
Participants					
Recruitment dates: NA **Total N of recruited patients:** 184 **Inclusion criteria:** Students with history of exposure to TB **Exclusion criteria:** NR **Total N of excluded patients:** 4 (procedural errors at the laboratory) **Total N of patients tested with both IGRA and TST:** 180 **Total N of patients with valid results for both IGRA and TST:** 143 **Methods of active TB diagnosis (if applicable):** NA **Outcomes (study-based) list:** Test results, specificity test **Characteristics of participants (total study sample)** Mean (range or SD) age (years): Median age 20 [17-47] Women (n [%]): 97 [53.9] Race/ethnicity (n [%]): US-born (165 [91.7]); White (135 [75]) Geographic origin (n[%]): NR BCG vaccination (n [%]): 7 [3.9] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): NR Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity (n [%]): NR Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): NR					
Number of patients tested					
	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (T-SPOT.TB):	180	5	138	15	143
TST (> 15mm):	180	6	137	22	143
Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 143					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group					
Non-exposed	Low-TB exposure risk group				
Exposed 1 **(specify):**	Non-low-TB exposure risk (any history of exposure to TB through country of birth, residence, or visits>3 weeks to high–TB burden areas [>40 cases/100,000				

	population], or occupational exposure)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA (T-SPOT.TB)	Blood was tested for LTBI by using T-SPOT.TB according to the manufacturer's instructions for use. Peripheral blood mononuclear cells (PBMCs) were harvested by Ficoll density gradient centrifugation, washed, counted, and plated at 2.5 × 105 cells per well into a membrane-bottomed plate coated with anti-interferon-γ antibody. PBMCs from each study participant were incubated overnight in the presence of the provided TB antigens ESAT-6 and CFP-10, along with controls (positive mitogen control and a nil control). The PBMCs producing interferon-γ were revealed as spots by incubation with an enzyme-conjugated secondary antibody for interferon-γ and a color-producing enzyme substrate. Spots were counted, and clinical results recorded according to the approved algorithm in the package insert where, compared to the nil control, 8 spots and above is positive and 4 spots and below is negative	Results with spot counts of 5–7 are regarded as borderline, and results with a low mitogen response or a high nil control response are indeterminate	NA
TST> 15mm	TSTs were administered by trained professionals who used the Mantoux method intradermally according to published guidelines	A TST was considered positive if there was an induration > 15mm for students with no risk factors for TB exposure	NA

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (TB exposure risk group)

IGRA (T-SPOT.TB)				TST≥15mm			
	Exposure level		Total		Exposure level		Total
	Non-low	Low			Non-low	Low	
IGRA (T-SPOT.TB) +	NR	0	NR	TST +	NR	2	NR
IGRA (T-SPOT.TB) -	NR	124	NR	TST -	NR	122	NR
Indeterminate	NR	NR	0	Indeterminate	NR	NR	0
Total	NR	124	NR	Total	NR	124	NR

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = 124/124 = 100.00% (95% CI: 97, 100.00)	Specificity = 122/124 = 98.39% (95% CI: 94.31, 99.56)
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				TST (>15 mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = NR OR (regression-based; reported)$_{TSPOT}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample			
	TST +	TST -	Total
IGRA +	4	1	5
IGRA -	2	136	138
Indeterminate	0	0	0
Total	6	137	143
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total			
TST + threshold: >15mm induration			
Parameters			
Kappa = 0.71, 95% CI (0.55, 0.88)			
% concordance = 140/143 = 97.9%, 95% CI (94.01, 99.28)			
% discordance = 3/143 = 2.01%, 95% CI (0.72, 5.99)			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
The authors concluded that T-SPOT.TB specificity in a low-TB incidence, largely immunocompetent, non-BCG-vaccinated population, is high. Further research is required to inform on the policy decisions for LTBI screening
Reviewers:
TBSPOT specificity was slightly higher than that of TST
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Tieu 2014[154]
Country: Thailand
Study design: cross-sectional/retrospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify): community-based
Number of centres: 3
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify): This study was funded by a competitive, investigator-initiated research grant from Tibotec REACH Initiative. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Aim of the study

To compare the performances of the IGRAs (T-Spot.TB, QuantiFERON-TB Gold In-tube) and TST at two different cut-off thresholds (10 mm and 15 mm) in Thai children who had recent exposure to an adult index case with TB

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: Between September 2009 and December 2011
Total N of recruited patients: 137 [TB exposed]
Inclusion criteria: Children between the ages of 2 months and 16 years with recent exposure (defined as having lived with and/or having had close contact with) to adults with active pulmonary TB (confirmed by
positive AFB stain, PCR for TB, or TB culture), with or without extra-pulmonary TB manifestations
Exclusion criteria: Children's caregivers refused study participation, if they were receiving anti-TB medications for TB disease (including isoniazid [INH] for latent TB), or if they had recently been diagnosed with active TB
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 137
Total N of patients with valid results for both IGRA and TST: 136
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: between test agreement, association between prior exposure and test results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 7.6 (4.3)
Women (n [%]): 67 (49.3)
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 132 (96.4)
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): None [for TB exposed]

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	136	40	96	0	136
TST:≥10mm	136	88	48	0	136

TST:≥15mm	136	48	88	0	136
TSPOT	136	36	100	0	136
Total N of patients with valid results for both IGRA and TST: 136					
Levels/groups of exposure to TB in increasing order (if applicable):					
1. Definition of exposure group – TB contact score (range 6-19)					
Non-exposed	TB contact score (8-10)				
Exposed 1 **(specify)**:	TB contact score (11-12)				
Exposed 2 **(specify)**:	TB contact score (13-14)				
Exposed 3 **(specify)**:	TB contact score (15-16)				
2. Definition of exposure group – TB contact score (range 6-19)					
Non-exposed	TB contact score (8-12)				
Exposed 1 **(specify)**:	TB contact score (≥13)				
3. Definition of exposure group – relationship to TB index case					
Non-exposed	Relative other contact in household with TB				
Exposed 1 **(specify)**:	Second caregiver in household with TB				
Exposed 2 **(specify)**:	Primary caregiver in household with TB				
4. Definition of exposure group – Duration of average contact per day with TB index case					
Non-exposed	0-7 hours				
Exposed 1 **(specify)**:	≥8 hours				
5. Definition of exposure group – Duration of contact with TB index case in last 12 months					
Non-exposed	≤7 months				
Exposed 1 **(specify)**:	>7 months				
6. Definition of exposure group – Index TB case history					
Non-exposed	Sputum acid fast smear negative				
Exposed 1 **(specify)**:	Sputum acid fast smear positive				
Tests					

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	The children had whole blood and peripheral blood mononuclear cells collection for the interferon-gamma release assay (QFNGIT) The blood samples were sent on the same day of collection to the laboratory for testing according to the manufacturers' instructions using positive and negative controls	Results were reported as positive, negative, or indeterminate according to the manufacturers' guidelines Positive cutoff values for the tests were defined using the manufacturers' standard guidelines	Study investigators, site coordinators, and clinicians were blinded to the results of the IGRAs until the study had completed enrollment and 9-month follow-up
TST≥10mm TST≥15mm	At the baseline visit, the children had a TST (0.1 ml solution or 10 international units of tuberculin purified protein derivative) implanted on the forearm followed by result reading by trained health care personnel in 48–72 hours, in accordance with Thai	The size of TST induration was determined by measuring the maximum width (or transverse diameter) of an indurated lesion; test positivity was defined at ≥10mm or ≥15mm	

	national guidelines		
T-SPOT.TB	The children had whole blood and peripheral blood mononuclear cells collection for the interferon-gamma release assay (TSPOT). The blood samples were sent on the same day of collection to the laboratory for testing according to the manufacturers' instructions using positive and negative controls	Results were reported as positive, negative, or indeterminate Positive cutoff values were defined using the manufacturers' standard guidelines	

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥10mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA

NPV= NA	NPV= NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = **TB contact score (range 6-19)** Score 8-10 (reference/non-exposed): 1.0 Score 11-12: 2.00 (95% CI: 0.38, 10.61) Score 13-14: 3.64 (95% CI: 0.75,17.77) Score 15-16: 7.50 (95% CI: 1.35, 41.71) **TB contact score (range 6-19)** Score 8-12 (reference/non-exposed): 1.0 Score ≥13: 4.04 (95% CI: 1.81, 8.99) **Relationship to TB index case** Relative other contact (reference/non-exposed): 1.0 Second caregiver: 3.95 (95% CI: 1.50, 10.43) Primary caregiver: 3.25 (95% CI: 1.36, 7.77) **Duration of average contact per day with TB index case** 0-7 hours (reference/non-exposed): 1.0 ≥8 hours: 1.75 (95% CI: 0.78, 4.00) **Duration of contact with TB index case in last 12 months** ≤7 months (reference/non-exposed): 1.0 >7 months: 1.96 (95% CI: 0.99, 3.84) **Index TB case history** Sputum acid fast smear negative (reference/non-exposed): 1.0 Sputum acid fast smear positive: 0.97 (95% CI: 0.27, 3.33)	OR (crude; for T^+ reported) = **TB contact score (range 6-19)** Score 8-10 (reference/non-exposed): 1.0 Score 11-12: 3.97 (95% CI: 1.19, 13.28) Score 13-14: 4.40 (95% CI: 1.38, 14.08) Score 15-16: 7.33 (95% CI: 1.67,32.21) **TB contact score (range 6-19)** Score 8-12 (reference/non-exposed): 1.0 Score ≥13: 2.59 (95% CI: 1.28, 5.23) **Relationship to TB index case** Relative other contact (reference/non-exposed): 1.0 Second caregiver: 0.87 (95% CI: 0.34, 2.23) Primary caregiver: 1.44 (95% CI: 0.61, 3.41) **Duration of average contact per day with TB index case** 0-7 hours (reference/non-exposed): 1.0 ≥8 hours: 2.27 (95% CI: 1.08, 4.76) **Duration of contact with TB index case in last 12 months** ≤7 months (reference/non-exposed): 1.0 >7 months: 2.04 (95% CI: 1.00, 4.16) **Index TB case history** Sputum acid fast smear negative (reference/non-exposed): 1.0 Sputum acid fast smear positive: 2.38 (95% CI: 0.49, 11.11)
OR (regression-based; reported) = **TB contact score (range 6-19)** Score 8-10 (reference/non-exposed): 1.0 Score 11-12: NR Score 13-14: NR Score 15-16: NR **TB contact score (range 6-19)** Score 8-12 (reference/non-exposed): 1.0 Score ≥13: 1.98 (95% CI: 0.64, 6.11) **Relationship to TB index case** Relative other contact (reference/non-exposed): 1.0 Second caregiver: 3.95 (95% CI: 1.25, 12.52) Primary caregiver: 4.07 (95% CI: 1.38, 11.99) **Duration of average contact per day with TB index case** 0-7 hours (reference/non-exposed): 1.0 ≥8 hours: NR	OR (regression-based; reported) = **TB contact score (range 6-19)** Score 8-10 (reference/non-exposed): 1.0 Score 11-12: NR Score 13-14: NR Score 15-16: NR **TB contact score (range 6-19)** Score 8-12 (reference/non-exposed): 1.0 Score ≥13: 2.21 (95% CI: 0.99, 4.98) **Relationship to TB index case** Relative other contact (reference/non-exposed): 1.0 Second caregiver: NR Primary caregiver: NR **Duration of average contact per day with TB index case** 0-7 hours (reference/non-exposed): 1.0

Duration of contact with TB index case in last 12 months ≤7 months (reference/non-exposed): 1.0 >7 months: 1.47 (95% CI: 0.62, 3.44) **Index TB case history** Sputum acid fast smear negative (reference/non-exposed): 1.0 Sputum acid fast smear positive: NR List of covariates: NR	≥8 hours: 1.61 (95% CI: 0.68, 3.84) **Duration of contact with TB index case in last 12 months** ≤7 months (reference/non-exposed): 1.0 >7 months: NR **Index TB case history** Sputum acid fast smear negative (reference/non-exposed): 1.0 Sputum acid fast smear positive: NR List of covariates: NR
Other reported measure = NR	Other reported measure =NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated)=NA
Ratio of OR (crude; for T^+ reported)= TB contact score: 13+ vs. 8-12 [GIT vs. TST-10mm]=1.56 (95% CI: 0.91, 2.69) Ratio of OR (crude; for T+ reported)=TB contact score: 13+ vs. 8-12 [GIT vs. TST-15mm]=1.84 (95% CI: 1.07, 3.18)
Ratio of ORs (regression-based; reported)=TB contact score: 13+ vs. 8-12 [GIT vs. TST-10mm]= 0.90 (95% CI: 0.44, 1.82) Ratio of ORs (regression-based; reported)=TB contact score: 13+ vs. 8-12 [GIT vs. TST-15mm]=2.39 (95% CI: 1.15, 4.93)
Other reported measure= NR

Association between test results and BCG status (if applicable)

IGRA (specify)				**TST (specify)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$= NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST ≥10mm	TST -	Total
IGRA [QFT-GIT] +	36	2	38
IGRA -	51	42	93
indeterminate	NR	NR	NR
Total	87	44	131

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total
TST + threshold: ≥10mm

Parameters

Kappa = 0.29 (95% CI 0.18, 0.40)
% concordance = [36+42]/131=59.54% (95% CI: 50.98, 67.56)

% discordance = 53/131=40.46% (95% CI: 32.44, 49.02)			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST ≥15mm	TST -	Total
IGRA [QFT-GIT] +	29	9	38
IGRA -	18	75	93
indeterminate	NR	NR	NR
Total	47	84	131
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥15mm			
Parameters			
Kappa = 0.53 (95% CI 0.38, 0.69)			
% concordance = [29+75]/131=79.39% (95% CI 71.67, 85.43)			
% discordance = 27/131=20.61% (95% CI 14.57, 28.33)			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST ≥10mm	TST -	Total
IGRA [TSPOT] +	32	3	35
IGRA -	55	41	96
indeterminate	NR	NR	NR
Total	87	44	131
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.23 (95% CI 0.12, 0.34)			
% concordance = [32+41]/131=55.73% (95% CI 47.18, 63.95)			
% discordance = 58/131=44.27% (95% CI 36.05, 52.82)			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST ≥15mm	TST -	Total
IGRA [TSPOT] +	27	8	35
IGRA -	20	76	96
indeterminate	NR	NR	NR
Total	47	84	131
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥15mm			
Parameters			
Kappa = 0.51 (95% CI 0.35, 0.66)			
% concordance = [27+76]/131 = 78.63% (95% CI 70.84, 84.78)			
% discordance = 28/131 = 21.37% (95% CI 15.22, 29.16)			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Conclusions			
Authors:			
Both QFNGIT and T-Spot.TB performed well in our generally healthy Thai pediatric study population with recent exposure to adults with active pulmonary TB, with no indeterminate or equivocal/borderline results. No significant differences were found between the performances of the IGRAs and TST at the two cut-offs with increasing TB exposure. Concordance for positive IGRAs and TST ranged from 42–46% for TST≥10 mm and 62–67% for TST≥15 mm. On multivariable analyses, exposure to household secondary caregiver with TB was associated with positive QFNGIT. Higher TB contact score was associated with positive T-Spot.TB.			
Reviewers:			
QFT and TSPOT had similar concordance with TST (at both thresholds); however, this concordance was higher when TST threshold was 15mm (vs. 10mm). On average, TSPOT and QFT performed similarly better in relation to TST, especially compared to TST 15mm			
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Tsolia 2010[113]
Country: Greece
Study design: Retrospective cohort/cross sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** TB clinic
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** The Bienmoyo Foundation

Aim of the study

To evaluate and compare the performance of the QFT-GIT assay and the TST among children with active TB or possible latent TB infection in a low endemicity setting.

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: 1st January 2007 to 31st December 2003
Total N of recruited patients: 295
Inclusion criteria: Adolescents ≤ 15 years
Exclusion criteria: NR
Total N of excluded patients: 9 (refusal, lost specimen, sample processing delay)
Total N of patients tested with both IGRA and TST:
Total N of patients with valid results for both IGRA and TST: 286 (total sample including active TB patients)
Methods of active TB diagnosis (if applicable): Based on CDC criteria and MTB isolation from culture
Outcomes (study-based) list: Agreement; association between test results and risk factors
Characteristics of participants (total study sample)
Mean (range or SD) age (years): NR
Women (n [%]): NR
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	99 (patients in contact with adult TB)	32	63	4	95
TST (≥ 5mm):	99 (patients in contact with adult TB)	55	44	0	99
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 95 (patients in contact with adult TB)

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group - Contact with an adult TB	
Non-exposed	Non-household occasional contact
Exposed 1 **(specify):**	Non-household regular contact
Exposed 2 **(specify):**	Household contact
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT (Cellestis Limited, Carnegie, Victoria, Australia)	> 10 IU/mL	Indeterminate results on the QFT-GIT were excluded from the analysis
TST ≥ 5mm or ≥10mm	Purified protein derivative (PPD) RT23 (Statens Serum Institut, Copenhagen, Denmark)	≥ 10mm for BCG immunized children ≥ 5mm for non-BCG immunized children	NA

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (Type of contact with TB case)							
IGRA (QFT-GIT)				TST≥5mm			
	Exposure level		Total		Exposure level		Total
	Non-household regular	Non-household occasional			Non-household regular	Non-household occasional	
IGRA +	9	1	10	TST +	18	7	25
IGRA -	18	10	28	TST -	10	4	14
Indeterminate	1	0	1	Indeterminate	0	0	0
Total	28	11	39	Total	28	11	39
Test performance parameters							
IGRA				**TST**			
Sensitivity = 9/27 = 33.33% (95% CI: 18.64, 52.18)				Sensitivity = 18/28 = 64.29% (95% CI: 45.83, 79.29)			
Specificity = 10/11 = 90.91% (95% CI: 62.26, 98.38)				Specificity = 4/11 = 36.36% (95% CI: 15.17, 64.62)			
PPV = 9/10 = 90.00% (95% CI: 59.58, 98.21)				PPV = 18/25 = 72.00% (95% CI: 52.42, 85.72)			
NPV = 10/28 = 35.71% (95% CI: 20.71, 54.17)				NPV = 4/14 = 28.57% (95% CI: 11.72, 54.65)			
DOR (for T^+ calculated) = 5.00 (95% CI: 0.55, 45.39)				DOR (for T^+ calculated) = 1.03 (95% CI: 0.24, 4.39)			
OR (crude; for T^+ reported) = NR				OR (crude; for T^+ reported) = NR			
OR (regression-based; reported) = NR List of covariates: NA				OR (regression-based; reported) = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 4.85 (95% CI: 1.26, 18.69)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NA							
Association between test results and levels of TB exposure (Type of contact with TB case)							
IGRA (QFT-GIT)				**TST≥5mm**			
	Exposure level		Total		Exposure level		Total
	Household	Non-household occasional			Household	Non-household occasional	
IGRA +	22	1	23	TST +	30	7	37
IGRA -	35	10	45	TST -	30	4	34
Indeterminate	3	0	3	Indeterminate	0	0	0
Total	60	11	71	Total	60	11	71
Test performance parameters							
IGRA				**TST**			
Sensitivity = 22/57 = 38.6% (95% CI: 27.06, 51.57)				Sensitivity = 30/60 = 50.00% (95% CI: 37.73, 62.27)			
Specificity = 10/11 = 90.91% (95% CI: 62.26, 98.38)				Specificity = 4/11 = 36.36% (95% CI: 15.17, 64.62)			
PPV = 22/23 = 95.65% (95% CI: 79.01, 99.23)				PPV = 30/37 = 81.08% (95% CI: 65.79, 90.52)			
NPV = 10/45 = 22.22% (95% CI: 12.54, 36.27)				NPV = 4/34 = 11.76% (95% CI: 4.67, 26.62)			
DOR (for T^+ calculated) = 6.28 (95% CI: 0.75, 52.56)				DOR (for T^+ calculated) = 0.57 (95% CI: 0.15, 2.15)			

OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 11.02 (95% CI: 3.07, 39.60)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				TST≥5mm			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = 0.19, 95% CI (0.06, 0.60) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 20.34, 95% CI (5.60, 73.89) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	29	3	32
IGRA -	24	39	63
Indeterminate	2	2	4
Total	55	44	99

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Total
TST + threshold: ≥5 mm

Parameters

Kappa = 0.45, 95% CI (0.27, 0.63)
% concordance = 68/95 = 71.58%, 95% CI (61.81, 79.67)
% discordance = 27/95 = 28.42%, 95% CI (20.33, 38.19)

Stratification (BCG vaccinated)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	43

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated
TST + threshold: ≥10 mm

Parameters

Kappa = 0.13 (p = 0.06)
% concordance = 20/43 = 46.50% (95% CI NR)

% discordance = NR			
Stratification (non-BCG vaccinated)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	52
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated			
TST + threshold: ≥5 mm			
Parameters			
Kappa = 0.91 (p = 0.06)			
% concordance = 50/52 = 96.20% (95% CI NR)			
% discordance = NR			
Stratification (Household contact)			
	TST +	TST -	Total
IGRA +	20	2	22
IGRA -	8	27	35
Indeterminate	2	1	3
Total	30	30	60
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Household contact with TB case			
TST + threshold: ≥5 mm			
Parameters			
Kappa = 0.65, 95% CI (0.39, 0.90)			
% concordance = 47/53 = 82.46%, 95% CI (70.63, 90.18)			
% discordance = 10/53 = 17.54%, 95% CI (9.81, 29.37)			
Stratification (Non-household regular contact)			
	TST +	TST -	Total
IGRA +	8	1	9
IGRA -	10	8	18
Indeterminate	0	1	1
Total	18	10	28
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Non-household regular contact with TB case			
TST + threshold: ≥5 mm			
Parameters			
Kappa = 0.27, 95% CI (-0.03, 0.56)			
% concordance = 16/27 = 59.26%, 95% CI (40.73, 75.49)			
% discordance = 11/27 = 40.74%, 95% CI (24.51, 59.27)			
Stratification (Non-household occasional contact)			
	TST +	TST -	Total
IGRA +	1	0	1
IGRA -	6	4	10
Indeterminate	0	0	0
Total	7	4	11
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify):			
TST + threshold:			
Parameters			
Kappa = 0.11, 95% CI (-0.15, 0.37)			

% concordance = 5/11 = 45.45%, 95% CI (21.27, 71.99)		
% discordance = 6/11 = 54.55%, 95% CI (28.01, 78.73)		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
QFT may improve the diagnosis of LTBI especially in BCG vaccinated children		
Reviewers:		
There was a better agreement in BCG non-immunized vs. BCG immunized children; QFT suggested strong associations with TB contact exposure but they were NS; TST was not associated with exposure (contact with TB); odds of TST positivity (unlike QFT-GIT) was greater in BCG vaccinated vs. not vaccinated		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Diel 2011[102]
Country: Germany
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community based contact study
Number of centres: Multi-center (NR)
Total length of follow up (if applicable): 2-4 yrs
Funding (government/private/manufacturer/other - specify)**:** NR (None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript)

Aim of the study

To compare the QuantiFERONTB Gold in-tube assay (QFT) with the tuberculin skin test (TST) in close contacts of patients with TB and evaluate progression to active TB for up to 4 years

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children (close contacts of smear-positive index cases)

Participants

Recruitment dates: May 2005 to April 2010
Total N of recruited patients: 141
Inclusion criteria: Close contacts of smear-positive and subsequently culture-confirmed source MTB index cases; aggregate exposure time of the contact in the 3 months before the diagnosis of respective index case (presumed
period of infectiousness > 40 hours indoors with shared air)
Exclusion criteria: Contacts with an exposure time of < 40 hours to the source
Total N of excluded patients: 15
Total N of patients tested with both IGRA and TST: 126
Total N of patients with valid results for both IGRA and TST: 106
Methods of active TB diagnosis (if applicable): CXR (and computerized tomography), identification of AFB in sputum samples by bronchoscopy or lavage of gastric secretions, conventional culture of M. tuberculosis, nucleic acid amplification assays and/or histopathology, assessment of preceding clinical suspicion of TB. In culture-negative cases, and given a CXR consistent with TB, subsequent clinical and radiographic response to multidrug therapy over an appropriate time course (1–3 mo) was considered sufficient to confirm the diagnosis of TB
Outcomes (study-based) list: Incidence of active TB, predictive values of IGRA and TST
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 10.4 (4.3) years
Women (n [%]): NR
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Germany (84 [66.7])
BCG vaccination (n [%]): 45 [35.7]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): 6/104 [5.7]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): anti TB chemoprophylaxis (2/106 [1.8])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)

IGRA (QFT-GIT):	126	23	83	NR	106
TST (>5mm):	126	40	66	NR	106
TST (>10mm):	126	20	86	NR	106

Total N of patients with valid results for both IGRA and TST: 104 (2 patients receiving chemoprophylaxis excluded)

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NR
Exposed 1 **(specify):**	NR
Exposed 2 **(specify):**	NR
Exposed 3 **(specify):**	NR
Exposed 4 **(specify):**	NR

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Performed according to the manufacturer's instructions (Cellestis Ltd, Carnegie, Australia) The maximal level of IFN-g accurately detected by the QFT ELISA is 10 IU/ml, and thus values greater than this are reported as 10 IU/ml	IFN-g of 0.35 IU/ml or greater	Assessors of the TST were blinded to QFT results and vice versa. Induration was read by trained and well-experienced public health nurses. If there was a borderline result (e.g., 5 mm exactly), a second reading was performed by a different nurse to verify this result. If there was disagreement, a third nurse read the TST and the consensus result used
TST	Administered by the Mantoux method; 0.1 ml of Tuberculin-10-GT (Chiron Behring, Marburg, Germany; bioequivalent to 5 units of the international purified protein derivative-Seifert [PPD-S] standard), and subsequently 0.1 ml (2 tuberculin units) of purified protein derivative RT23 (Statens Serum Institute, Copenhagen, Denmark), which is equivalent to Tuberculin-10-GT (Chiron Behring)	TST reaction was scored as positive at > 5mm or > 10mm	

Association between test results and incidence of active TB (if applicable)

IGRA				**TST (>5mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	6	15	21	TST +	6	34	40
IGRA -	0	83	83	TST -	0	64	64
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	6	98	104	Total	6	98	104

Test performance parameters

IGRA	**TST**
Sensitivity = 6/6 = 100% (95% CI: 60.97, 100)	Sensitivity = 6/6 = 100% (95% CI: 60.97, 100)
Specificity = 83/98 = 84.69% (95% CI: 76.27, 90.5)	Specificity = 64/98 = 65.31% (95% CI: 55.47, 73.99)
PPV = 6/21 = 28.57% (95% CI: 13.81, 49.96)	PPV = 6/40 = 15.00% (95% CI: 7.06, 29.07)
NPV = 83/83 = 100% (95% CI: 95.58, 100)	NPV = 64/64 = 100% (95% CI: 94.34, 100)

Cumulative Incidence $_{IGRA+}$ = 6/21 = 28.57% (95% CI: 13.81, 49.96)	Cumulative Incidence $_{TST+}$ = 6/40 = 15.00% (95% CI: 7.06, 29.07)
Cumulative Incidence $_{IGRA-}$ = 0/83 = 1.20% (95% CI: 0.03, 6.53)	Cumulative Incidence $_{TST-}$ = 0/64 = 1.55% (95% CI: 0.04, 8.4)
Cumulative Incidence Ratio $_{IGRA}$ = 23.7% (95% CI: 2.57, 110.3)	Cumulative Incidence Ratio $_{TST}$ = 9.6% (95% CI: 1.08, 448.2)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = 2.47(95% CI: 0.40, 15.12)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and incidence of active TB (if applicable)	

IGRA				**TST (>10mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	6	15	21	TST +	4	36	40
IGRA -	0	83	83	TST -	2	62	64
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	6	98	104	Total	6	98	104

Test performance parameters	
IGRA	**TST**
Sensitivity = 6/6 = 100% (95% CI: 60.97, 100)	Sensitivity = 4/6 = 66.67% (95% CI: 30.00, 90.32)
Specificity = 83/98 = 84.69% (95% CI: 76.27, 90.5)	Specificity = 62/98 = 63.27% (95% CI: 53.39, 72.14)
PPV = 6/21 = 28.57% (95% CI: 13.81, 49.96)	PPV = 4/40 = 10% (95% CI: 3.96, 23.05)
NPV = 83/83 = 100% (95% CI: 95.58, 100)	NPV = 62/64 = 96.88% (95% CI: 89.3, 99.14)
Cumulative Incidence $_{IGRA+}$ = 6/21 = 28.57% (95% CI: 13.81, 49.96)	Cumulative Incidence $_{TST+}$ = 4/40 = 10.00% (95% CI: 3.958, 23.05)
Cumulative Incidence $_{IGRA-}$ = 0/83 = 1.20% (95% CI: 0.03, 6.53)	Cumulative Incidence $_{TST-}$ = 2/64 = 3.12% (95% CI: 0.22, 11.33
Cumulative Incidence Ratio $_{IGRA}$ = 23.7% (95% CI: 2.57, 110.3)	Cumulative Incidence Ratio $_{TST}$ = 3.20% (95% CI: 0.61, 16.67)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = 7.41(95% CI: 2.06, 26.57)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and levels of TB exposure (if applicable)	

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA
Test performance parameters							

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA	BCG status		Total	TST	BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported) $_{IGRA}$ = NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify):
TST + threshold: NR

Parameters
Kappa = NR
% concordance = NR
% discordance = NR

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
Results suggest that QFT is more reliable than the TST for identifying those who will soon progress to active TB, especially in children		
Reviewers:		
Overall, QFT performed better (sensitivity, specificity, predictive values) than TST in identifying LTBI by predicting the occurrence of active TB		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Tara Gurung
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Mahomed 2011a[103]
Country: South Africa
Study design: Longitudinal cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** High school (TB vaccine trial site in the town of Worcester (and surrounding villages) (high burden of TB)
Number of centres: 11
Total length of follow up (if applicable): 3.8 years
Funding (government/private/manufacturer/other - specify)**:** The Aeras Global TB Vaccine Foundation with some support from the Gates Grand Challenge 6 and Gates Grand Challenge 12 grants for the QuantiFERON testing.

Aim of the study

To compare the predictive value of a baseline tuberculin skin test (TST) with that of the QuantiFERON TB Gold (In-tube) assay (QFT) for subsequent microbiologically confirmed TB disease among adolescents.

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Adolescents from high burden TB area

Participants

Recruitment dates: From 2005 to 2006
Total N of recruited patients: 6,363
Inclusion criteria: adolescents aged 12 to 18 years
Exclusion criteria: NR
Total N of excluded patients: 1,119 (those with prior or current TB, indeterminate QFT results, or missing QFT or TST results)
Total N of patients tested with both IGRA and TST: 5,244
Total N of patients with valid results for both IGRA and TST: 5,244
Methods of active TB diagnosis (if applicable): Two sputum samples for smear microscopy on two separate occasions. If any single sputum was smear positive, a mycobacterial culture, chest x-ray, and HIV test were performed
Outcomes (study-based) list: Test results, concordance between TST and QTB, TB disease incidence rate
Characteristics of participants (total study sample)
Mean (range or SD) age (years): NR
Women (n [%]): 2842 [54.2]
Race/ethnicity (n [%]): Black (995 [19.0]); Mixed race (3839 [73.2]); Indian/white (410 [7.8])
BCG vaccination (n [%]): Yes (4917 [93.8]; Unknown (281 [5.4])
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): 52 [1.0]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (specify): QFT-GIT	5244	2669	2575	NR	5244
TST≥5mm:	5244	2894	2350	NR	5244

Test 3 (specify)	NR	NR	NR	NR	NR
Total N of patients with valid results for both IGRA and TST: 5244					
Levels/groups of exposure to TB in increasing order (if applicable):					

Definition of exposure group	
Non-exposed	NA
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA	QFT-GIT, In-tube method, (Cellestis Limited, Carnegie, Victoria, Australia)	≥ 0.35 IU/mL	NA
TST	Mantoux method on either forearm, using 2 tuberculin units of RT23, induration was read 48-96 hours later with a ruler or caliper by trained personnel, (Statens Serum Institut, Denmark)	≥ 5mm	People with a recent household contact, TB related symptoms, a positive TST ≥10 mm induration or a positive QFT were referred for two sputum smears. If results of either or both were sputum positive for acid fast bacilli, the sputum were cultured, and a chest x-ray and HIV test were undertaken.

Association between test results and incidence of active TB (if applicable)

IGRA (QFT-GIT)				**TST≥5mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	39	2630	2669	TST +	40	2854	2894
IGRA -	13	2562	2575	TST -	12	2338	2350
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	52	5192	5244	Total	52	5192	5244

Test performance parameters

IGRA	**TST**
Sensitivity = 39/52 = 75.00%, 95% CI (61.79, 84.77)	Sensitivity = 40/52 = 76.92%, 95% CI (63.87, 86.28)
Specificity = 2562/5192 = 49.35%, 95% CI (47.99, 50.71)	Specificity = 2338/5192 = 45.03%, 95% CI (43.68, 46.39)
PPV = 39/2669 = 1.46%, 95% CI (1.07, 1.99)	PPV = 40/2894 = 1.38%, 95% CI (1.02, 1.88)
NPV = 2562/2575 = 99.50%, 95% CI (99.14, 99.7)	NPV = 2338/2350 = 99.49%, 95% CI (99.11, 99.71)
Cumulative Incidence $_{IGRA+}$ = 39/2669 = 1.46%, 95% CI (1.07, 1.99)	Cumulative Incidence $_{TST+}$ = 40/2894 = 1.38%, 95% CI (1.02, 1.87)
Cumulative Incidence $_{IGRA-}$ = 13/2575 = 0.50%,	Cumulative Incidence $_{TST-}$ = 12/2350 = 0.51%,

95% CI (0.28, 0.87)	95% CI (0.28, 0.90)
Cumulative Incidence Ratio $_{IGRA}$ = 2.89, 95% CI (1.55, 5.40)	Cumulative Incidence Ratio $_{TST}$ = 2.71 (95% CI: 1.42, 5.14)
Incidence density rate $_{IGRA+}$ = 0.64 per 100 person years, 95% CI (0.45, 0.87)	Incidence density rate $_{TST+}$ = 0.60 per 100 person years, 95% CI (0.43, 0.82)
Incidence density rate $_{IGRA-}$ = 0.22 per 100 person years, 95% CI (0.12, 0.38)	Incidence density rate $_{TST-}$ = 0.22 per 100 person years, 95% CI (0.11, 0.39)
Incidence density rate ratio $_{IGRA}$ = 2.92, 95% CI (1.58, 5.67)	Incidence density rate ratio $_{TST}$ = 2.73, 95% CI (1.45, 5.42)
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence = 1.07, (95% CI: 0.68, 1.68)	
Ratio of incidence density rate ratios = 1.07, (95% CI: 0.67, 1.71)	
Other reported measure = NR	

Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	2383	286	2669
IGRA -	511	2064	2575
Indeterminate	0	0	0
Total	2894	2350	5244

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total
TST + threshold: ≥5 mm induration
Parameters
Kappa = 0.69 95% CI, (0.66, 0.72)
% concordance = 4447/5244 = 84.80%, 95% CI (83.80, 85.75)
% discordance = 797/5244 = 15.20%, 95% CI (14.25, 16.20)
Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
Based on the findings from this study, these authors concluded/demonstrated that TST and QFT-GIT are equally predictive of progression to active TB in a cohort of adolescents in a high TB burden population. They further stated that their results do not support that QFT-GIT is more superior to TST in its predictive value
Reviewers:
Authors reported that Isoniazid prevention therapy is not standard care for people with LTBI except for children under the age of five years old. TST and QFT-GIT are equally predictive of progression to active TB in a cohort of adolescents in a high TB burden population
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Tara Gurung
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Noorbakhsh 2011[104] **Country:** Iran **Study design:** Cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Pulmonary and infectious diseases department of Rasul hospital in Tehran **Number of centres:** 1 **Total length of follow up (if applicable):** 1 year **Funding** (government/private/manufacturer/other - specify)**:** Research Centre of Paediatric Infectious Diseases, Iran University of Medical Sciences.
Aim of the study
To detect the agreement between TST and QTB in young household contacts (aged < 20 years) of cases of proven active pulmonary TB in a BCG-vaccinated population in Tehran, Islamic Republic of Iran, and to compare subjects progressing to TB with non-progressive subjects
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Children
Participants
Recruitment dates: 2006-2008 **Total N of recruited patients:** NR **Inclusion criteria:** all young (< 20 years old) close or household contacts of people (as any person who had lived with the index case for more than 3 months) with confirmed active pulmonary TB and previous BCG vaccination received at birth. The subjects were invited to our research centre for clinical and laboratory follow-up **Exclusion criteria:** Household contacts were excluded if they had been treated for TB in the past year or had a known immunodeficiency state on history or clinical signs (malignancy, corticosteroid therapy, HIV, etc.). **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** NR **Total N of patients with valid results for both IGRA and TST:** 58 **Methods of active TB diagnosis (if applicable):** Person diagnosed by an internist in the pulmonary and infectious ward of Rasht hospital. The index cases were confirmed by positive culture for M. tuberculosis or sputum smear-positive TB **Outcomes (study-based) list:** Test results, concordance between TST and QTB, progression to TB disease **Characteristics of participants (total study sample)** Mean (range or SD) age (years): NR Women (n [%]): 34 [57.6] Race/ethnicity (n [%]): NR BCG vaccination (n [%]): NR History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): 10 [16.9] Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): NR Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): NR
Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**

IGRA (QFT-G):	NR	18	41	NR	59
TST (≥ 10mm):	NR	8	50	1	58
Test 3 (specify)	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 48

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NR
Exposed 1 **(specify):**	NR
Exposed 2 **(specify):**	NR
Exposed 3 **(specify):**	NR
Exposed 4 **(specify):**	NR

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-G)	For the QTB fresh blood samples from all of the participants were processed on site according to the manufacturer's instruction (Gold Quantiferon-TB, Cellestis). First, 1 mL of heparinized whole blood was incubated with aliquots of antigen-free control and antigens for 16–24 hours at 37 °C in a carbon dioxide incubator. After overnight incubation, 200 µL plasma was removed from each well and the concentration of IFN-γ was determined using the assay kits	Not reported	NA
TST (≥ 10mm)	For the TST a test dose (0.1 mL) of 5 tuberculin units of purified protein derivative solution (Pasteur Institute, Tehran) was injected intradermally into the volar aspect of the forearm with a 26–27 gauge needle by trained field worker. The induration diameter of the raised, blanched weal (not the erythema) was read after 48–72 hours	A reactive TST was an induration diameter of ≥ 10mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA (QFT-G)				**TST≥ 10mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	10	8	18	TST +	3	5	8
IGRA -	0	41	41	TST -	7	43	50
Indeterminate	NR	NR	NR	Indeterminate	0	1	1
Total	10	49	59	Total	10	49	59

Test performance parameters

IGRA	**TST**
Sensitivity = 10/10 = 100.00%, 95% CI (72.25, 100.00)	Sensitivity = 3/10 = 30.00%, 95% CI (10.78, 60.32)
Specificity = 41/49 = 83.67%, 95% CI (70.96, 91.49)	Specificity = 43/48 = 89.58%, 95% (77.83, 95.47)
PPV = 10/18 = 55.56%, 95% CI (33.72, 75.44)	PPV = 3/8 = 37.50%, 95% CI (13.68, 69.43)

NPV = 41/41 = 100%, 95% CI (91.43, 100)	NPV = 43/50 = 86.00%, 95% CI (73.81, 93.05)
Cumulative Incidence $_{IGRA+}$ = 10/18 = 55.56%, 95% CI (33.72, 75.44)	Cumulative Incidence $_{TST+}$ = 3/8 = 37.5%, 95% CI (13.49, 69.62)
Cumulative Incidence $_{IGRA-}$ = 0/41 = 2.41% (95% CI: 0.06, 12.9)	Cumulative Incidence $_{TST-}$ = 7/50 = 14.00%, 95% CI (6.63, 26.50)
Cumulative Incidence Ratio $_{IGRA}$ = 22.78% (95% CI: 2.75, 101.1)	Cumulative Incidence Ratio $_{TST}$ = 2.68% (95% CI: 0.86, 8.27)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence = 8.50% (95% CI: 2.87, 25.17)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	

Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample			
	TST +	TST -	Total
IGRA +	NR	NR	18
IGRA -	NR	NR	41
Indeterminate	NR	NR	NR
Total	8	51	59

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): total
TST + threshold: ≥10mm
Parameters
Kappa = NR
% concordance = NR
% discordance = NR

Stratification (non-progressive)			
	TST +	TST -	Total
IGRA +	39	4	43
IGRA -	2	3	5
Indeterminate	0	0	0
Total	41	7	48
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): 49 children who did not progress to active TB			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.43 (95% CI: 0.15, 0.70)			
% concordance = 42/48 = 87.60% (95% CI:75.3, 94.14)			
% discordance = 6/48 = 12.5% (95% CI: 5.85, 24.70)			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
From this study, the authors demonstrated that QTB assay can reflect recent rather than remote TB infections compared with TST in an adolescent population who had previously received BCG vaccination
Reviewers:
QFT performed better than TST in detecting LTBI by predicting development of active TB
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Song 2014[152]
Country: South Korea
Study design: prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify): community-based
Number of centres: 1 (children sampled from 45 schools)
Total length of follow up (if applicable): 24 months
Funding (government/private/manufacturer/other - specify): This research was supported by a fund (2008-E00226-00, 2009-E46002-00, 2010-E46003-00, 2011-E46006-00, and 2012-E46001-00) by Research of Korea
Centers for Disease Control and Prevention. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Aim of the study

To determine the agreement between IGRA (QFT-GIT) and TST and identify the relationships between the results of these tests and the development of active tuberculosis in middle and high school students in close contact with tuberculosis patients in South Korea

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Children

Participants

Recruitment dates: Between 2008 and 2012
Total N of recruited patients: 3,202
Inclusion criteria: Close contacts of identified smear-positive tuberculosis cases with normal chest X-ray aged 11–19 years
Exclusion criteria: Participants showing (1) abnormal findings in simple chest radiographs, (2) they had taken immunosuppressive agents or anticancer drugs earlier, and (3) they had been treated with antituberculous drugs or chemoprophylaxis earlier
Total N of excluded patients: 220 (at baseline)
Total N of patients tested with both IGRA and TST: 2,982
Total N of patients with valid results for both IGRA and TST: 2,966
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: between test agreement, incidence of active TB
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 15.1 (1.3)
Women (n [%]): 1,356 (45.5)
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 1,818 (61.0)
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): 23/2,982 (0.77)
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): 5/215 [2.32] (isoniazid)

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	2982	317	2649	16	2966
TST≥10mm	2982	663	2319	0	2982
TST≥15mm	2982	231	2751	0	2982

Test 3 (specify)					
Total N of patients with valid results for both IGRA and TST: 2,966					
Levels/groups of exposure to TB in increasing order (if applicable): NA					
Definition of exposure group –					
Non-exposed	NA				
Exposed 1 **(specify)**:	NA				
Exposed 2 **(specify)**:	NA				
Exposed 3 **(specify)**:	NA				
Exposed 4 **(specify)**:	NA				
Tests					
	Assay used, methodology, timing for test measurement, manufacturer		**Cut-off values/thresholds Definition of test+**		**Other information**
IGRA –[QFT-GIT]	QFT Gold In-Tube (Cellestis Inc, Valencia, CA) tests were performed according to the manufacturer's instructions. Briefly, whole blood was collected by venipuncture from each subject at the date of injection of PPD and incubated for 16–24 hours in 3 separate conditions: 1) a mixture of 3 TB antigens from RD1 and RD11 (ESAT-6, CFP-10, and TB7.7); 2) a mitogen as a positive control; and 3) a mock stimulation as a negative control (nil). Following the stimulations, 150 mL of the supernatant was harvested from each tube. Then, 50 mL of each supernatant was used to determine its interferon gamma (IFN-c) concentration by the ELISA		A QuantiFERON value of 0.35 international units or more was deemed positive according to manufacturer's instructions		To eliminate the possibility of false-positive IGRA results due to PPD reagents, blood samples were collected before PPD injection
TST≥10mm	Intradermal injection (0.1 ml) of 2 tuberculin units of purified protein derivative (RT 23; Statens Serum Institute, Copenhagen, Denmark) into the anterior surface of the forearm with a disposable syringe and a		The maximal transverse size of induration was read 48–72 hours later with a ruler or a caliper by a research nurse ≥10mm ≥15mm		

	27-gauge needle by using the Mantoux technique		

Association between test results and incidence of active TB (if applicable)							
IGRA (QFT-GIT)				**TST≥10mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	11	306	317	TST +	13	650	663
IGRA -	12	2637	2649	TST -	10	2309	2319
indeterminate	NR	NR	16	indeterminate	0	0	0
Total	23	2943	2966	Total	23	2959	2982

Test performance parameters	
IGRA	**TST**
Sensitivity = 11/23=47.83% (95% CI: 29.24, 67.04)	Sensitivity =13/23=56.52% (95% CI: 36.81, 74.37)
Specificity = 2637/2943=89.6% (95% CI: 88.45, 90.65)	Specificity = 2309/2959=78.03% (95% CI: 76.51, 79.49)
PPV= 11/317=3.47% (95% CI: 1.94, 6.10)	PPV= 13/663=1.96% (95% CI: 1.14, 3.32)
NPV= 2637/2649=99.55% (95% CI: 99.21, 99.74)	NPV= 2309/2319=99.57% (95% CI: 99.21, 99.77)
Cumulative Incidence $_{IGRA+}$ = 11/317=3.47% (95% CI: 1.87, 6.17)	Cumulative Incidence $_{TST+}$ = 13/663=1.96% (95% CI: 1.11, 3.36)
Cumulative Incidence $_{IGRA-}$ = 12/2649=0.45% (95% CI: 0.24, 0.79)	Cumulative Incidence $_{TST-}$ = 10/2319=0.43% (95% CI: 0.22, 0.80)
Cumulative Incidence Ratio $_{IGRA}$ =7.66 (95% CI: 3.41, 17.21)	Cumulative Incidence Ratio $_{TST}$ =4.55 (95% CI: 2.00, 10.32)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$= NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$= NR
Other reported measure $_{IGRA}$ =OR=7.90 (95% CI: 3.46, 18.06)	Other reported measure $_{TST}$ = OR=4.62 (95% CI: 2.02, 10.58)

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios=1.68 (95% CI: 0.94, 3.03)
Ratio of incidence density rate ratios=NA
Other reported measure= OR = 1.71 (95% CI: 0.94, 3.11)

Association between test results and incidence of active TB (if applicable)							
IGRA (QFT-GIT)				**TST≥15mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	11	306	317	TST +	13	218	231
IGRA -	12	2637	2649	TST -	10	2741	2751
indeterminate	NR	NR	16	indeterminate	0	0	0
Total	23	2943	2966	Total	23	2959	2982

Test performance parameters	
IGRA	**TST**
Sensitivity = 11/23=47.83% (95% CI: 29.24, 67.04)	Sensitivity =13/23=56.52% (95% CI: 36.81, 74.37)
Specificity = 2637/2943=89.6% (95% CI: 88.45, 90.65)	Specificity = 2741/2959=92.63% (95% CI: 91.64, 93.52)
PPV= 11/317=3.47% (95% CI: 1.94, 6.10)	PPV= 13/231=5.62% (95% CI: 3.31, 9.38)
NPV= 2637/2649=99.55% (95% CI: 99.21, 99.74)	NPV= 2741/2751=99.64% (95% CI: 99.33, 99.80)

Cumulative Incidence IGRA+ = 11/317=3.47% (95% CI: 1.87, 6.17)	Cumulative Incidence $_{TST+}$ = 13/231=5.62% (95% CI: 3.23, 9.47)
Cumulative Incidence IGRA- = 12/2649=0.45% (95% CI: 0.24, 0.79)	Cumulative Incidence $_{TST-}$ = 10/2741=0.36% (95% CI: 0.18, 0.67)
Cumulative Incidence Ratio IGRA =7.66 (95% CI: 3.41, 17.21)	Cumulative Incidence Ratio $_{TST}$ =15.48 (95% CI: 6.86, 34.92)
Incidence density rate IGRA+ = NR	Incidence density rate $_{TST+}$= NR
Incidence density rate IGRA- = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio IGRA = NR	Incidence density rate ratio $_{TST}$= NR
Other reported measure IGRA =OR=7.90 (95% CI: 3.46, 18.06)	Other reported measure $_{TST}$ = OR=16.35 (95% CI: 7.08, 37.71)

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios=0.49 (95% CI: 0.28, 0.89)
Ratio of incidence density rate ratios=NA
Other reported measure= 0.48 (95% CI: 0.27, 0.88)

Association between test results and levels of TB exposure (if applicable)

IGRA (specify)				TST (specify)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (specify)				TST (specify)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported) $_{IGRA}$ = NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA

Other reported measure = NA		Other reported measure = NA	
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST ≥10mm	TST -	Total
IGRA +	231	86	317
IGRA -	430	2,219	2,649
indeterminate	2	14	16
Total	663	2,319	2982
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.38 (95% CI: 0.342, 0.424)			
% concordance = [231+2,219]/2,966 = 82.6% (95% CI: 81.2, 83.92)			
% discordance = [430+86]/2,966 = 17.4% (95% CI: 16.08, 18.80)			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST ≥15mm	TST -	Total
IGRA +	163	154	317
IGRA -	68	2,581	2,649
indeterminate	0	16	16
Total	231	2,751	2,982
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥15mm			
Parameters			
Kappa = 0.55 (95% CI: 0.50, 0.61)			
% concordance = [163+2581]/2,966 = 92.52% (95% CI: 91.51, 93.41)			
% discordance = [68+154]/2,966 = 7.48% (95% CI: 6.59, 8.48)			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			

Parameters
Kappa = NA
% concordance = NA
% discordance = NA
Conclusions
Authors:
TST at 15 mm had a higher OR for the development of active tuberculosis compared to TST 10mm and QFT-GIT. The agreement between TST and QFT was better when TST had 15 mm threshold
Reviewers:
Children testing positive on both tests had a greater risk of developing active TB; TST at 15mm performed better in diagnosing LTBI compared to TST 10mm or QFT-GIT; TST 15mm agreed with QFT GIT better than TST 10 mm
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation

Immunocompromised

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Ahmadinejad 2013[120]
Country: Iran
Study design: Cross sectional/retrospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Tertiary care teaching hospital
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Tehran University of Medical Sciences and Health Services grant

Aim of the study

To compare the QFT and TST in diagnosis of LTBI in solid organ transplant (SOT) candidates (kidney, liver, lung)

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (SOT candidates**:** kidney, liver, lung)

Participants

Recruitment dates: March 2008 through September 2011
Total N of recruited patients: 187
Inclusion criteria: SOT candidates who were referred to the transplant clinic
Exclusion criteria: (i) failure to return to the clinic for reading the results of TST within 5 days of the initial intradermal injection, or (ii) unwillingness to continue the study at any stage
Total N of excluded patients: 23 (dropouts)
Total N of patients tested with both IGRA and TST: 164
Total N of patients with valid results for both IGRA and TST:TST (n = 164), IGRA (n = 159)
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Agreement/disagreement, association between test results and exposure to active TB
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 39.9 (12.7) yrs
Women (n [%]): 76 [46.3]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 151 [92.1]
History of anti-TB treatment (n [%]): 1/164 [0.6]
Total incidence of active TB (n [%]): 1/164 [0.6]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): End-stage renal disease (64 [39.0]), chronic hepatic failure (97 [59.2]), Pulmonary failure (3 [1.8])
Co-morbidity (n [%]): NA
Type of during-study treatment (n [%]): Patients with positive TST received chemoprophylaxis with 300 mg isoniazid for 9 months; immunosuppressive medication (24 [14.6])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	164	33	126	5	159
TST:	164	26	138	0	164
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 164			
Levels/groups of exposure to TB in increasing order (if applicable):			
Definition of exposure group			
Non-exposed	No history of exposure to active TB		
Exposed 1 **(specify):**	Exposure history to active TB		
Exposed 2 **(specify):**	NA		
Exposed 3 **(specify):**	NA		
Exposed 4 **(specify):**	NA		
Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QuantiFERON-TB Gold In-Tube test (QFT-GiT) Blood sample of 3 mL was obtained, and 1 mL was added to each of the 3 tubes designated as the nil, mitogen, and antigen tubes. After vigorous shaking of the tubes, they were sent to the laboratory up to 6 h after acquisition The tubes were reshaken and incubated for 24 h at 37°C. Then the samples were centrifuged at 2000–3000 RCF rate for 15 min, and the resulting plasma samples were kept at >70°C for the measurement of interferon-gamma (IFN-c) with enzyme-linked immunosorbant assay (ELISA)	NR	For prevention of potential boosting effect of TST on QFT, blood sampling and purified protein derivative (PPD) injection were done simultaneously for all patients
TST	0.1 mL from 5 tuberculin units of PPD solution was injected intradermally 2–4 inches (~5–10 cm) lower than the elbow, with an angle of about 5–15 degrees, and the induration size was measured after 48–72h	If the induration is ≥10 mm in largest diameter, the test was considered positive	

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA

Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥10mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	0	33	33	TST +	0	26	26
IGRA -	5	121	126	TST -	5	133	138
Indeterminate	0	5	5	Indeterminate	0	0	0
Total	5	159	164	Total	5	159	164

Test performance parameters

IGRA	TST
Sensitivity = 0/5 = 0.00%	Sensitivity = 0/5 = 0.00%
Indeterminate excluded Specificity = 121/154 = 78.57% (95% CI: 71.44, 84.32) **Indeterminate included** Specificity = 126/159 = 79.25% (95% CI: 72.29, 84.82)	Specificity = 133/159 = 83.65% (95% CI: 77.12, 88.59)
PPV = 0/33 = 0.00%	PPV = 0/26 = 0.00%
Indeterminate excluded NPV = 121/126 = 96.03% (95% CI: 91.05, 98.29) **Indeterminate included** NPV = 126/131 = 96.18% (95% CI: 91.38, 98.36)	NPV = 133/138 = 96.38% (95% CI: 91.8, 98.44)
DOR (for T^+ calculated) = 0.00	DOR (for T^+ calculated) = 0.00
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates:	OR (regression-based; reported) = NR List of covariates:
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = NR
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				TST (≥10mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	28	5	33	TST +	23	3	26
IGRA -	118	8	126	TST -	128	10	138
Indeterminate	5	0	5	Indeterminate	0	0	0
Total	151	13	164	Total	151	13	164

Test performance parameters

IGRA	TST

DOR (for T^+ calculated)$_{IGRA}$ = 0.38 (95% CI: 0.11, 1.24)	DOR (for T+ calculated)$_{TST}$ = 0.60 (95% CI: 0.15, 2.34)
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	13	20	33
IGRA -	12	114	126
Indeterminate	1	4	5
Total	26	138	164

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥10mm

Parameters

Indeterminate excluded
Kappa = 0.32 (95% CI: 0.17, 0.48)
Indeterminate included
Kappa = 0.32 (95% CI: 0.17, 0.47)

Indeterminate excluded
% concordance = 127/159 = 79.87% (95% CI: 72.97, 85.37)
Indeterminate included
% concordance = 131/164 = 79.88% (95% CI: 73.09, 85.3)

% discordance = 20.13% (95% CI: 14.63, 27.03)

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR

% discordance = NR

Stratification (specify group 2)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR

% discordance = NR

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
Considering the fair overall agreement between the 2 tests, and greater ease of the QFT from the patient's point of view, QFT is recommended for detection of LTBI in SOT candidates		
Reviewers:		
The tests performed similarly in relation to construct of validity (exposure to active TB) in terms of sensitivity (low), specificity (high), DOR (low), and NPV (high); agreement between the tests was fair (0.32); neither test was influenced by BCG status		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Al Jahdali 2013[121]
Country: Saudi Arabia
Study design: retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** outpatient hemodialysis unit hospital-based
Number of centres: one
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** No funding sources

Aim of the study

To compare the performance of the QTF-GIT test and the TST for detecting LTBI among hemodialysis patients and to investigate the agreement between these 2 tests in the detection of tuberculosis infection in a population showing an intermediate TB prevalence

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (hemodialysis patients)

Participants

Recruitment dates: August to December 2010
Total N of recruited patients: 215
Inclusion criteria: Hemodialysis patients
Exclusion criteria: NR
Total N of excluded patients: 15 (active TB)
Total N of patients tested with both IGRA and TST: 215
Total N of patients with valid results for both IGRA and TST: 200
Methods of active TB diagnosis (if applicable): positive tuberculosis culture or biopsy showing granuloma and good response to anti-tuberculosis therapy
Outcomes (study-based) list: test result association with construct of validity (high likelihood of LTBI) and between-test agreement
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 58.42 (17.65) yrs
Women (n [%]):103 [51.5]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 28 [14.0]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): Hemodialysis patients
Co-morbidity (n [%]): diabetic nephropathy (127 [63.5]), kidney transplant failed (21 [10.5]), NR (52 [26.0])
Type of during-study treatment (n [%]): Immunosuppressant in the last 12mo (2 [1.0])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	NR	65	135	NR	200
TST (≥10mm):	NR	26	174	NR	200
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 200

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group - High likelihood of LTBI	
Non-exposed	No high likelihood of LTBI
Exposed 1 **(specify):**	High likelihood of LTBI (contact with TB case, abnormal chest X-ray, DM, immunosuppressant in the last 12 M, failed kidney transplant or BMI≤20)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA	Test was performed according to the manufacturer's instructions. One ml of whole blood was collected in each of 3 separate test tubes: 1 containing no antigen (nil control), 1 with a mitogen (phytohemagglutinin, positive control) and 1 with TB antigens (ESAT-6, CFP-10 and TB7.7). The 3 tubes were incubated overnight for 18-20 h at 37 ◦C. Following incubation, the tubes were centrifuged, and the plasma was removed from each tube and frozen at −20 ◦C. Measurement of IFN-γ via ELISA was subsequently performed in batch testing	A value of 0.35 IU/ml or more for the relationship ([IFN-γ in the TB antigen tube] − [IFN-γ in the negative control tube]) was considered to be a positive result. If the IFN- γ level was <0.35 IU/ml in the TB antigen tube and the mitogen control was positive (≥0.5 IU/ml), the test was recorded as negative	IGRA blood was collected before the administration of the TST
TST	The TST employed in this study was Tubersol —Tuberculin Purified Protein Derivative (Mantoux), 5 TU per 0.1 ml, test manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada. A trained and experienced public health nurse performed all TSTs. Five tuberculin units (0.1 ml) of the purified protein derivative (PPD) were administered via intradermal injection on the volar surface of the forearm that did not have the arteriovenous vessel. The responses were read within 72 h by the same nurse, usually during the next regularly scheduled HD visit	An induration of 10mm or more in transverse diameter was used as the threshold to classify the test results as positive for LTBI. Patients with an induration of less than 10mm upon initial testing were considered to be negative and were administered a second TST within 3—6 weeks to elicit a potential booster response. The results obtained from the 2-step testing were used in all further analyses. The TST was considered to be positive if either the 1st or 2nd test showed a response of 10mm or more	NA

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA

IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	51	14	65	TST +	19	7	26
IGRA -	103	32	135	TST -	135	39	174
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	154	46	200	Total	154	46	200

Test performance parameters	
IGRA	**TST**
Sensitivity = 51/154 = 33.12% (95% CI: 26.00, 41.00)	Sensitivity = 19/154 = 12.34% (95% CI: 8.04, 18.47)
Specificity = 32/46 = 69.57% (95% CI: 55.19, 80.92)	Specificity = 39/46 = 84.78% (95% CI: 71.78, 92.43)
PPV = 51/65 = 78.46% (95% CI: 67.03, 86.71)	PPV = 19/26 = 73.08% (95% CI: 53.92, 86.3)
NPV = 32/135 = 23.70% (95% CI: 17.32, 31.54)	NPV = 39/174 = 22.41% (95% CI: 16.85, 29.17)
DOR (for T+ calculated) = 1.13 (95% CI: 0.55, 2.31)	DOR (for T^+ calculated) = 0.78 (95% CI: 0.31, 2.00)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates:	OR (regression-based; reported) = NR List of covariates:
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 1.45 (95% CI: 0.79, 2.64)
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = NR
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR

IGRA -	NR	NR	NR	TST -	NR	NR	NR
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	21	44	65
IGRA -	5	130	135
indeterminate	NR	NR	NR
Total	26	174	200
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.34 (95% CI: 0.22, 0.45)			
% concordance = 151/200 = 75.50% (95% CI: 69.10, 80.94)			
% discordance = 49/200 = 24.5% (95% CI: 19.06, 30.90)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if	**Adverse events n/N (%)**	**Health related quality**

applicable)	(specify)	of life mean score (SD) (specify)
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
The discriminatory ability of the QTF-G test is superior to that of the TST. The QTFG test was more sensitive but less specific than the TST in predicting LTBI		
Reviewers:		
There was fair agreement between the tests (k = 0.34); In general, QFT-GIT performed better than TST in terms of sensitivity; specificity was higher for TST vs. QFT-GIT		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Ates 2009[122]
Country: Turkey
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Outpatient hemodialysis hospital centers
Number of centres: 5
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Grant from University of Dicle

Aim of the study

To assess the efficacy of QTF-GIT test for detection of LTBI and determine the degree of agreement between the results of TST and QTFGIT tests in hemodialysis patients

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (hemodialysis patients)

Participants

Recruitment dates: March 15 and April 15 of 2008
Total N of recruited patients: 290
Inclusion criteria: Hemodialysis patients 18 yrs or older
Exclusion criteria: The patients diagnosed with active tuberculosis and receiving treatment for the last 12 months, or taking immunosuppressive medicine or younger than 18 years old were excluded from the present study
Total N of excluded patients: 15 (rejected tests, improper blood sampling, and unsuccessful phlebotomy)
Total N of patients tested with both IGRA and TST: 275
Total N of patients with valid results for both IGRA and TST: 230
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Agreement, risk factors for positive test
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 51.9 (16.2) yrs
Women (n [%]):137 [50.0]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 134 [48.72]
History of anti-TB treatment (n [%]): 17 [7.4%]
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): hemodialysis
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	275	115	131	29	246
TST (≥10mm):	275	92	167	16	259
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 230

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group

Non-exposed	No Tuberculosis exposure
Exposed 1 **(specify):**	Tuberculosis exposure
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA	The QTF-GIT test was performed in two steps. Whole blood was collected first into each of the QTF-GIT blood collection tubes, consisting of a nil control tube, a tuberculosis antigen tube, and a mitogen tube. The tubes were incubated at 37°C as soon as possible. After a 16-20 hours incubation period, the tubes were centrifuged and the plasma was removed and frozen at -70oC until the ELISA was performed. The ELISA for IFN-g was performed according to manufacturer's specifications and the ELISA readout was analyzed using the QTF-GIT analysis software	According to the QTF-GIT analysis software results were recorded as positive, negative and indeterminate. The whole blood was drawn just before hemodialysis	Observers were blinded to the results of the TST
TST	TST were administered and its results were interpreted in relation to American Thoracic Society Guidelines (1). Briefly, a trained nurse performed one-step tuberculin skin test using the Mantoux technique through the injection of 0.1 ml (5 tuberculin units) of purified protein derivative (PPD; Tween 80, BB-NCIPD Ltd, Sofia, Bulgaria) into the volar surface of the forearm	A skilled nurse measured the transverse axis of indurations with a flexible ruler, and an experienced physician verified all the results. A positive TST result was defined as an induration diameter of 10 mm or larger	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA

Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST≥10mm			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	10	105	115	TST +	5	87	92
IGRA -	7	124	131	TST -	12	155	167
Indeterminate	NR	NR	29	Indeterminate	NR	NR	16
Total			275	Total			275

Test performance parameters

IGRA	TST
Sensitivity = 10/17 = 58.82% (95% CI: 36.01, 78.39)	Sensitivity = 5/17 = 29.41% (95% CI: 13.28, 53.13)
Specificity = 124/229 = 54.15% (95% CI: 47.68, 60.48)	Specificity = 155/243 = 64.05% (95% CI: 57.83, 69.83)
PPV = 10/115 = 8.69% (95% CI: 4.792, 15.27)	PPV = 5/92 = 5.43% (95% CI: 2.34, 12.10)
NPV = 124/131 = 94.66% (95% CI: 89.38, 97.39)	NPV = 155/167 = 92.81% (95% CI: 87.86, 95.84)
DOR (for T^+ calculated) = 1.68 (95% CI: 0.62, 4.58)	DOR (for T^+ calculated) = 0.74 (95% CI: 0.25, 2.17)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = 1.30 (0.43, 3.91) List of covariates: NR	OR (regression-based; reported) = 0.49 (0.17, 1.45) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 2.27 (95% CI: 1.07, 4.81)
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = 2.65 (95% CI: 1.21, 5.82)
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA				TST			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	57	58	115	TST +	45	47	92
IGRA -	61	70	131	TST -	88	79	167
Indeterminate	NR	NR	29	Indeterminate	NR	NR	16
Total			275	Total			275

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = 1.13 (95% CI: 0.68, 1.86)	DOR (for T+ calculated)$_{TST}$ = 0.85 (95% CI: 0.51, 1.43)
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = 1.14 (95% CI: 0.68, 1.92) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 0.87 (95% CI: 0.50, 1.51) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)

This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST +	TST -	Total
IGRA +	58	49	107
IGRA -	25	98	123
indeterminate	NR	NR	29
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.34 (95% CI: 0.21, 0.47)			
% concordance = 156/230 = 67.83% (95% CI: 61.54, 73.53)			
% discordance = 74/230 = 32.17% (95% CI: 26.47, 38.46)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
QTF-GIT is more sensitive than TST in the detection of LTBI among renal dialysis patients; both QTF-GIT and TST results were not correlated with contact to the patients with tuberculosis; we observed no association among the results of both TST & QTF-GIT and BCG vaccination status; agreement between tests was fair (k = 0.34)

Reviewers:
See above
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Casas 2011a[123] **Country:** Spain **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Outpatient clinics **Number of centres:** 4 **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** The first author received research grant from the University Barcelona (October 2006–January 2010). This study was supported by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III-FEDER, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008)
Aim of the study
To assess the prevalence of LTBI obtained by the whole blood-based QFT-GIT and TST in patients with IMID, and second, to determine whether QFT-GIT performs in the same way as in healthy people
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people (immune-mediated inflammatory diseases [IMID] before anti–TNF-α therapy)
Participants
Recruitment dates: NR **Total N of recruited patients:** 323 **Inclusion criteria:** Patients with immune-mediated inflammatory diseases (IMID) before anti–TNF-α therapy **Exclusion criteria:** NR **Total N of excluded patients:** n = 9 (no IMID: n = 2 and problems with QFT-GIT plasma sample storage: n = 7) **Total N of patients tested with both IGRA and TST:** 323 **Total N of patients with valid results for both IGRA and TST:** 314 (214 IMID and 100 healthy controls) **Methods of active TB diagnosis (if applicable):** NR **Outcomes (study-based) list:** Associations between test positivity and risk factors of LTBI, BCG status, type of treatment; agreement; influence of risk factors on indeterminate results **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 49.1 (12.9) Women (n [%]): 109 [50.9] Race/ethnicity (n [%]): NR Geographic origin (n[%]): Born in a high TB incidence country (16 [7.5]) BCG vaccination (n [%]): 56 [26.2] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): NA Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity (n [%]): Rheumatoid arthritis (91 [42.5]); Cutaneous psoriasis (57 [26.6]); Spondylarthropathies (29 [13.6]); Psoriatic arthropathy (21 [9.8]); Inflammatory bowel disease (14 [6.5]); Others (2 [0.9]) Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): Immunosuppressive treatment (163 [76.2]); Corticosteroids (91 [42.5]); Methotrexate (91 [42.5]); Leflunomide (36 [16.8]); Cyclosporine A (22 [10.3]); azathioprine/efalizumab (13 [6.1])
Number of patients tested

	Total N	**Total**	**Total N**	**Total N**	**Total N**

	(tested)	N (test+)	(test-)	(indeterminate)	(test results available)
IGRA (QFT-GIT):	214	45	157	12	214
TST (≥5 mm):	214	52	162	0	214
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 214

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group - risk factors for TB infection	
Non-exposed	No risk factors for TB infection
Exposed 1 **(specify):**	Risk factors for TB infection (birth or residence for ≥6 months in a high TB incidence country, TB contact, prior prison stay, intravenous drug abuse, health care worker, abnormal chest X-ray, and history of past TB)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QuantiFERON®-TB Gold in-Tube test samples were collected just before TST was performed (Nil, TB-antigens [ESAT-6, CFP-10 and TB-7.7] and phytohemagglutinin [PHA] tubes). All plasma samples were stored and analyzed in the Mycobacterial Laboratory (Clinical Microbiology Department) in accordance with the manufacturer's instructions	According to manufacturer QFT-GIT results could be positive, negative, or indeterminate depending on the IFN-γ production. Plasma samples with indeterminate results were retested	NA
TST	TST was performed according to the Mantoux method using 2 U of tuberculin RT-23 (Statens Serum Institute, Copenhagen, Denmark)	TST was administered and read by experienced staff following the standard protocol (in the left forearm and transverse diameter measurement). Any induration of ≥5 mm at 48–72 h was considered as positive	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA

Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥5mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	45	TST +	NR	NR	52
IGRA -	NR	NR	157	TST -	NR	NR	162
indeterminate	NR	NR	12	indeterminate	0	0	0
Total	NR	NR	214	Total	NR	NR	214

Test performance parameters

IGRA	TST
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = 2.50 (95% CI: 1.20, 5.10)	OR (crude; for T^+ reported) = 2.80 (95% CI: 1.40, 5.50)
OR (regression-based; reported) = 2.90 (95% CI: 1.30, 6.30) List of covariates: age, gender, BCG vaccination, and immunosuppressive treatment	OR (regression-based; reported) = 2.90 (95% CI: 1.40, 6.00) List of covariates: age, gender, BCG vaccination, and immunosuppressive treatment
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 0.89 (95% CI: 0.54, 1.48)
Ratio of ORs (regression-based; reported) = 1.00 (95% CI: 0.58, 1.73)
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				TST (≥5mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	45	TST +	NR	NR	52
IGRA -	NR	NR	157	TST -	NR	NR	162
indeterminate	NR	NR	12	indeterminate	0	0	0
Total	NR	NR	214	Total	NR	NR	214

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = 1.20 (95% CI: 0.50, 3.20)	OR (crude; for T+ reported) = 1.70 (95% CI: 0.90, 3.40)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = 1.50 (95% CI: 0.70, 3.40)

	List of covariates: age, gender, risk factors for TB, and immunosuppressive treatment
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	32	13	45
IGRA -	19	138	157
indeterminate	1 (excluded)	11 (excluded)	12 (excluded)
Total	51	151	202
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total (IMID n = 202)			
TST + threshold: ≥5mm			
Parameters			
Kappa = 0.56 (95% CI: 0.42, 0.70)			
% concordance = 170/202 = 84.16% (95% CI: 78.49, 88.55)			
% discordance = 32/202 = 15.84% (95% CI: 11.45, 21.51)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		

Reviewers:
Association between immunosuppression therapy and TST positivity (adjusted OR, 0.50, 95% CI 0.24, 1.04; P = 0.07) was lower compared with that for QFT-GIT positivity (adjusted OR 0.53, 95% CI 0.24, 1.19); similar results in corticosteroid users (OR for TST was lower than OR for QFT); immunosuppression therapy was a predictor of indeterminate results (OR 4.87, 95% CI 1.05, 22.60); agreement was 0.56; there was no association between test positivity (for QFT or TST) and BCG status (no influence of BCG status on test positivity); TST and QFT had a similar association with risk of LTBI (risk factor for TB)
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Casas 2011b[124] **Country:** Spain **Study design:** Retrospective/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** hospital-based **Number of centres:** one **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify) grants from the Spanish Ministry for Health and Consumer Affairs and the Carlos III Health Institute through the Fund for Health Investigations (PI070810, 2007-2010) and from the Carlos III Health Institute and Spanish Federation for Rare Diseases through the Spanish Network for Research in Infectious Diseases; research grant from the University of Barcelona
Aim of the study
To compare the performance of the TST and the QuantiFERON-TB Gold In-Tube (QFT-IT) test (a commercially available, whole blood–based IGRA) in detecting latent TB infection in patients with end-stage liver disease (ESLD) requiring liver transplant (LT)
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people: ESLD patients requiring LT
Participants
Recruitment dates: From July 2008 to July 2010 **Total N of recruited patients:** 110 **Inclusion criteria:** All patients with ESLD who were being considered for LT were invited to participate in the study **Exclusion criteria:** Patients younger than 18 years, patients with a previous history of TB, patients who had recently been tested with the TST, and patients with known immunosuppressive conditions **Total N of excluded patients:** 15 (previous TB infection, HIV, dropouts, anti-TNF-alpha agents, incomplete IGRA results) **Total N of patients tested with both IGRA and TST:** 95 **Total N of patients with valid results for both IGRA and TST:** 95 **Methods of active TB diagnosis (if applicable):** all patients underwent a chest x-ray examination; the findings were defined as normal or abnormal according to the presence or absence of lesions suggestive of past TB **Outcomes (study-based) list:** associations between test positivity and risk factors of LTBI, BCG status, agreement **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 56.4 (7.6) Women (n [%]): 23 [24.2] Race/ethnicity (n [%]): Spanish (89 [93.7]) Geographic origin (n[%]): Born or residing in a country with a high TB burden (6 [6.3]) BCG vaccination (n [%]): 30 [31.6] History of anti-TB treatment (n [%]): None Total incidence of active TB (n [%]): NA Chest radiography (yes/no): Yes Clinical examination (yes/no): NR Morbidity (n [%]): Cirrhosis (52 [54.7]), hepatocellular carcinoma (35 [36.8]), and other hepatopathies (8 [8.4]) Co-morbidity (n [%]): Diabetes mellitus 28 [29.5], chronic pulmonary obstructive disease 3 (3.2), renal failure 12 [12.6] Type of during-study treatment (n [%]): NR
Number of patients tested

	Total N	**Total**	**Total N**	**Total N**	**Total N**

	(tested)	N (test+)	(test-)	(indeterminate)	(test results available)
IGRA (QFT-GIT):	95	42	51	2	95
TST (2 step; ≥5mm):	95	44	51	0	95
Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 95					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group - risk factors for TB					
Non-exposed	No risk factors for TB				
Exposed 1 **(specify):**	Risk factors for TB (previous contact with TB, abnormal chest x-rays, birth or prolonged residence in a country with a high TB burden, alcoholism, drug abuse, a previous stay in prison, and involvement with health care)				
Exposed 2 **(specify):**	NA				
Exposed 3 **(specify):**	NA				
Exposed 4 **(specify):**	NA				

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	The QFT-IT test was performed in accordance with the manufacturer's instructions. Briefly, 3 tubes with 1 mL of whole blood were filled for each patient**:** a tube with no antigens (the nil tube), a tube with M. tuberculosis–specific antigens, and a tube with phytohemagglutinin (the mitogen tube). The blood samples were stored and analyzed at the Mycobacterial Laboratory. The blood samples for QFT-IT testing were collected immediately before the TST was performed	Results were scored as positive [interferon-c level ≥0.35 IU/mL (the M. tuberculosis–specific antigen tube minus the nil tube)], negative [interferon-c level < 0.35 IU/mL (the M. tuberculosis–specific antigen tube minus the nil tube)], or indeterminate [interferon-c level < 0.5 (the mitogen tube minus the nil tube) or > 8.0 IU/mL (the nil tube)] according to the production of interferon-c. Plasma samples with indeterminate results were retested	NA
TST (2 step; ≥ 5 mm)	The TST was performed in the left forearm according to the Mantoux method with purified protein derivative RT-23 (2 U/0.1 mL; Statens Serum Institute, Copenhagen, Denmark). In all cases, the TST was administered and evaluated by experienced staff. If the result for the first test was negative, the test was administered again 7 to 10 days later (the 2-step TST), and that result was considered definitive	Any induration ≥ 5 mm at 48 to 72 hours was considered a positive result in accordance with the national transplant guidelines	NA

Association between test results and incidence of active TB (if applicable)					
IGRA			**TST**		
	Incidence	Total		Incidence of	Total

	of active TB				active TB		
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST (2 step; ≥ 5 mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	27	15	42	TST +	30	14	44
IGRA -	33	20	53	TST -	30	21	51
Indeterminate	NR	NR	2 (excluded)	Indeterminate	0	0	0
Total	60	35	95	Total	60	35	95

Test performance parameters	
IGRA	**TST**
Sensitivity = 27/60 = 45.00% (95% CI: 33.09, 57.51)	Sensitivity = 30/60 = 50.00% (95% CI: 37.73, 62.27)
Specificity = 20/35 = 57.14% (95% CI: 40.86, 72.02)	Specificity = 21/35 = 60.00% (95% CI: 43.57, 74.45)
PPV = 27/42 = 64.29% (95% CI: 49.17, 77.01)	PPV = 30/44 = 68.18% (95% CI: 53.44, 80.00)
NPV = 20/53 = 37.74% (95% CI: 25.94, 51.19)	NPV = 21/51 = 41.18% (95% CI: 28.75, 54.83)
DOR (for T^+ calculated) = 1.01 (95% CI: 0.47, 2.52)	DOR (for T^+ calculated) = 1.50 (95% CI: 0.64, 3.49)
OR (crude; for T^+ reported) = 1.66 (95% CI: 0.66, 3.33)	OR (crude; for T^+ reported) = 1.25 (95% CI: 0.50, 2.50)
OR (regression-based; reported) = 1.50 (95% CI: 0.50, 4.10) List of covariates: age, sex, albumin, BCG status, Model for End-Stage Liver Disease (MELD) score	OR (regression-based; reported) = 1.80 (95% CI: 0.60, 5.10) List of covariates: age, sex, albumin, BCG status, Model for End-Stage Liver Disease (MELD) score
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 0.67 (95% CI: 0.37, 1.24)

Ratio of OR (crude; for T^+ reported) = 1.33 (95% CI: 0.74, 2.38)							
Ratio of ORs (regression-based; reported) = 0.83 (95% CI: 0.39, 1.79)							
Other reported measure = NR							
Association between test results and BCG status (if applicable)							
IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	11	31	42	TST +	13	31	44
IGRA -	19	34	53	TST -	17	34	51
Indeterminate	NR	NR	2 (excluded)	Indeterminate	0	0	0
Total	30	65	95	Total	30	65	95
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = 0.63 (95% CI: 0.26, 1.54)				DOR (for T+ calculated)$_{TST}$ = 0.83 (95% CI: 0.35, 2.00)			
OR (crude; for T^+ reported) = 0.62 (95% CI: 0.26, 1.42)				OR (crude; for T+ reported) = 0.83 (95% CI: 0.35, 2.00)			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample							
	TST +		TST -		Total		
IGRA +	33		9		42		
IGRA -	11		42		53		
Indeterminate	NR		NR		2 (excluded)		
Total	44		51		95		
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total							
TST + threshold: ≥ 5 mm							
Parameters							
Kappa = 0.57 (95% CI: 0.37, 0.77)							
% concordance = 75/95 = 78.95% (95% CI: 69.71, 85.94)							
% discordance = 20/95 = 36.36% (95% CI: 24.93, 49.58)							
Stratification (specify group 1)							
	TST +		TST -		Total		
IGRA +	NR		NR		NR		
IGRA -	NR		NR		NR		
Indeterminate	NR		NR		NR		
Total	NR		NR		NR		
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR							
TST + threshold NR							
Parameters							
Kappa = NR							
% concordance = NR							
% discordance = NR							
Stratification (specify group 2)							
	TST +		TST -		Total		
IGRA +	NR		NR		NR		
IGRA -	NR		NR		NR		

Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
We conclude that the QFT-IT test and the TST detect latent TB infection at similar rates in patients with ESLD who require LT, but the QFT-IT test performs better in patients with more severe liver disease			
Reviewers:			
No difference in performance of the two tests irrespective of disease severity; however, in patients with more severe disease (MELD =>18), the QFT positivity rates were higher (OR = 0.20, 95% CI: 0.04, 0.70) compared to TST positivity rates (OR = 0.80, 95% CI: 0.20, 2.80)			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Chkhartishvili 2013[125]
Country: Georgia
Study design: Retrospective/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** National referral institution for HIV diagnosis, treatment and care
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** the U.S. Civilian Research and Development Foundation (CRDF) award; the NIH/FIC through the Emory AIDS International Training and Research Program award and the Emory-Georgia Tuberculosis Research Training Program award

Aim of the study

To assess the performance of two commercially available IGRAs (QuantiFERON-TB Gold in Tube [QFT-GIT] and TSPOT. TB [TSPOT]) compared to the TST for the diagnosis of LTBI in HIV-infected patients, and to identify risk factors for LTBI in effort to improve the TB prevention and care among HIV patients

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people: HIV patients

Participants

Recruitment dates: November 2009 and June 2011
Total N of recruited patients: NR
Inclusion criteria: Age ≥18 years old, confirmed HIV infection, and ability to provide written informed consent
Exclusion criteria: Patients with a history of active TB disease
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 240 (QFT, TST), 238 (TSPOT)
Total N of patients with valid results for both IGRA and TST: 237 (QFT), 238 (TST), 218 (TSPOT)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Agreement, test positivity and risk factor association
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median 38.0 (range 32.8-43.8)
Women (n [%]): 81 [33.75]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 219 [94%]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): NR
Clinical examination (yes/no): NR
Morbidity (n [%]): HIV
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT)	240	70	167	3	237
IGRA (TSPOT)	240	56	162	22	218

TST (≥ 5 mm)	240	41	195	4	236

Total N of patients with valid results for both IGRA and TST: 240

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group - Household Member treated for TB	
Non-exposed	No household member treated for TB
Exposed 1 **(specify):**	Household member treated for TB
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Each participant had approximately 12 ml of blood drawn, which was performed according to the manufacturer's instructions	the QFT-GIT result was considered positive if the interferon-gamma response to TB antigens minus the negative control was ≥ 0.35 IU/ml and also > 25% of the negative control; negative if these criteria were not met; and indeterminate if either the negative control had a result of > 8 IU/ml or the positive control had a result of < 0.5 IU/ml	Blood was drawn for the IGRAs prior to the placement of the TST
IGRA (TSPOT)	Each participant had approximately 12 ml of blood drawn, which was performed according to the manufacturer's instructions	For TSPOT 250,000 peripheral blood mononuclear cells (PBMCs) were isolated and plated per well: a nil control, a positive control containing phytohemagglutinin and TB specific antigens (CFP-10 and ESAT-6). Spot forming units were counted using AID Eli-Spot Reader System (Autoimmun Diagnostika, Germany). The test result was considered reactive if the response to either CFP-10 or ESAT-6 minus the nil control was ≥ 6 spot forming cells, or twice the nil control. The result was considered indeterminate if nil control spot count was > 10 spot forming cells or if the reading in the positive control was < 20 spot forming cells	Blood was drawn for the IGRAs prior to the placement of the TST
TST	The TST was performed using the Mantoux method. An intradermal injection of 0.1 ml purified protein derivative was administered into the volar surface of the forearm. The transverse diameter of induration was recorded in millimeters 48–72 hours after administration	An induration of ≥ 5 mm of induration was considered positive	

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST ≥ 5 mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	70	TST +	NR	NR	41
IGRA -	NR	NR	167	TST -	NR	NR	195
Indeterminate	NR	NR	3	Indeterminate	NR	NR	4
Total	13	227	240	Total	13	227	240

Test performance parameters	
IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = 0.43 (95% CI: 0.09, 1.97)	OR (crude; for T^+ reported) = 1.48 (95% CI: 0.39, 5.62)
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 0.29 (95% CI: 0.10, 0.82)
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)					
IGRA (TSPOT)			**TST ≥ 5 mm**		
	Exposure level	Total		Exposure level	Total

	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	56	TST +	NR	NR	41
IGRA -	NR	NR	162	TST -	NR	NR	195
Indeterminate	NR	NR	22	Indeterminate	NR	NR	4
Total	13	227	240	Total	13	227	240

Test performance parameters	
IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = 1.48 (95% CI: 0.44, 5.00)	OR (crude; for T^+ reported) = 1.48 (95% CI: 0.39, 5.62)
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = 1.00 (95% CI: 0.40, 2.51)	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Association between test results and BCG status (if applicable)							
IGRA (QFT-GIT)				**TST ≥ 5 mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	70	TST +	NR	NR	41
IGRA -	NR	NR	167	TST -	NR	NR	195
Indeterminate	NR	NR	3	Indeterminate	NR	NR	4
Total	173	67	240	Total	173	67	240

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = 1.41 (95% CI: 0.38, 5.29)	OR (crude; for T+ reported) = 2.55 (95% CI: 0.32, 20.18)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Association between test results and BCG status (if applicable)							
IGRA (TSPOT)				**TST ≥ 5 mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	56	TST +	NR	NR	41
IGRA -	NR	NR	162	TST -	NR	NR	195
Indeterminate	NR	NR	22	Indeterminate	NR	NR	4
Total	173	67	240	Total	173	67	240

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = 1.78 (95% CI: 0.38, 8.28)	OR (crude; for T+ reported) = 2.55 (95% CI: 0.32, 20.18)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA

Other reported measure = NR		Other reported measure = NR	
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST + (≥ 5 mm)	TST -	Total
IGRA (QFT-GIT) +	25	44	69
IGRA (QFT-GIT) -	16	148	164
Indeterminate	0	3	3
Total	41	195	236
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): QFT-GIT (total)			
TST + threshold: ≥ 5 mm			
Parameters			
Kappa = 0.30 (95% CI: 0.17, 0.42) calculated – indeterminate excluded Kappa = 0.29 (95% CI: 0.16, 0.42) reported			
% concordance = 173/233 = 74.25% (95% CI: 68.27, 79.44) calculated– indeterminate excluded			
% discordance = 60/233 = 25.75% (95% CI: 20.56, 31.73) calculated– indeterminate excluded			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST + (≥ 5 mm)	TST -	Total
IGRA (TSPOT) +	20	36	56
IGRA (TSPOT) -	18	143	161
Indeterminate	3	16	19
Total	41	195	236
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): TSPOT (total)			
TST + threshold: =>5mm			
Parameters			
Kappa = 0.27 (95% CI: 0.14, 0.40) calculated – indeterminate excluded Kappa = 0.22 (95% CI: 0.07, 0.29) reported			
% concordance = 163/217 = 75.12% (95% CI: 68.96, 80.4) calculated– indeterminate excluded			
% discordance = 54/217 = 24.88% (95% CI: 19.6, 31.04) calculated– indeterminate excluded			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR		
TST + threshold: NR		
Parameters		
Kappa = NR		
% concordance = NR		
% discordance = NR		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
There was very poor agreement among all tests. This lack of agreement makes it difficult to know which test is superior and most appropriate for LTBI testing among HIV-infected patients; Multivariate analysis did not identify one specific population subgroup at higher risk of LTBI		
Reviewers:		
There were no differences in the association between the test results for QFT (or TSPOT) vs. TST and risk of LTBI (exposure measured as household member treated for TB); BCG vaccination status did not appear to influence test positivity for either of the tests; agreement measured with kappa was fair		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Chung 2010a[126]
Country: Korea
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Medical Centre
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** funding from the Gil Medical Centre

Aim of the study

Two IGRAs (QFT-GIT and TSPOT) were simultaneously compared with the TST for their diagnostic efficacy for latent TB infection in Korea, an intermediate TB-burden country

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people - haemodialysis patients with end stage renal disease (ESRD)

Participants

Recruitment dates: 1 March to 30 April 2008
Total N of recruited patients: NR
Inclusion criteria: Hemodialysis patients with ESRD
Exclusion criteria: Those patients who had taken empirical anti-TB medications and patients taking anti-TB medication for active TB infection
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 167 (total), 146 (review-relevant population), 21 (patients with a cured TB infection)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list:
Characteristics of participants (total study sample): n = 167
Mean (range or SD) age (years): 54.1 (14.4)
Women (n [%]): 71 [42.5]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 111 [67.3]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): ESRD due to Diabetes mellitus (67 [40.1]), Hypertension (18 [10.8]), Glomerulonephritis (12 [7.2]), Others (11 [6.6]), Unknown (59 [35.3])
Co-morbidity (n [%]): History of cancer (12 [7.2]), Cardiac disease (46 [27.5]), Cerebrovascular accident (13 [7.8]), History of TB infection (21 [12.6])
Type of during-study treatment (n [%]): Immunosuppressant medication (9 [5.4])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	NR	56	90	NR (for n = 146)	146
IGRA (TSPOT):	NR	83	63	NR (for n = 146)	146
TST ≥10 mm:	NR	32	114	NR (for n = 146)	146

Total N of patients with valid results for both IGRA and TST: 146

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – High vs. low risk	
Non-exposed	Low risk

Exposed 1 **(specify):**	The high-risk group for latent TB infection consisted of patients with a history of close contact with TB patients, old TB lesions on CXR, or a history of TB infection
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA (QFT-GIT)	Whole blood was extracted just before dialysis for the two IFN-c tests. The QFT-G was performed according to the manufacturer's instructions (Cellestis Ltd., Carnegie, Victoria, Australia)	Results of each test were classified as positive, negative or indeterminate, as previously described	NA
IGRA (TSPOT)	The TSPOT was also performed according to the manufacturer's instructions (Oxford Immunotec, Oxford, UK)	Results of each test were classified as positive, negative or indeterminate, as previously described	NA
TST	Within a week after the IGRAs, 2-TU of purified protein derivative RT23 (Statens Serum Institute, Copenhagen, Denmark) was intradermally injected on the volar side of the forearm contralateral to the patient's vascular access. Two physicians, blind to the patients' clinical information, measured the main diameter of the induration after 48 h independently	The positive criterion was ≥10 mm size of the mean values of two measurements	NA

Association between test results and incidence of active TB (if applicable)

IGRA	Incidence of active TB		Total	TST	Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)							
Ratio of cumulative incidence ratios = NA							
Ratio of incidence density rate ratios = NA							
Other reported measure = NA							
Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				**TST≥10mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	9	47	56	TST +	2	30	32
IGRA -	8	82	90	TST -	15	99	114
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	17	129	146	Total	17	129	146
Test performance parameters (based on 146 patients; 21 with previous TB excluded)							
IGRA				**TST**			
Sensitivity = 9/17 = 52.94% (95% CI: 30.96, 73.84)				Sensitivity = 2/17 = 11.76% (95% CI: 3.28, 34.34)			
Specificity = 82/129 = 63.57% (95% CI: 54.98, 71.37)				Specificity = 99/129 = 76.74% (95% CI: 68.75, 83.20)			
PPV = 9/56 = 16.07% (95% CI: 8.69, 27.81)				PPV = 2/32 = 6.25% (95% CI: 1.73, 20.15)			
NPV = 82/90 = 91.11% (95% CI: 83.43, 95.43)				NPV = 99/114 = 86.84% (95% CI: 79.42, 91.86)			
DOR (for T^+ calculated) = 1.96 (95% CI: 0.71, 5.43)				DOR (for T^+ calculated) = 0.44 (95% CI: 0.09, 2.03)			
OR (crude; for T^+ reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients)				OR (crude; for T^+ reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients)			
OR (regression-based; reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients) List of covariates: NA				OR (regression-based; reported) = (reported only for total sample of 167 patients that included 21 previous TB patients) List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 4.45 (95% CI: 1.72, 11.51)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NA							
Association between test results and levels of TB exposure (if applicable)							
IGRA (TSPOT)				**TST≥10mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	8	75	83	TST +	2	30	32
IGRA -	9	54	63	TST -	15	99	114
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	17	129	146	Total	17	129	146
Test performance parameters (based on 146 patients; 21 with previous TB excluded)							
IGRA				**TST**			
Sensitivity = 8/17 = 47.06% (95% CI: 26.16, 69.04)				Sensitivity = 2/17 = 11.76% (95% CI: 3.28, 34.34)			
Specificity = 54/129 = 41.86% (95% CI: 33.70, 50.49)				Specificity = 99/129 = 76.74% (95% CI: 68.75, 83.20)			
PPV = 8/83 = 9.64% (95% CI: 4.96, 17.88)				PPV = 2/32 = 6.25% (95% CI: 1.73, 20.15)			
NPV = 54/63 = 85.71% (95% CI: 75.03, 92.30)				NPV = 99/114 = 86.84% (95% CI: 79.42, 91.86)			
DOR (for T^+ calculated) = 0.64 (95% CI: 0.23, 1.76)				DOR (for T^+ calculated) = 0.44 (95% CI: 0.09, 2.03)			

OR (crude; for T^+ reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients)	OR (crude; for T^+ reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients)
OR (regression-based; reported) = NA (reported only for total sample of 167 patients that included 21 previous TB patients) List of covariates: NA	OR (regression-based; reported) = (reported only for total sample of 167 patients that included 21 previous TB patients) List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 1.45 (95% CI: 0.56, 3.76)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (QFT-G)				**TST ≥10mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	47	TST +	NR	NR	30
IGRA -	NR	NR	82	TST -	NR	NR	99
Indeterminate	NR	NR		Indeterminate	NR	NR	
Total	NR	NR	129	Total	NR	NR	129

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NA (reported only for 129 low risk patients that also included 21 previous TB patients)	OR (crude; for T+ reported) = NA (reported only for 129 low risk patients that also included 21 previous TB patients)
OR (regression-based; reported) $_{IGRA}$ = NA (reported only for 129 low risk patients that also included 21 previous TB patients) List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA (reported only for 129 low risk patients that also included 21 previous TB patients) List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	75	TST +	NR	NR	30
IGRA -	NR	NR	54	TST -	NR	NR	99
Indeterminate	NR	NR		Indeterminate	NR	NR	
Total	NR	NR	129	Total	NR	NR	129

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NA (reported only for 129 low risk patients that also included 21 previous TB patients)	OR (crude; for T+ reported) = NA (reported only for 129 low risk patients that also included 21 previous TB patients)
OR (regression-based; reported) $_{IGRA}$ = NA (reported only for 129 low risk patients that also included 21 previous TB patients) List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA (reported only for 129 low risk patients that also included 21 previous TB patients) List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total of 167			
TST + threshold: =>10mm			
Parameters			
Kappa = NA (reported only for total 167 patient sample that included 21 patients with previous TB)			
% concordance = NA			
% discordance = NA			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
Previous BCG vaccination increased the TST-positive rate in the low-risk group (OR 4.438), whereas it affected neither QFT nor TSPOT. The QFT was associated with the high-risk group (OR 2.578), whereas the TST and TSPOT were not. The frequency of indeterminate results was higher for the QFT (12.6%) compared with the TSPOT (4.8%). In conclusion, the IGRAs can be useful for the diagnosis of latent TB infection in haemodialysis patients
Reviewers:

The only relevant data available in this study was for the association between test positivity and exposure groups (n = 146; which excluded 21 patients with previous TB). All the other analyses (agreement, BCG status influence) were based on a total sample of 167 patients that included 21 patients with previously cured TB QFT performed better than TST and TSPOT (in DORs) due its higher sensitivity relative to the other tests; TST had better specificity than the two IGRAs
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Costantino 2013[127]
Country: France
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Rheumatology Department of Nancy University Hospital
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** NR

Aim of the study

To compare TST and IGRA results in screening for LTBI in a large population of patients with chronic inflammatory
arthritis requiring biologic treatment and to investigate predictive factors of results of these 2 tests, with special
attention for indeterminate IGRA results

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people: chronic inflammatory arthritis before anti TNF treatment

Participants

Recruitment dates: Between 2005 and 2009
Total N of recruited patients: NR
Inclusion criteria: Patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA)requiring TNF antagonists (first-line therapy or switch)
Exclusion criteria: Patients with previous antituberculous chemoprophylaxis
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 563
Total N of patients with valid results for both IGRA and TST: IGRA (n = 475), TST (n = 514)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Association between test positivity and conventional risk factors (CRF) of LTBI; agreement; association between test positivity and patient characteristics
Characteristics of participants (total study sample)
Mean (range or SD) age (years**):** 51.0 (39.0–59.0)
Women (n [%]): 321 [57.0]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Birth in endemic zone of TB (52 [9.2])
BCG vaccination (n [%]): 439 [78.0]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): Rheumatoid arthritis (293 [52.0]), spondyloarthritis (270 [48.0])
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): DMARD (277 [49.2]), Corticosteroids (254 [45.1]), NSAID (255 [45.4])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT):	563	122	353	88	475
TST (≥ 5 mm):	563	196	318	49	514

Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 563					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group - conventional risk factors (CRF) of LTBI					
Non-exposed	No CRF of LTBI				
Exposed 1 **(specify)**:	CRF of LTBI: history of active TB treated before 1970 or not treated for at least 6 months including 2 months with a combination of rifampicine and pyrazinamide, close contact with a patient with active TB, and chest radiograph suggestive of previous TB infection				
Exposed 2 **(specify):**	NA				
Exposed 3 **(specify):**	NA				
Exposed 4 **(specify):**	NA				

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	T-SPOT.TB assays were performed according to the manufacturer's instructions	Assays were considered indeterminate if the negative control (cell suspension in medium alone) spot count yielded more than 10 spots (referred to hereafter as a high nil control) or if the positive control (cell suspension stimulated with phytohemagglutinin) spot count yielded fewer than 20 spots (low positive control). For determinate tests, T-SPOT.TB assays were interpreted according to the manufacturer's recommendations by subtracting the spot count of the negative control from the highest spot count between panels A (TB-specific antigen ESAT-6) and B (TB-specific antigen CFP-10). A test was considered positive if this difference was equal to, or higher than, 6 spots; otherwise, the test was considered negative	To avoid any potential boosting effect of TST on IGRA results, all T-SPOT.TB assays were performed before initiating TST
TST ≥ 5 mm	The TST was performed with 5 tuberculin units corresponding to 0.1 ml of purified protein derivative (Tubertest, Sanofi Pasteur MSD, SNC) according to the Mantoux method. Tuberculin was injected intradermally in the forearm, and 72 h later the diameter of skin induration was recorded	An induration diameter of 5 mm or more was considered a positive test	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA

Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				TST ≥ 5 mm			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	23	99	122	TST +	31	165	196
IGRA -	25	328	353	TST -	18	300	318
Indeterminate	16	72	88	Indeterminate	15	34	49
Total	64	499	563	Total	64	499	563

Test performance parameters

IGRA	TST
Indeterminate included Sensitivity = 23/64 = 35.94% (95% CI: 25.29, 48.18) **Indeterminate excluded** Sensitivity = 23/48 = 47.92% (95% CI: 34.47, 61.67)	**Indeterminate included** Sensitivity = 31/64 = 48.44% (95% CI: 36.63, 60.42) **Indeterminate excluded** Sensitivity = 31/49 = 63.27% (95% CI: 49.27, 75.34)
Indeterminate included Specificity = 400/499 = 80.16% (95% CI: 76.44, 83.42) **Indeterminate excluded** Specificity = 328/427 = 76.81% (95% CI: 72.58, 80.57)	**Indeterminate included** Specificity = 334/499 = 66.93% (95% CI: 62.69, 70.92) **Indeterminate excluded** Specificity = 300/465 = 64.52% (95% CI: 60.06, 68.73)
PPV = 23/122 = 18.85% (95% CI: 12.9, 26.70)	PPV = 31/196 = 15.82% (11.37, 21.58)
Indeterminate included NPV = 400/441 = 90.70% (95% CI: 87.63, 93.07) **Indeterminate excluded** NPV = 328/353 = 92.92% (95% CI: 89.75, 95.16)	**Indeterminate included** NPV = 334/367 = 91.01% (95% CI: 87.64, 93.53) **Indeterminate excluded** NPV = 300/318 = 94.34% (95% CI: 91.23, 96.39)
Indeterminate included DOR (for T^+ calculated) = 2.26 (95% CI: 1.30, 3.95) **Indeterminate excluded**	**Indeterminate included** DOR (for T^+ calculated) = 1.90 (95% CI: 1.12, 3.21) **Indeterminate excluded**

DOR (for T+ calculated) = 3.05 (95% CI: 1.65, 5.60)	DOR (for T+ calculated) = 3.13 (95% CI: 1.70, 5.77)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = 2.70 (95% CI: 1.49, 4.89) List of covariates: NR	OR (regression-based; reported) = 1.95 (95% CI: 1.13, 3.36) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 0.97 (95% CI: 0.63, 1.51)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = 1.38 (95% CI: 0.92, 2.09)
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				**TST ≥ 5 mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	80	NR	122	TST +	162	NR	196
IGRA -	NR	NR	353	TST -	NR	NR	318
Indeterminate	NR	NR	88	Indeterminate	NR	NR	49
Total	439	124	563	Total	439	124	563

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{IGRA}$ = 0.39 (95% CI: 0.24, 0.62) List of covariates: NR	OR (regression-based; reported)$_{TST}$ = NR (p = 0.11, NS) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + ≥ 5 mm	TST -	Total
IGRA (TSPOT) +	59	51	110
IGRA (TSPOT) -	114	220	334
Indeterminate			
Total	173	271	444

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total
TST + threshold: ≥ 5 mm

Parameters

Kappa = 0.16 (95% CI: 0.07, 0.25)
% concordance = 279/444 = 62.84% (95% CI: 58.25, 67.2)
% discordance = 165/444 = 37.16% (95% CI: 32.8, 41.75)

Stratification (BCG vaccinated)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated
TST + threshold: ≥ 5 mm

Parameters

Kappa = 0.15 (95% CI: NA)			
% concordance = NA			
% discordance = NA			
Stratification (BCG not vaccinated)			
	TST +	TST -	Total
IGRA (TSPOT) +	NR	NR	NR
IGRA (TSPOT) -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG not vaccinated			
TST + threshold: ≥ 5 mm			
Parameters			
Kappa = 0.22 (95% CI: NA)			
% concordance = NA			
% discordance = NA			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
It is confirmed that there is poor agreement between TST and IGRA results, especially in a population largely vaccinated by BCG. The results suggest that IGRA should be included in the strategy to identify LTBI in patients with chronic inflammatory diseases before starting anti-TNF therapy. The data indicate that replacement of TST by IGRA in the screening would have led to a 27% reduction of antibiotics prophylaxis introduction
Reviewers:
T-SPOT.TB was less influenced by BCG than TST; specificity and DOR of T-SPOT.TB was higher than those of TST; sensitivity of TST was slightly higher than that of T-SPOT.TB; kappa for agreement was low, especially for BCG-vaccinated patients
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Hadaya 2013[128] **Country:** Switzerland **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Geneva University Hospital **Number of centres:** NR **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Ligue Pulmonaire Genevoise, a non-profit organisation
Aim of the study
To compare the diagnostic performance of the TST and two IGRAs (T-SPOT.TB and QuantiFERON Gold In-Tube [QGIT]) in renal transplant recipients (RTRs) under stable immunosuppression
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people - renal transplant recipients (RTRs)
Participants
Recruitment dates: November 2009 and December 2011 **Total N of recruited patients:** 205 **Inclusion criteria:** > 18 years, being able to provide informed consent, having had a renal transplant at least 12 months before inclusion, and having a stable immunosuppression. **Exclusion criteria:** treatment for acute rejection within the preceding 3 months and signs or symptoms of acute infection **Total N of excluded patients:** 5 (indeterminate IGRAs) **Total N of patients tested with both IGRA and TST:** 205 **Total N of patients with valid results for both IGRA and TST:** 200 **Methods of active TB diagnosis (if applicable):** NR **Outcomes (study-based) list:** Agreement; association of test results with the risk of LTBI **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 59.0 (13.2) Women (n [%]): 84 (42.0) Race/ethnicity (n [%]): NR Geographic origin (n[%]): High incidence of TB in country of origin (24 [12.0]) BCG vaccination (n [%]): 155 [77.5] History of anti-TB treatment (n [%]): Active therapy (9 [4.5]), LTBI treatment (12 [6.0]) Total incidence of active TB (n [%]): NA Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): Renal transplant recipients Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): Prednisone (88 [44.0]), Tacrolimus, (127 [63.5]), Cyclosporine (41 [20.5]) Mycophenolate mofetil (159 [79.5]), Azathioprine (17 [8.5]), Sirolimus (12 [6.0])

Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (QFT-GIT):	205	47	155	3	202
IGRA (TSPOT):	205	41	162	2	203
TST (≥5 mm):	205	9	191	0	200

Total N of patients with valid results for both IGRA and TST: 200

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group- Composite outcome 2 (risk for LTBI)	
Non-exposed	No risk for LTBI

Exposed 1 **(specify):**	Risk for LTBI**:** Chest X-ray suggestive of prior infection (calcified granuloma or adenopathy, suggestive fibrotic scars) and/or close contact with TB patient
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Blood samplings for determination of M. tuberculosis-specific QGIT (Cellestis) were processed, and scored according to the manufacturer's recommendations. Peripheral venous blood samples were processed by our laboratory within 3 hr	According to the manufacturer's recommendations	Blood samplings for determination of M. tuberculosis-specific QGIT (Cellestis) and interferon-F-secreting T cells (T-SPOT.TB (Oxford Immunotec) were performed simultaneously
IGRA (TSPOT)	Blood samplings for determination of M. tuberculosis-specific interferon-F-secreting T cells (T-SPOT.TB (Oxford Immunotec) were processed, and scored according to the manufacturer's recommendations. Peripheral venous blood samples were processed by our laboratory within 3 hr	According to the manufacturer's recommendations	NA
TST≥5mm	A TST was performed intradermally, according to the Mantoux technique, using two units of purified protein derivative (RT-23; Statens Serum Institute, Copenhagen, Denmark), which is the biological equivalent of five units of US purified protein derivative	Results of TST were considered positive if the transverse diameter, measured 48 to 72 hr after injection, was ≥ 5 mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA

Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = Na	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST≥5mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	14 (calculated)	28 (calculated)	42 (calculated)	TST +	3 (calculated)	6 (calculated)	9 (calculated)
IGRA -	28 (calculated)	113 (calculated)	141 (calculated)	TST -	39 (calculated)	135 (calculated)	174 (calculated)
Indeterminate	NR	NR	3 (excluded)	Indeterminate	NR	NR	0
Total	42	141	183	Total	42	141	183

Test performance parameters

IGRA	**TST**
Sensitivity = 33.30% (95% CI: 19.60, 49.50) reported	Sensitivity = 7.10% (95% CI: 1.50, 19.50)
Specificity = 80.10% (95% CI: 72.90, 86.20) reported	Specificity = 95.50% (95% CI: 90.80, 98.20)
PPV = 33.33% (95% CI: 21.01, 48.45) calculated	PPV = 33.33% (95% CI: 12.06, 64.58) calculated
NPV = 81.10% (95% CI: 73.80, 87.00) reported	NPV = 78.40% (95% CI: 71.70, 84.20)
DOR (for T^+ calculated) = 2.01 (95% CI: 0.94, 4.32)	DOR (for T^+ calculated) = 1. 73 (95% CI: 0.41, 7.24)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 1.16 (95% CI: 0.51, 2.66)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST≥5mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	14 (calculated)	20 (calculated)	34 (calculated)	TST +	3 (calculated)	6 (calculated)	9 (calculated)
IGRA -	28 (calculated)	121 (calculated)	149 (calculated)	TST -	39 (calculated)	135 (calculate)	174 (calculated)
Indeterminate	NR	NR	2 (excluded)	Indeterminate	NR	NR	0
Total	42	141	183	Total	42	141	183

Test performance parameters

IGRA	**TST**
Sensitivity = 33.30% (95% CI: 19.60, 49.50)	Sensitivity = 7.10% (95% CI: 1.50, 19.50)
Specificity = 85.50% (95% CI: 78.90, 90.70)	Specificity = 95.50% (95% CI: 90.80, 98.20)
PPV = 41.18% (95% CI: 26.37, 57.78) calculated	PPV = 33.33% (95% CI: 12.06, 64.58) calculated

NPV = 81.90% (95% CI: 75.00, 87.60)	NPV = 78.40% (71.70, 84.20)
DOR (for T^+ calculated) = 3.02 (95% CI: 1.36, 6.71)	DOR (for T^+ calculated) = 1.73 (95% CI: 0.41, 7.24)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 1.75 (95% CI: 0.76, 4.04)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA (QFT-GIT) +	NR	NR	47
IGRA (QFT-GIT) -	NR	NR	153
indeterminate	NR	NR	3 (excluded)
Total	9	191	200

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total (n = 200)
TST + threshold: ≥5mm

Parameters

Kappa = 0.11 (P = 0.010)
% concordance = NR
% discordance = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA (TSPOT) +	NR	NR	41
IGRA (TSPOT) -	NR	NR	159
Indeterminate	NR	NR	2 (excluded)
Total	9	191	200

Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total (n = 200)			
TST + threshold: ≥5mm			
Parameters			
Kappa = 0.09 (P = 0.034)			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
Neither the TST nor the IGRAs are sensitive enough in RTRs to exclude a diagnosis of TB or LTBI. Combining IGRAs did not significantly improve sensitivity			
Reviewers:			
Although low (33.3%), sensitivities of IGRAS were greater than that of TST (7%); agreement between IGRAs and TST was low (kappa = 0.09-0.11)			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Hsia 2012[129] **Country:** US **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** NR **Number of centres:** 340 **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Johnson & Johnson, honoraria from Genentech, Pfizer, Celgene, Corrona, Amgen, Bristol-Myers Squibb, and Janssen
Aim of the study
To evaluate the performance of an interferon- release assay (IGRA) versus the standard tuberculin skin test (TST) as a screening tool for latent tuberculosis (TB) infection prior to the initiation of anti–tumor necrosis factor therapy in patients with autoimmune inflammatory diseases
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis prior to the initiation of anti–tumor necrosis factor therapy)
Participants
Recruitment dates: NR **Total N of recruited patients:** 2303 **Inclusion criteria:** No history of latent/active TB prior to screening (except in GO-AFTER, which allowed the inclusion of patients with a history of latent TB who had been treated within the last 3 years) and having no signs or symptoms of active TB or no recent close contact with anyone with active TB. All patients were required to have a chest radiograph, obtained within 3 months before the first dose of study agent, that showed no evidence of active TB or old inactive TB. **Exclusion criteria:** NR **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** 2282 **Total N of patients with valid results for both IGRA and TST:** 2241 **Methods of active TB diagnosis (if applicable):** NR **Outcomes (study-based) list:** Agreement; exposure-based **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 48.58 (12.6) Women (n [%]): 1515 [65.7] Race/ethnicity (n [%]): NR Geographic origin (n[%]): North America (962 [41.8]), Western Europe (440 [19.1]), Eastern Europe (432 [18.8]), Latin America (203 [8.8]), Asia (266 [11.6]) BCG vaccination (n [%]): 788 [34.2] History of anti-TB treatment (n [%]): 317 [13.8] Total incidence of active TB (n [%]): NR Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): Rheumatoid arthritis (1,542 [67.0]), Psoriatic arthritis (405 [17.6]), Ankylosing spondylitis (356 [15.5]) Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): Methotrexate (571 [24.8]), Corticosteroids (1,000 [43.4])
Number of patients tested

	Total N (tested)	**Total N (test +)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**

IGRA (QFT-GIT):	2282	160	2081	41	2241
TST (≥5mm):	2282	215	2067	0	2282
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 2241

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – geographic region	
Non-exposed	North America
Exposed 1 **(specify):**	Western Europe
Exposed 2 **(specify):**	Asia
Exposed 3 **(specify):**	Eastern Europe
Exposed 4 **(specify):**	Latin America

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	The QFT-GIT test was the IGRA assay used. For this procedure, standard venipuncture is performed at a single visit to collect blood in tubes that contain the M tuberculosis–specific antigens. The QFT-GIT test also contains an extra antigen, TB7.7 (p4) that was not present in the original version of this IGRA and is thought to improve sensitivity. In addition, this version of the IGRA shortens the manual processing time, since antigens are already present in the tubes. Initial IGRA sample-handling procedures were performed at investigational sites, and a central laboratory performed the enzyme-linked immunosorbent assay–based testing and reported the results for each patient according to the manufacturer's interpretation criteria	According to the manufacturer Positive results were confirmed by duplicate testing of the same sample. Any results initially indeterminate on the IGRA required a second sample to be drawn and tested, and the final results were used to determine study eligibility	NA
TST	The TST was performed according to the Mantoux method, using 5 tuberculin units (TU) of purified protein derivative (PPD) standard or 2 TU of PPD RT-23 (Statens Serum Institut). A trained health-care worker recorded each patient's reaction to the TST at 48–72 hours after placement	The TST was deemed positive for latent TB infection according to the local country guidelines for defining an immunosuppressed host or, in the absence of local guidelines, according to the presence of induration 5 mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**

Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = NA	
Ratio of incidence density rate ratios = NA	
Other reported measure = NA	

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST≥5 mm**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	160	TST +	NR	NR	215
IGRA -	NR	NR	2081	TST -	NR	NR	2067
Indeterminate	NR	NR	41	Indeterminate	NR	NR	0
Total	Vary by geographic region		2282	Total	Vary by geographic region		2282

Test performance parameters

IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = Western Europe vs. North America: 3.41 (95% CI: 1.99, 5.83) Latin America vs. North America: 3.43 (95% CI: 1.64, 7.19) Eastern Europe vs. North America: 3.58 (95% CI: 1.93, 6.63) Asia vs. North America: 8.48 (95% CI: 4.78, 15.03) List of covariates: baseline methotrexate use, baseline steroid use, disease type, age, and prior BCG vaccination	OR (regression-based; reported) = Western Europe vs. North America: 2.10 (95% CI: 1.30, 3.38) Latin America vs. North America: 1.56 (95% CI: 0.80, 3.05) Eastern Europe vs. North America: 0.95 (95% CI: 0.53, 1.70) Asia vs. North America: 7.47 (95% CI: 4.61, 12.08) List of covariates: : baseline methotrexate use, baseline steroid use, disease type, age, and prior BCG vaccination
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = Western Europe vs. North America: 1.62 (95% CI: 1.13, 2.34) Latin America vs. North America: = 2.20 (95% CI: 1.32, 3.66)	

Eastern Europe vs. North America: = 3.77 (95% CI: 2.44, 5.81)
Asia vs. North America: = 1.14 (95% CI: 0.77, 1.66)

Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				**TST ≥5 mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	71	72	143	TST +	119	62	181
IGRA -	NR	NR	1853	TST -	NR	NR	1848
Indeterminate	9	24	33	Indeterminate	NR	NR	0
Total	781	1248	2029	Total	781	1248	2029

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = 1.00 (95% CI: 0.66, 1.51) List of covariates: baseline methotrexate use, baseline steroid use, disease type, age, and geographic region	OR (regression-based; reported) $_{TST}$ = 2.47 (95% CI: 1.71, 3.55) List of covariates: baseline methotrexate use, baseline steroid use, disease type, age, and geographic region
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	59	101	160
IGRA -	NR	NR	2081
Indeterminate	NR	NR	41
Total	215	2067	2282

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥5 mm

Parameters

Kappa = 0.22 (95% CI: 0.15, 0.27)

% concordance = NR

% discordance = NR

Stratification (specify group 1): BCG-vaccinated

	TST +	TST -	Total
IGRA +	28	43	71
IGRA -	91	619	710
Indeterminate	0 (excluded)	9 (excluded)	9 (excluded)
Total	119	662	781

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated

TST + threshold: ≥5 mm

Parameters

Kappa = 0.20 (95% CI: 0.13, 0.27) calculated

% concordance = 647/781 = 82.84% (95% CI: 80.04, 85.32) calculated

% discordance = 134/781 = 17.16% (95% CI: 14.68, 19.96) calculated

Stratification (specify group 2): BCG non-vaccinated

	TST +	TST -	Total

IGRA +	24	48	72
IGRA -	38	1138	1176
Indeterminate	6 (excluded)	18 (excluded)	24 (excluded)
Total	62	1186	1248
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG non-vaccinated			
TST + threshold: ≥5 mm			
Parameters			
Kappa = 0.32 (95% CI: 0.26, 0.37) calculated			
% concordance = 1162/1248 = 93.11% (95% CI: 91.57, 94.39) calculated			
% discordance = 86/1248 = 6.89% (95% CI: 5.61, 8.43) calculated			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
Thus, in the absence of a true gold standard test to screen for latent TB infection, results of this large cohort comparison of an IGRA (the QFT-GIT test) and the TST in patients with rheumatic disease suggest that the IGRA provides greater specificity and possibly greater sensitivity than the TST			
Reviewers:			
BCG vaccination influenced TST but not IGRA (indicating better specificity of IGRA); agreement was higher in BCG non-vaccinated vs. vaccinated patients; exposure-based (geographic location) ORs were stronger for IGRA vs. TST, indicating better specificity and/or sensitivity of IGRA vs. TST			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Kim 2010[130]
Country: Korea
Study design: Retrospective/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Clinic based
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Korea Research Foundation

Aim of the study

To compare the results of the ELISPOT assay T-SPOT.TB with those of the TST in renal transplant candidates before transplantation in a country with an intermediate TB burden

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (kidney transplant candidates before transplantation)

Participants

Recruitment dates: June 2008 and May 2009
Total N of recruited patients: 213
Inclusion criteria: Kidney transplant adult candidates before transplantation
Exclusion criteria: If abnormal chest radiograph findings were observed, a sputum acid-fast bacilli smear and a computed tomography scan were performed to rule out active pulmonary TB
Total N of excluded patients: 4 (n = 1 refusal, n = 1 active TB, n = 2 cancer)
Total N of patients tested with both IGRA and TST: 209
Total N of patients with valid results for both IGRA and TST: 184
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Agreement, association of test positivity with risk factors, influence of BCG vaccination
Characteristics of participant (total study sample)
Mean (range or SD) age (years): NR
Women (n [%]): NR
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 163 [78.0]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): End-stage renal disease
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Isoniazid for 9 months immediately after renal transplantation (5 [19%])

Number of patients tested

	Total N (tested)	**Total N (test +)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (TSPOT):	209	65	119	25	184
TST (≥5mm):	209	47	162	0	209
TST (≥10mm):	209	21	188	0	209

Total N of patients with valid results for both IGRA and TST: 209

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – LTBI group

Non-exposed	No LTBI group
Exposed 1 **(specify):**	(i) close contact with a person with pulmonary tuberculosis within the last year, (ii) abnormal chest radiography, (iii) a history of untreated or inadequately treated TB, or (iv) newly acquired infection (recent conversion of the tuberculin skin test to positive status)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	A peripheral venous blood sample was collected from each patient for the ELISPOT assay for the IFN-g-producing T-cell response (i.e., T-SPOT.TB, Oxford Immunotec, Abingdon, UK). Peripheral blood mononuclear cells (PBMC) were separated from peripheral venous blood within 4 h from sampling, and 2.5 x 10^5 PBMC were plated per well in wells precoated with anti-human IFN-g antibody The PBMC were cultured at 37◦C for 18h, and spots were counted with an automated microscope (ELiSpot04 HR, Autoimmun Diagnostika GmbH, Strassberg, Germany)	We used the criteria for positive, negative, and indeterminate outcomes that were recommended by the manufacturer	All blood samples were collected before TST to avoid the possible boosting effect of TST on the ELISPOT assay
TST (≥5mm or ≥10mm)	The Mantoux technique, injecting a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm	The positive criterion for TST was ≥10 mm size of induration 48-72 h after injection	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥5mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/ No	
IGRA +	10	55	65	TST +	8	39	47
IGRA -	9	110	119	TST -	14	148	162
Indeterminate	3 (excluded)	22 (excluded)	25 (excluded)	Indeterminate	0	0	0
Total	22	187	209	Total	22	187	209

Test performance parameters

IGRA	**TST**
Sensitivity = 10/19 = 52.63% (95% CI: 31.71, 72.67)	Sensitivity = 8/22 = 36.36% (95% CI: 19.73, 57.05)
Specificity = 110/165 = 66.67% (95% CI: 59.17, 73.41)	Specificity = 148/187 = 79.14% (95% CI: 72.76, 84.35)
PPV = 10/65 = 15.38% (95% CI: 8.57, 26.06)	PPV = 8/47 = 17.02% (95% CI: 8.88, 30.14)
NPV = 110/119 = 92.44% (95% CI: 86.25, 95.97)	NPV = 148/162 = 91.36% (95% CI: 86.02, 94.78)
DOR (for T^+ calculated) = 2.22 (95% CI: 0.85, 5.78)	DOR (for T^+ calculated) = 2.17 (95% CI: 0.85, 5.54)
OR (crude; for T^+ reported) = 2.35 (95% CI: 0.90, 6.12)	OR (crude; for T^+ reported) = 2.17 (95% CI: 0.85, 5.54)
OR (regression-based; reported) = 2.38 (95% CI: 0.87, 6.52) List of covariates: age	OR (regression-based; reported) = 2.11 (95% CI: 0.82, 5.46) List of covariates: age
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 1.02 (95% CI: 0.52, 2.03)
Ratio of OR (crude; for T^+ reported) = 1.08 (95% CI: 0.55, 2.15)
Ratio of ORs (regression-based; reported) = 1.13 (95% CI: 0.56, 2.28)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥10mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/ No	
IGRA +	10	55	65	TST +	4	17	21
IGRA -	9	110	119	TST -	18	170	188
Indeterminate	3 (excluded)	22(excluded)	25(excluded)	Indeterminate	0	0	0
Total	22	187	209	Total	22	187	209

Test performance parameters

IGRA	**TST**
Sensitivity = 10/19 = 52.63% (95% CI: 31.71, 72.67)	Sensitivity = 4/22 = 18.18% (95% CI: 7.31, 38.52)

Specificity = 110/165 = 66.67% (95% CI: 59.17, 73.41)	Specificity = 170/187 = 90.91% (95% CI: 85.92, 94.25)
PPV = 10/65 = 15.38% (95% CI: 8.57, 26.06)	PPV = 4/21 = 19.05% (95% CI: 7.66, 40.00)
NPV = 110/119 = 92.44% (95% CI: 86.25, 95.97)	NPV = 170/188 = 90.43% (95% CI: 85.37, 93.86)
DOR (for T^+ calculated) = 2.22 (95% CI: 0.85, 5.78)	DOR (for T^+ calculated) = 2.22 (95% CI: 0.67, 7.32)
OR (crude; for T^+ reported) = 2.35 (95% CI: 0.90, 6.12)	OR (crude; for T^+ reported) = 2.22 (95% CI: 0.67, 7.32)
OR (regression-based; reported) = 2.38 (95% CI:0.87, 6.52) List of covariates: age	OR (regression-based; reported) = 2.12 (95% CI: 0.60, 7.49) List of covariates: age
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 1.00 (95% CI: 0.46, 2.19)
Ratio of OR (crude; for T^+ reported) = 1.06 (95% CI: 0.48, 2.31)
Ratio of ORs (regression-based; reported) = 1.12 (95% CI: 0.49, 2.56)
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				**TST (≥5mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	48	17	65	TST +	38	9	47
IGRA -	97	22	119	TST -	125	37	162
Indeterminate	18 (excluded)	7 (excluded)	25 (excluded)	Indeterminate	0	0	0
Total	163	46	209	Total	163	46	209

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = 0.64 (95% CI: 0.31, 1.32)	DOR (for T+ calculated)$_{TST}$ = 1.25 (95% CI: 0.55, 2.82)
OR (crude; for T^+ reported) = 0.69 (95% CI: 0.36, 1.34)	OR (crude; for T+ reported) = 1.25 (95% CI: 0.55, 2.82)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				**TST (≥10mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	48	17	65	TST +	16	5	21
IGRA -	97	22	119	TST -	147	41	188
Indeterminate	18 (excluded)	7 (excluded)	25 (excluded)	Indeterminate	0	0	0
Total	163	46	209	Total	163	46	209

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = 0.64 (95% CI: 0.31, 1.32)	DOR (for T+ calculated)$_{TST}$ = 0.89 (95% CI: 0.30, 2.58)
OR (crude; for T^+ reported) = 0.69 (95% CI: 0.36, 1.34)	OR (crude; for T+ reported) = 0.89 (95% CI: 0.31, 2.58)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA

Other reported measure = NR		Other reported measure = NR	
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST + (≥10mm)	TST -	Total
IGRA (TSPOT) +	15	48	63
IGRA (TSPOT) -	5	116	121
Indeterminate	1 (excluded)	24 (excluded)	25 (excluded)
Total	20	164	184
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.23 (95% CI: 0.12, 0.34)			
% concordance = 131/184 = 71.2% (95% CI: 64.27, 77.25)			
% discordance = 53/184 = 28.8% (95% CI: 22.75, 35.73)			
Stratification (BCG vaccinated):			
	TST + (≥10mm)	TST -	Total
IGRA (TSPOT) +	10	38	48
IGRA (TSPOT) -	5	92	97
Indeterminate	NR	NR	NR
Total	15	130	145
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.19 (95% CI: 0.06, 0.31)			
% concordance = 102/145 = 70.34% (95% CI: 62.46, 77.18)			
% discordance = 43/145 = 29.66% (95% CI: 22.82, 37.54)			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
T-SPOT.TB test was more frequently positive than TST in renal transplant candidates. However, further longitudinal studies are awaited to determine whether the ability of T-SPOT.TB assay to detect			

LTBI in renal transplant recipients can better predict the development of TB than can TST after transplantation. Neither univariate nor multivariate analysis showed any association between the clinical risk for LTBI and positivity on TSPOT or TST
Reviewers:
TSPOT had better sensitivity but lower specificity than TST regardless of the two thresholds; the DORs showed similar strength of association with LTBI composite risk factor; BCG status did not influence the test positivity of TST and IGRA differentially, neither did it influence corresponding kappas
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Kim 2013b[131]
Country: Korea
Study design: Retrospective/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Clinic based
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea

Aim of the study

To compare the results of the TST and QFTGIT as methods for screening for LTBI and determined the agreement between the TST and QFT-GIT in renal transplant candidates before transplantation in a country with an intermediate TB burden

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (kidney transplant candidates before transplantation)

Participants

Recruitment dates: May 2010 and February 2012
Total N of recruited patients: NR
Inclusion criteria: Kidney transplant adult candidates before transplantation
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 126
Total N of patients with valid results for both IGRA and TST: 113
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Agreement, association of test positivity with risk factors, influence of BCG vaccination
Characteristics of participant (total study sample)
Mean (range or SD) age (years): 47 (20–69)
Women (n [%]): 55 [43.6]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 115 [91.3]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): End-stage renal disease (100 [79.4]), hemodialysis, (12 [9.5]), PD peritoneal dialysis, no dialysis (14 [11.1])
Co-morbidity (n [%]): Hypertension (60 [47.6]), Diabetes (31 [24.6])
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	126	53	67	6	120
TST (≥10mm):	126	35	91	7	119
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 113

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – LTBI group

Non-exposed	No LTBI group
Exposed 1 **(specify):**	(1) patients with a history of LTBI or active TB; (2) patients with abnormal chest radiograph findings consistent with previously healed TB; and (3) patients with a history of close contact with active pulmonary TB patients within the past year
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QuantiFERON-TB Gold In-Tube test Peripheral venous blood samples were collected from all patients for QFT-GIT assays. We performed the test according to the manufacturer's instructions (Cellestis Ltd., Carnegie, Victoria, Australia). Blood samples were divided into three blood collection tubes (1 mL each): one containing heparin alone (Nil tube, negative control), one with phytohemagglutinin (mitogen tube, positive control), and one with TB-specific antigens (ESAT-6, CFP-10, and TB 7.7). The three tubes were incubated for 20 h at 37◦C. The concentration of IFN-c was measured by the QFT enzymelinked immunosorbent assay. QFT-GIT software provided by the manufacturer was used for calculating the results	A positive QFT-GIT result was defined as IFN-c response of TB antigen minus that of the Nil tube ≥0.35 IU/mL and ≥25 % of the negative control value	NA
TST (≥5mm or ≥10mm)	The TST was performed by injecting a 2-TU dose of PPDRT 23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm, which was in accordance with the Mantoux method	The transverse induration site was measured by a trained nurse in mm after 48–72 h Induration ≥10 mm was defined as a positive TST result	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

<table>
<tr><th colspan="8">Test performance parameters</th></tr>
<tr><th colspan="4">IGRA</th><th colspan="4">TST</th></tr>
<tr><td colspan="4">Sensitivity = NA</td><td colspan="4">Sensitivity = NA</td></tr>
<tr><td colspan="4">Specificity = NA</td><td colspan="4">Specificity = NA</td></tr>
<tr><td colspan="4">PPV = NA</td><td colspan="4">PPV = NA</td></tr>
<tr><td colspan="4">NPV = NA</td><td colspan="4">NPV = NA</td></tr>
<tr><td colspan="4">Cumulative Incidence $_{IGRA+}$ = NA</td><td colspan="4">Cumulative Incidence $_{TST+}$ = NA</td></tr>
<tr><td colspan="4">Cumulative Incidence $_{IGRA-}$ = NA</td><td colspan="4">Cumulative Incidence $_{TST-}$ = NA</td></tr>
<tr><td colspan="4">Cumulative Incidence Ratio $_{IGRA}$ = NA</td><td colspan="4">Cumulative Incidence Ratio $_{TST}$ = NA</td></tr>
<tr><td colspan="4">Incidence density rate $_{IGRA+}$ = NA</td><td colspan="4">Incidence density rate $_{TST+}$ = NA</td></tr>
<tr><td colspan="4">Incidence density rate $_{IGRA-}$ = NA</td><td colspan="4">Incidence density rate $_{TST-}$ = NA</td></tr>
<tr><td colspan="4">Incidence density rate ratio $_{IGRA}$ = NA</td><td colspan="4">Incidence density rate ratio $_{TST}$ = NA</td></tr>
<tr><td colspan="4">Other reported measure $_{IGRA}$ = NA</td><td colspan="4">Other reported measure $_{TST}$ = NA</td></tr>
<tr><th colspan="8">Comparison between tests (IGRA vs. TST)</th></tr>
<tr><td colspan="8">Ratio of cumulative incidence ratios = NA</td></tr>
<tr><td colspan="8">Ratio of incidence density rate ratios = NA</td></tr>
<tr><td colspan="8">Other reported measure = NA</td></tr>
<tr><th colspan="8">Association between test results and levels of TB exposure (if applicable)</th></tr>
<tr><th colspan="4">IGRA (QFT-GIT)</th><th colspan="4">TST (≥10mm)</th></tr>
<tr><td></td><td colspan="2">Exposure level</td><td>Total</td><td></td><td colspan="2">Exposure level</td><td>Total</td></tr>
<tr><td></td><td>High/Yes</td><td>Low /No</td><td></td><td></td><td>High/Yes</td><td>Low/ No</td><td></td></tr>
<tr><td>IGRA +</td><td>11</td><td>42</td><td>53</td><td>TST +</td><td>13</td><td>10</td><td>23</td></tr>
<tr><td>IGRA -</td><td>4</td><td>63</td><td>67</td><td>TST -</td><td>2</td><td>94</td><td>96</td></tr>
<tr><td>Indeterminate</td><td>1</td><td>5</td><td>6 (excluded)</td><td>Indeterminate</td><td>1</td><td>6</td><td>7 (excluded)</td></tr>
<tr><td>Total</td><td>16</td><td>110</td><td>126</td><td>Total</td><td>16</td><td>110</td><td>126</td></tr>
<tr><th colspan="8">Test performance parameters</th></tr>
<tr><th colspan="4">IGRA</th><th colspan="4">TST</th></tr>
<tr><td colspan="4">Sensitivity = 11/15 = 73.33% (95% CI: 48.05, 89.1)</td><td colspan="4">Sensitivity = 13/15 = 86.67% (95% CI: 62.12, 96.26)</td></tr>
<tr><td colspan="4">Specificity = 63/105 = 60.00% (95% CI: 50.44, 68.86)</td><td colspan="4">Specificity = 94/104 = 90.38% (95% CI: 83.2, 94.69)</td></tr>
<tr><td colspan="4">PPV = 11/53 = 20.75% (95% CI: 12.00, 33.46)</td><td colspan="4">PPV = 13/23 = 56.52% (95% CI: 36.81, 74.37)</td></tr>
<tr><td colspan="4">NPV = 63/67 = 94.03% (95% CI: 85.63, 97.65)</td><td colspan="4">NPV = 94/96 = 97.92% (95% CI: 92.72, 99.43)</td></tr>
<tr><td colspan="4">DOR (for T^+ calculated) = 4.12 (95% CI: 1.23, 13.82)</td><td colspan="4">DOR (for T^+ calculated) = 61.1 (95% CI: 12.03, 310.4)</td></tr>
<tr><td colspan="4">OR (crude; for T^+ reported) = 4.13 (95% CI: 1.23, 13.82)</td><td colspan="4">OR (crude; for T^+ reported) = 0.61 (95% CI: 0.13, 2.91) -error</td></tr>
<tr><td colspan="4">OR (regression-based; reported) = 4.62 (95% CI: 1.15, 18.64)
List of covariates: NR</td><td colspan="4">OR (regression-based; reported) = 0.40 (95% CI: 0.07. 2.20) -error
List of covariates: NR</td></tr>
<tr><td colspan="4">Other reported measure = NR</td><td colspan="4">Other reported measure = NR</td></tr>
<tr><th colspan="8">Comparison between tests (IGRA vs. TST)</th></tr>
<tr><td colspan="8">Ratio of DORs (for T^+ calculated) = 0.07 (95% CI: 0.02, 0.19)</td></tr>
<tr><td colspan="8">Ratio of OR (crude; for T^+ reported) = NA</td></tr>
<tr><td colspan="8">Ratio of ORs (regression-based; reported) = NA</td></tr>
<tr><td colspan="8">Other reported measure = NA</td></tr>
<tr><th colspan="8">Association between test results and BCG status (if applicable)</th></tr>
<tr><th colspan="4">IGRA (QFT-GIT)</th><th colspan="4">TST (≥10mm)</th></tr>
</table>

	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	50	3	53	TST +	22	1	23
IGRA -	60	7	67	TST -	86	10	96
Indeterminate	5	1	6 (excluded)	Indeterminate	7	0	7 (excluded)
Total	115	11	126	Total	115	11	126

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = 1.94 (95% CI: 0.47, 7.91)	DOR (for T^+ calculated)$_{TST}$ = 2.55 (95% CI: 0.32, 21.06)
OR (crude; for T^+ reported) = 1.94 (95% CI: 0.48, 7.91)	OR (crude; for T^+ reported) = 2.56 (95% CI: 0.31, 21.06)
OR (regression-based; reported) $_{IGRA}$ = 2.32 (95% CI: 0.50, 10.66) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 3.32 (95% CI: 0.38, 28.97) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + (≥10mm)	TST -	Total
IGRA (QFT-GIT) +	17	33	50
IGRA (QFT-GIT) -	6	57	63
Indeterminate	0	6	6 (excluded)
Total	23	96	119

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥10mm

Parameters

Kappa = 0.26 (95% CI: 0.10, 0.41)

% concordance = 74/113 = 65.49% (95% CI: 56.34, 73.61)

% discordance = 39/113 = 34.51% (95% CI: 26.39, 43.66)

Stratification (specify group 2):

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR

% discordance = NR

Other outcomes

Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
The positive results for QFT-GIT were associated with risk for LTBI, however not for TST (error); agreement between the two tests was fair
Reviewers:
TST better performed than GIT in accuracy measures (sensitivity, PPV, specificity, DOR); BCG did not influence TST and IGRA differentially
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Kim 2013c[132]
Country: Korea
Study design: Retrospective cohort/cross-sectional study (with prospective part)
Study setting (e.g., outbreak investigation, community-based - specify)**:** NR
Number of centres: NA
Total length of follow up (if applicable): Mean 24.6 ±14.4 months
Funding (government/private/manufacturer/other - specify)**:** The Korea health care technology R & D project, ministry for health, welfare and family affair, republic of Korea.

Aim of the study

To compare the QuantiFERON-TB Gold In tube test (QFT-GIT) with the tuberculin skin test (TST) for screening of LTBI in kidney transplant recipients (KTRs)

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Kidney transplant recipients (KTRs)

Participants

Recruitment dates: Between July 2008 and July 2012
Total N of recruited patients: 109
Inclusion criteria: Kidney transplant recipients
Exclusion criteria: NR
Total N of excluded patients: 4 with indeterminate QFT-GIT results (excluded for analysis)
Total N of patients tested with both IGRA and TST: 97
Total N of patients with valid results for both IGRA and TST: 93
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Test results, concordance between TST and QFT-GIT
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 44.7 ±11.5
Women (n [%]): 41 (38)
Race/ethnicity (n [%]): NR
Geographic origin (n[%]):NR
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): 3 [2.8]
Total incidence of active TB (n [%]):1 [0.9]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): Glomerulonephritis (19 [17.4]); hypertensive nephrosclerosis (11 [10.1]); diabetes mellitus (31 [28.4]); Unknown (34 [31.2]); polycystic kidney disease (2 [1.8]); Others (12 [11.0])
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (specify): QFT-GIT	106	21	81	4	102
TST≥10mm:	97	12	81	0	93
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 97

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NR

Exposed 1 **(specify):**	History of treated tuberculosis
Exposed 2 **(specify):**	Abnormal chest radiograph
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA	QuantiFERON- Gold In-Tube (QFT-GIT) was performed according to the manufacturer's instructions (Cellestic Ltd, Carnegie, Victoria, Australia)	A positive QFT-GIT was defined as ≥ 0.35 IU/mL and ≥ 25% in the presence of TB-specific antigen minus that of the Nil tude	NA
TST≥10 mm	TST was performed on the volar side of the forearm by injection of a 2 tuberculin unit dose of perified protein derivative RT-23 according to the Mantoux method	The TST was considered positive if the size of the induration was ≥10 mm at 48 to 72 hours after the injection.	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (History of treated tuberculosis)

IGRA (QFT-GIT)				**TST≥10 mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	2	17	19	TST +	NR	NR	12
IGRA -	0	74	74	TST -	NR	NR	81
Indeterminate	NR	NR	4	Indeterminate	NR	NR	0

			(excluded)				
Total	2	91	93	Total	NR	NR	93
Test performance parameters							
IGRA				**TST**			
Sensitivity = 2/2 = 100%, 95% CI (34.24, 100)				Sensitivity = NR			
Specificity = 74/91 = 81.32%, 95% CI (72.10, 88.00)				Specificity = NR			
PPV = 2/19 = 10.53%, 95% CI (2.93, 31.39)				PPV = NR			
NPV = 74/74 = 100%, 95% CI (95.06, 100)				NPV = NR			
DOR (for T^+ calculated) = NA				DOR (for T^+ calculated) = NR			
OR (crude; for T^+ reported) = NR				OR (crude; for T^+ reported) = NR			
OR (regression-based; reported) = 9.21, 95% CI (NR) List of covariates: NR				OR (regression-based; reported) = NR (NS) List of covariates:			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = NR							
Ratio of ORs (regression-based; reported) = NR							
Other reported measure = NR							
Association between test results and levels of TB exposure (Abnormal chest radiograph)							
IGRA (QFT-GIT)				**TST TST≥10 mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	3	16	19	TST +	NR	NR	12
IGRA -	1	73	74	TST -	NR	NR	81
Indeterminate	0	0	4 (excluded)	Indeterminate	NR	NR	0
Total	4	89	93	Total	NR	NR	93
Test performance parameters							
IGRA				**TST**			
Sensitivity = 3/4 = 75.00%, 95% CI (30.06, 95.44)				Sensitivity = NR			
Specificity = 73/89 = 82.02%, 95% CI (72.77, 88.62)				Specificity = NR			
PPV = 3/19 = 15.79%, 95% CI (5.52, 37.57)				PPV = NR			
NPV = 73/74 = 98.65%, 95% CI (92.73, 99.76)				NPV = NR			
DOR (for T^+ calculated) = 13.69, 95% CI (1.33, 140.30)				DOR (for T^+ calculated) = NR			
OR (crude; for T^+ reported) = NR				OR (crude; for T^+ reported) = NR			
OR (regression-based; reported) = 27.95, 95% CI (1.22, 636.62) List of covariates: NR				OR (regression-based; reported) = NR (NS) List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = NR							
Ratio of ORs (regression-based; reported) = NR							
Other reported measure = NR							
Association between test results and BCG status (if applicable)							
IGRA (TSPOT/QFT)				**TST (≥10 mm)**			
	BCG status		Total		BCG status		Total

	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA (TSPOT/QFT)	**TST (>5 mm)**
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = NR OR (regression-based; reported)$_{TSPOT}$ = NR List of covariates:NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	6	13	19
IGRA -	6	68	74
Indeterminate	0	0	0
Total	12	81	93
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total less Indeterminate results			
TST + threshold: ≥10 mm			
Parameters			
Kappa = 0.27, 95% CI (0.07, 0.46)			
% concordance = 74/93 = 79.57%, 95% CI (70.28, 86.51)			
% discordance = 19/93 = 20.43%, 95% CI (13.49, 29.72)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			

% concordance = NR		
% discordance = NR		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
The authors concluded that there was overall fair agreement between the QFT-GIT and TST. Furthermore, they stated that a superiority of QFT-GIT [and] TST was not demonstrated and this may be a result of the clinical risk factors for LTBI		
Reviewers:		
No TST based ORs data reported		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Kleinert 2012[133]
Country: Germany
Study design: Retrospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Hospital-based
Number of centres: 62
Total length of follow up (if applicable): NA (no prospective follow-up)
Funding (government/private/manufacturer/other - specify)**:** Abbott, Pfizer, Roche and Wyeth, Chugai, Cellestis Ltd, Oxford Immunotec Ltd, Pharmore Ltd, and Roche

Aim of the study

To compare the utility of IGRA and TST in LTBI screening in a large cohort of patients with rheumatic diseases receiving immunosuppressive therapy

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) prior to the initiation of anti-tumour necrosis factor therapy)

Participants

Recruitment dates: NR
Total N of recruited patients: NR
Inclusion criteria: Patients with rheumatic diseases
Exclusion criteria: NR
Total N of excluded patients: None
Total N of patients tested with both IGRA and TST: 1609
Total N of patients with valid results for both IGRA and TST: 1529 (80 had indeterminate IGRA)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Influence of risk factors on test results, agreement/disagreement (total, by age, sex, and risk factor), association between test and clinical risk factors for LTBI (construct)
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean age range (50.8-59.5)
Women (n [%]): 937 [61.3]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 204 [13.3]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): 852 [55.7] Rheumatoid arthritis (RA), (294 [19.2]), ankylosing spondylitis (AS) (215 [14.0]), psoriatic arthritis (PsA) (92 [6.0]), undifferentiated spondyloarthropathy (SpA) and (76 [5.0]) various other rheumatologic disorders
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Immunosuppressive therapy (not specified)

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-G):	NR	50	635	NR	685
IGRA (TSPOT):	NR	70	774	NR	844
TST (≥5mm):	1609	173	1356	80 (QFT + TSPOT)	1529

Total N of patients with valid results for both IGRA and TST: 1529

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	None of the compound risk factors (CRF) were present
Exposed 1 **(specify):**	A compound risk factor (CRF) defined as the presence of at least one of these three risk factors: 1) history of prior TB, 2) close contact to a patient with TB, or 3) CXR suggestive of LTBI
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-G)	Quantiferon TB Gold administered in accordance with contemporary guidelines for immunosuppressed patients; IGRAs were mainly based on the two peptide antigens ESAT-6 and CFP-10	NR	All patients received one type of IGRA, either TSPOT.TB or QFT, depending on what was available in the corresponding laboratory
IGRA (TSPOT)	TSPOT.TB (TSPOT) administered in accordance with contemporary guidelines for immunosuppressed patients; IGRAs were mainly based on the two peptide antigens ESAT-6 and CFP-10	The cut-off for TSPOT positivity was ≥6 spots	All patients received one type of IGRA, either TSPOT.TB or QFT, depending on what was available in the corresponding laboratory
TST	NR	TST with a diameter of ≥5 mm skin induration was considered positive	All patients received a TST

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-G)				TST (≥5 mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	9	41	50	TST +	48	125	173
IGRA -	45	590	635	TST -	74	1282	1356
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	54	631	685	Total	122	1407	1529

Test performance parameters

IGRA(QFT-G)	TST (>5 mm)
Sensitivity = 9/54 = 16.67% (95% CI: 9.02, 28.74)	Sensitivity = 48/122 = 39.34% (95% CI: 31.13, 48.21)
Specificity = 590/631 = 93.5% (95% CI: 91.3, 95.17)	Specificity = 1282/1407 = 91.12% (95% CI: 89.52, 92.49)
PPV = 9/50 = 18.00% (95% CI: 9.77, 30.8)	PPV = 48/173 = 27.75% (95% CI: 21.61, 34.85)
NPV = 590/635 = 92.91% (95% CI: 90.65, 94.66)	NPV = 1282/1356 = 94.54% (95% CI: 93.2, 95.63)
DOR (for T^+ calculated) = 2.88 (95% CI: 1.31, 6.29)	DOR (for T^+ calculated) = 6.65 (95% CI: 4.42, 9.99)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = 2.63 (95% CI: 1.15, 5.98) List of covariates: NR	OR (regression-based; reported) = 6.20 (95% CI: 4.08, 9.44) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (QFT vs. TST)

Ratio of DORs (for T^+ calculated) = 0.43 (95% CI: 0.28, 0.68)
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = 0.42 (95% CI: 0.26, 0.68)
Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				TST (≥5 mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	24	46	70	TST +	48	125	173
IGRA -	44	730	774	TST -	74	1282	1356
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	68	776	844	Total	122	1407	1529

Test performance parameters

IGRA (TSPOT)	TST (≥5 mm)
Sensitivity = 24/68 = 35.29% (95% CI: 25.00, 47.16)	Sensitivity = 48/122 = 39.34% (95% CI: 31.13, 48.21)
Specificity = 730/776 = 94.07% (95% CI: 92.18, 95.53)	Specificity = 1282/1407 = 91.12% (95% CI: 89.52, 92.49)
PPV = 24/70 = 34.29% (95% CI: 24.25, 45.96)	PPV = 48/173 = 27.75% (95% CI: 21.61, 34.85)
NPV = 730/774 = 94.32% (95% CI: 92.45, 95.74)	NPV = 1282/1356 = 94.54% (95% CI: 93.2, 95.63)

DOR (for T^+ calculated) = 8.65 (95% CI: 4.84, 15.46)	DOR (for T+ calculated) = 6.65 (95% CI: 4.42, 9.99)
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) = 8.74 (95% CI: 4.83, 15.82) List of covariates: NR	OR (regression-based; reported) = 6.20 (95% CI: 4.08, 9.44) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 1.30 (95% CI: 0.91, 1.87)
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = 1.41 (95% CI: 0.97, 2.04)
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT/QFT)				TST (≥5 mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	14	106	120	TST +	50	123	173
IGRA -	190	1219	1409	TST -	154	1202	1356
Indeterminate				Indeterminate			
Total	204	1325	1529	Total	204	1325	1529

Test performance parameters

IGRA (TSPOT/QFT)	TST (≥5 mm)
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = 0.84 (95% CI: 0.47, 1.51)	DOR $_{TST}$ (for T+ calculated) = 3.17 (95% CI: 2.19, 4.58)
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = 0.43 (95% CI: 0.17, 1.10) OR (regression-based; reported)$_{TSPOT}$ = 1.07 (95% CI: 0.47, 2.43) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 2.95 (95% CI: 2.00, 4.35) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + (≥5 mm)	TST -	Total
IGRA (QFT/TSPOT) +	66	54	120
IGRA (QFT/TSPOT) -	107	1302	1409
Indeterminate	NR	NR	NR
Total	173	1356	1529

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total
TST + threshold: >5 mm

Parameters

Kappa = 0.39 (95% CI: 0.34, 0.44)
% concordance = 1368/1529 = 89.47% (95% CI: 87.83, 90.91) between IGRA (QFT/TSPOT) vs. TST % concordance = 87.60% (95% CI: NR) between QFT vs. TST (raw 2 x 2 cell counts: NR) % concordance = 91.10% (95% CI: NR) between TSPOT vs. TST (raw 2 x 2 cell counts: NR)
% discordance = 161/1529 = 10.53% (95% CI: 9.09, 12.17)

Stratification (BCG vaccinated)

	TST +	TST -	Total
IGRA (QFT/TSPOT) +	11	3	14
IGRA (QFT/TSPOT) -	39	152	191
Indeterminate			

Total	50	155	205
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated			
TST + threshold: ≥5 mm			
Parameters			
Kappa = 0.26 (95% CI: 0.15, 0.37)			
% concordance = 163/205 = 79.5% (95% CI: 73.47, 84.47)			
% discordance = 42/205 = 20.49% (95% CI: 15.53, 26.53)			
Stratification (non-BCG vaccinated)			
	TST +	TST -	Total
IGRA (QFT/TSPOT) +	55	51	106
IGRA (QFT/TSPOT) -	68	1150	1218
Indeterminate	NR	NR	NR
Total	123	1201	1324
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): non-BCG vaccinated			
TST + threshold:≥5 mm			
Parameters			
Kappa = 0.43 (95% CI: 0.37, 0.48)			
% concordance = 1205/1324 = 91.01% (95% CI: 89.35, 92.44)			
% discordance = 119/1324 = 8.98% (95% CI: 7.56, 10.65)			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**	
IGRA:	NR	NR	
TST:	NR	NR	
Test 3 (specify):	NR	NR	
Conclusions			
Authors:			
In patient populations with low rates of TB incidence and BCG vaccination, the use of both TST and IGRA may maximise sensitivity in detecting LTBI but may also reduce specificity; CRF influenced the results for all three of the tests but had less influence on QFT than on the other test systems. By this standard, TSPOT appears to perform better than QFT due to its greater correlation with known LTBI risk factors. Nevertheless, we cannot exclude the possibility that a poorer correlation with clinical risk factors is due to a higher specificity rather than a lower sensitivity. A better understanding of the relative merit of QFT versus TSPOT will require head-to-head tests under real-world conditions			
Reviewers:			
DOR of TST was higher than DOR for QFT, but it was similar to DOR of TSPOT; BCG influenced TST positivity (odds of TST positivity was higher in BCG vaccinated vs. non-vaccinated; OR>1) but not IGRA positivity (odds of IGRA positivity was the same in BCG vaccinated vs. non-vaccinated; OR = 1); between test agreement was higher in non-vaccinated vs. vaccinated group			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Laffitte 2009[134]
Country: Switzerland
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Hospital-based
Number of centres: 2
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** NR

Aim of the study

The aim of this study was (i) to determine the frequency of LTBI in a population of patients with psoriasis before anti-TNF treatment, (ii) to compare the TST with T-SPOT.TB for detecting LTBI, and (iii) to evaluate the tolerance and effectiveness of treatment for LTBI under anti-TNF therapy in our patients.

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (patients with psoriasis before anti-TNF treatment)

Participants

Recruitment dates: November 2004 and March 2008
Total N of recruited patients: NR
Inclusion criteria: Patients with moderate to severe psoriasis qualifying for anti-TNF-a therapy
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 50
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Agreement, association between test positivity and selected patient characteristics
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 48 (17–74)
Women (n [%]): 15 [30]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): High TB incidence in country of origin (10 [20])
BCG vaccination (n [%]): 45 (90)
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): None
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): Psoriasis
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): 12 patients treated for LTBI (9 with rifampicin and 3 with isoniazid) before anti TNF

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT):	NR	10	40	NR	50
TST (≥5mm):	NR	20	30	NR	50
TST (≥10mm):	NR	18	32	NR	50

Total N of patients with valid results for both IGRA and TST: 50

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – probable LTBI	
Non-exposed	No probable LTBI

Exposed 1 **(specify):**	Probable LTBI defined as having a history of definite exposure to a case of active tuberculosis and/or having a chest X-ray suggestive of prior tuberculosis infection (granulomas, calcified adenopathy) and/or originating from a high-incidence country (defined as > 40 cases in 100 000 per year)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	NR	NR	NA
TST (≥ 5mm or ≥10mm)	NR	The TST was considered positive if the induration diameter was ≥ 5mm or ≥10mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥5mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	8	2	10	TST +	11	9	20
IGRA -	14	26	40	TST -	11	19	30
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR

Total	22	28	50	Total	22	28	50
Test performance parameters							
IGRA				**TST**			
Sensitivity = 8/22 = 36.36% (95% CI: 19.73, 57.05)				Sensitivity = 11/22 = 50.00% (95% CI: 30.72, 69.28)			
Specificity = 26/28 = 92.86% (95% CI: 77.35, 98.02)				Specificity = 19/28 = 67.86% (95% CI: 49.34, 82.07)			
PPV = 8/10 = 80.00% (95% CI: 49.02, 94.33)				PPV = 11/20 = 55.00% (95% CI: 34.21, 74.18)			
NPV = 26/40 = 65.00% (95% CI: 49.51, 77.87)				NPV = 19/30 = 63.33% (95% CI: 45.51, 78.13)			
DOR (for T^+ calculated) = 7.43 (95% CI: 1.38, 39.87)				DOR (for T^+ calculated) = 2.11 (95% CI: 0.67, 6.68)			
OR (crude; for T^+ reported) = 7.43 (95% CI: 1.38, 39.90)				OR (crude; for T^+ reported) = 3.00 (95% CI: 0.93, 9.70)			
OR (regression-based; reported) = NR List of covariates: NA				OR (regression-based; reported) = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 3.52 (95% CI: 1.25, 9.96)							
Ratio of OR (crude; for T^+ reported) = 2.48 (95% CI: 0.87, 7.05)							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NA							
Association between test results and levels of TB exposure (if applicable)							
IGRA (TSPOT)				**TST (≥10mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	8	2	10	TST +	12	6	18
IGRA -	14	26	40	TST -	10	22	32
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	22	28	50	Total	22	28	50
Test performance parameters							
IGRA				**TST**			
Sensitivity = 8/22 = 36.36% (95% CI: 19.73, 57.05)				Sensitivity = 12/22 = 54.55% (95% CI: 34.66, 73.08)			
Specificity = 26/28 = 92.86% (95% CI: 77.35, 98.02)				Specificity = 22/28 = 78.57% (95% CI: 60.46, 89.79)			
PPV = 8/10 = 80.00% (95% CI: 49.02, 94.33)				PPV = 12/18 = 66.67% (95% CI: 43.75, 83.72)			
NPV = 26/40 = 65.00% (95% CI: 49.51, 77.87)				NPV = 22/32 = 68.75% (95% CI: 51.43, 82.05)			
DOR (for T^+ calculated) = 7.43 (95% CI: 1.38, 39.87)				DOR (for T^+ calculated) = 4.40 (95% CI: 1.28, 15.09)			
OR (crude; for T^+ reported) = 7.43 (95% CI: 1.38, 39.90)				OR (crude; for T^+ reported) = 2.08 (95% CI: 0.64, 6.73)			
OR (regression-based; reported) = NR List of covariates: NA				OR (regression-based; reported) = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 1.69 (95% CI: 0.58, 4.89)							
Ratio of OR (crude; for T^+ reported) = 3.57 (95% CI: 1.25, 10.18)							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NA							

Association between test results and BCG status (if applicable)							
IGRA (TSPOT)				**TST (≥5mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	9	1	10	TST +	19	1	20
IGRA -	36	4	40	TST -	26	4	30
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	45	5	50	Total	45	5	50
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = 1.00 (95% CI: 0.01, 10.07)				DOR (for T+ calculated)$_{TST}$ = 2.92 (95% CI: 0.30, 28.29)			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Association between test results and BCG status (if applicable)							
IGRA (TSPOT)				**TST (≥10mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	9	1	10	TST +	17	1	18
IGRA -	36	4	40	TST -	28	4	32
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	45	5	50	Total	45	5	50
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = 1.00 (95% CI: 0.01, 10.07)				DOR (for T+ calculated)$_{TST}$ = 2.43 (95% CI: 0.25, 23.57)			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample							
	TST (≥5mm) +		TST -		Total		
IGRA (TSPOT) +	8		2		10		
IGRA (TSPOT) -	12		28		40		
Indeterminate	NR		NR		NR		
Total	20		30		50		
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total							
TST + threshold: ≥5mm							
Parameters							
Kappa = 0.36 (95% CI: 0.12, 0.61) calculated Kappa = 0.33 (CI NR) reported							
% concordance = 36/50 = 72.00% (95% CI: 58.33, 82.53)							
% discordance = 14/50 = 28.00% (95% CI: 17.47, 41.67)							
Stratification (specify group 1):							
	TST +		TST -		Total		
IGRA +	NR		NR		NR		
IGRA -	NR		NR		NR		
Indeterminate	NR		NR		NR		

Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
T-SPOT.TB IGRA is strongly associated with the presence of risk factors for LTBI. This association was not found for the TST, and agreement between the T-SPOT.TB and TST was poor, probably because of a high rate of BCG-vaccinated patients (90%) acting as a confounding factor
Reviewers:
T-SPOT.TB IGRA is strongly associated with the presence of risk factors for LTBI (but not TST≥5mm). Strong association was also found for the TST≥10mm. Agreement between the T-SPOT.TB and TST≥5mm was poor. Influence of BCG on test positivity was slightly higher for TST (both thresholds) than TSPOT, but given the small sample and that 90% were BCG vaccinated, there results are inconclusive due to wide CIs
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details

First author surname year of publication: Maritsi 2011[135]
Country: UK
Study design: Retrospective case study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Pediatric rheumatology centre
Number of centres: One centre
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Authors report that there is no source of funding

Aim of the study

To describe the findings of QTB test when applied to a paediatric rheumatology population and to assess the efficacy of this test versus the methods previously used for the exclusion of TB infection prior to starting anti-TNFα treatment

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (Paediatric Rheumatology prior to Initiation of Infliximab)

Participants

Recruitment dates: NR
Total N of recruited patients: 27
Inclusion criteria: Children on infliximab since 2007
Exclusion criteria: NR
Total N of excluded patients: 4 (no record of the QTB test)
Total N of patients tested with both IGRA and TST: 27
Total N of patients with valid results for both IGRA and TST: 23
Methods of active TB diagnosis (if applicable):
Outcomes (study-based) list: Test results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median age 8.9 years (1.5 to 13 years)
Women (n [%]): 12 (52.1)
Race/ethnicity (n [%]): Caucasian [55%], Afro-Caribbean [19%], Asian [26%]
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 5 [22%]
History of anti-TB treatment (n [%]): 5 [22]
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): No
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Methotrexate (5 [22]), infliximab (23 [100])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	23	1	20	2	23
TST (NR):	14	0	14	0	14
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 23

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – Risk for LTBI

Non-exposed	Low-risk group
Exposed 1 **(specify):**	High-risk group (TB risk evaluation was performed using the questionnaire formulated by the United States Pediatric Tuberculosis Collaborative Group, which was published in 2004 [3])
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Quantiferon-TB gold in-tube (QTB), Cellestis Corp. Australia. The methodology and timing of the test have not been reported.	Not reported	Authors suggested that results for the QTB are reported as positive, negative and indeterminate.
TST	Not reported	Not reported	Not reported

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (high-risk group)

IGRA (GIT)				**TST (NR)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	1	0	1	TST +	0	0	0
IGRA -	2	18	20	TST -	3	11	14
Indeterminate	0	2	2	Indeterminate	NR	NR	9

							(exclude)
Total	3	20	23	Total	3	11	14

Test performance parameters	
IGRA (exclude indeterminate)	**TST (exclude indeterminate)**
Sensitivity = 1/3 = 33.33%, 95% (6.149, 79.23)	Sensitivity = 0/3 = 0.0%, 95% CI (0.0, 56.15)
Specificity = 18/18 = 100.00%, 95% CI (82.41, 100.00)	Specificity = 11/11 = 100.00%, 95% CI (74.12, 100.00)
PPV = 1/1 = 100.00%, 95% CI (20.65, 100.00)	PPV = NA
NPV = 18/20 = 90.00%, 95% CI (69.9, 97.21)	NPV = 11/14 = 78.57%, 95% CI (52.41, 92.43)
DOR (for T^+ calculated) = Undefined	DOR (for T^+ calculated) = Undefined
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NR	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = NR
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT/QFT)				**TST (NR mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA (TSPOT/QFT)	**TST (NR mm)**
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = NR OR (regression-based; reported)$_{TSPOT}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR
TST + threshold: NR
Parameters
Kappa = NR
% concordance = NR
% discordance = NR

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR

IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
The authors concluded that QTB is a useful screening tool for LTBI. Additionally, indeterminate results warrant careful assessment and re-evaluation, but should not preclude from initiation of anti-TNF treatment. Furthermore, the authors suggested that a negative TST in children receiving immunosuppressive treatment is not adequate in excluding LTBI
Reviewers:
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Mutsvangwa 2010[136]
Country: Zimbabwe
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** NR
Number of centres: NR
Total length of follow up (if applicable): NR
Funding (government/private/manufacturer/other - specify)**:** The Wellcome Trust

Aim of the study

We tested for LTBI using ELISpot and TST, correlated test results with TB exposure in household contacts of TB cases and assessed the impact of HIV co-infection on test results in these contacts

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (HIV positive adult contacts)

Participants

Recruitment dates: February 2002 to November 2004
Total N of recruited patients: NR
Inclusion criteria: All consenting individuals over the age of 10 years living with the TB cases (index case household contacts) and those (household contacts of controls) living with controls (no TB), TB cases were sampled from factories in Harare and controls samples randomly from the same factories
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 73 (HIV positives)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Agreement, association of test positive results with exposure to TB, degree of TB exposure
Characteristics of participants (total study sample)
Mean (range or SD) age (years): NR
Women (n [%]): 65 [89.0]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Sub-Saharan Africa
BCG vaccination (n [%]): 63 [86.0]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): NR
Clinical examination (yes/no): NR
Morbidity (n [%]): HIV infected
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT):	NR	22	51	NR	73
TST (≥10mm):	NR	33	40	NR	73
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 73

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – household contact	
Non-exposed	Contact of index control (no TB)

Exposed 1 **(specify):**	Contact of index TB case
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA
Definition of exposure group – smear status of index cases	
Non-exposed	Smear negative, culture negative
Exposed 1 **(specify):**	Smear negative, culture positive
Exposed 2 **(specify):**	Smear positive, culture positive

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	Blood was drawn for ELISpot testing before or after the TST was placed. ELISpot assays were carried out as described elsewhere. Duplicate wells contained no antigen (negative control), phytohaemagglutinin (positive control) (ICN Biomedical, Aurora, Ohio, USA) at 5 mg/ml or 13 pairs of duplicate wells each containing one of 13 peptide pools incorporating 5-7 overlapping 15-mer peptides spanning the length of early secretory antigenic target-6 and culture filtrate protein-10, on which T-SPOT.TB is based. The final concentration of each peptide was 10 mg/ml	ELISpot plates were sent to Oxford for automated spot counting (AID, Strassberg, Germany)	Persons performing and reading the assays were blind to all personal identifiers and TST results
TST (two stage; ≥10mm)	A two-step TST protocol was used to provide a suitable baseline for identifying subsequent TST conversions. As recommended by the manufacturer, 2 units of RT-23 PPD (purified protein derivative) in Tween-80 (Statens Serum Institut, Copenhagen, Denmark) were injected intradermally into the forearm and results read at 48-72h. Placement and assessment followed recommended techniques	If the first reaction was <10 mm, then a second TST was placed after 7-14 days. Results were expressed as the greater of the two reactions. Reaction sizes ≥10 mm were considered positive	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA

IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)							
IGRA (TSPOT)				**TST (≥10 mm; two step)**			
	Exposure level		Total		Exposure level		Total
	Index case	Index control			Index case	Index control	
IGRA +	19	3	22	TST +	27	6	33
IGRA -	36	15	51	TST -	28	12	40
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	55	18	73	Total	55	18	73

Test performance parameters	
IGRA	**TST**
Sensitivity = 19/55 = 34.55% (95% CI: 23.36, 47.75)	Sensitivity = 27/55 = 49.09% (95% CI: 36.38, 61.92)
Specificity = 15/18 = 83.33% (95% CI: 60.78, 94.16)	Specificity = 12/18 = 66.67% (95% CI: 43.75, 83.72)
PPV = 19/22 = 86.36% (95% CI: 66.66, 95.25)	PPV = 27/33 = 81.82% (95% CI: 65.61, 91.39)
NPV = 15/51 = 29.41% (95% CI: 18.71, 43.0)	NPV = 12/40 = 30.00% (95% CI: 18.07, 45.43)
DOR (for T^+ calculated) = 2.64 (95% CI: 0.67, 10.27)	DOR (for T^+ calculated) = 1.93 (95% CI: 0.63, 5.87)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 1.37 (95% CI: 0.56, 3.36)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)							
IGRA (TSPOT)				**TST (≥10 mm; two-step)**			
	Exposure level		Total		Exposure level		Total
	High	Low			High	Low	
IGRA +	NR	NR	NR	TST +	NR	NR	NR

IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = Smear $^-$ culture $^-$ = 1.00 (reference group) Smear $^-$ culture $^+$ = 1.60 (95% CI: 0.20, 12.69) Smear $^+$ culture $^+$ = 4.80 (95% CI: 1.05, 21.91)	**OR (crude; for T^+ reported) =** Smear $^-$ culture $^-$ = 1.00 (reference group) Smear $^-$ culture $^+$ = 1.50 (95% CI: 0.24, 9.46) Smear $^+$ culture $^+$ = 3.50 (95% CI: 0.88, 13.93)
OR (regression-based; reported) = Smear $^-$ culture $^-$ = 1.00 (reference group) Smear $^-$ culture $^+$ = 1.87 (95% CI: 0.22, 16.16) Smear $^+$ culture $^+$ = 5.36 (95% CI: 1.11, 25.93) List of covariates: NR	**OR (regression-based; reported) =** Smear $^-$ culture $^-$ = 1.00 (reference group) Smear $^-$ culture $^+$ = 1.09 (95% CI: 0.13, 9.42) Smear $^+$ culture $^+$ = 3.43 (0.76 to 15.52) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 1.37 (95% CI: 0.48, 3.91) [Smear + culture + vs. Smear – culture –]
Ratio of ORs (regression-based; reported) = 1.56 (95% CI: 0.51, 4.76) [Smear + culture + vs. Smear – culture –]
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (specify)				**TST (specify)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR
TST + threshold: NR

Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (contacts with TB index case):			
	TST + (≥ 10mm)	TST -	Total
IGRA (TSPOT) +	15	4	19
IGRA (TSPOT) -	12	24	36
Indeterminate	NR (excluded)	NR (excluded)	NR (excluded)
Total	27	28	55
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): contacts with TB index case			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.41 (95% CI: 0.16, 0.66)			
% concordance = 39/55 = 70.91% (95% CI: 57.86, 81.23)			
% discordance = 16/55 = 29.09% (95% CI: 18.77, 42.14)			
Stratification (contacts with control index):			
	TST + (≥ 10mm)	TST -	Total
IGRA (TSPOT) +	2	1	3
IGRA(TSPOT) -	4	11	15
Indeterminate	NR (excluded)	NR (excluded)	NR (excluded)
Total	6	12	18
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): contacts with control index			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.28 (95% CI: -0.13, 0.70)			
% concordance = 13/18 = 72.22% (95% CI: 49.13, 87.5)			
% discordance = 5/18 = 27.78% (95% CI: 12.5, 50.87)			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
Our findings suggest that ELISpot is a more accurate test than TST in HIV-infected persons recently infected with TB in a high-burden setting for both these infections. The increased accuracy of ELISpot testing compared with TST could improve targeting of preventive treatment to HIV-infected recent contacts of TB with LTBI which could further reduce the risk of active TB			
Reviewers:			
TSPOT performed better than TST in correctly identifying LTBI amongst HIV infected adult contacts due to higher specificity; agreement was higher amongst index case contacts vs. control contacts			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Papay 2011[137]
Country: Austria
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Outpatient clinic
Number of centres: One
Total length of follow up (if applicable): NR
Funding (government/private/manufacturer/other - specify)**:** NR

Aim of the study

To evaluate the impact of IM treatment on results from TST and IGRA in IBD patients before starting therapy with a biologic agent

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Inflammatory bowel disease (IBD) patients

Participants

Recruitment dates: December 2006 to August 2009
Total N of recruited patients: 208
Inclusion criteria: IBD patients
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 208
Total N of patients with valid results for both IGRA and TST: 192
Methods of active TB diagnosis (if applicable):
Outcomes (study-based) list: Test results, concordance of TST and IGRA, risk factor for LTB
Characteristics of participants (total study sample)
Mean (range or SD) age (years): age at screening 36.6 ± 11.3
Women (n [%]): 107 [51.4]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]):NR
BCG vaccination (n [%]): All subjects underwent BCG vaccination during childhood
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): Medically confirmed active TB (1 [0.5])
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): Crohn's disease (152 [73.1]); Ulcerative colitis (56 [26.9])
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Immunotherapy

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	192	15	177	0	192
TST:	192	26	166	0	192
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 192

Levels/groups of exposure to TB in increasing order (if applicable):

	Definition of exposure group
Non-exposed	NR
Exposed 1 **(specify):**	Origin from a high-prevalent country
Exposed 2 **(specify):**	History of contact with active TB
Exposed 3 **(specify):**	Chest x-ray indicative of LTBI

Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA	QFT-GIT, Cellestis, Carnegie, Australia	≥0.35 IU/mL	NA
TST	Tuberculin purified protein derivative (PPD RT23, Staten Serum Institute, Copenhagen, Denmark), Mantoux method	For people with IM, TST was considered positive if the size of the induration was ≥ 5mm. For people without IM but have IBD a positive test result was >10 mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (Presence of risk factors for LTBI)

IGRA (QFT-GIT)				**TST (≥5 mm)**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	9	6	15	TST +	15	11	26
IGRA -	56	121	177	TST -	54	128	182
Indeterminate	4	12	16 (excluded)	Indeterminate	0	0	0
Total	69	139	208	Total	69	139	208

Test performance parameters

IGRA (excluding Indeterminate**)**	**TST**
Sensitivity = 9/65 = 13.85% (95% CI: 7.45, 24.27)	Sensitivity = 15/69 = 21.74% (95% CI: 13.64, 32.82)

Specificity = 121/127 = 95.28% (95% CI: 90.08, 97.82)	Specificity = 128/139 = 92.09% (95% CI: 86.38, 95.52)
PPV = 9/15 = 60.00% (95% CI: 35.75, 80.18)	PPV = 15/26 = 57.69% (95% CI: 38.95, 74.46)
NPV = 121/177 = 68.36% (95% CI: 61.18, 74.76)	NPV = 128/182 = 70.33% (95% CI: 63.33, 76.49)
DOR (for T^+ calculated) = 3.24 (95% CI: 1.10, 9.54)	DOR (for T^+ calculated) = 3.23 (95% CI: 1.39, 7.49)
OR (crude; for T^+ reported) = 3.20 (95% CI: 1.10, 10.10)	OR (crude; for T^+ reported) = 3.20 (95% CI: 1.40, 7.50)
OR (regression-based; reported) = 3.50 (95% CI: 1.20, 11.30) List of covariates: NR	OR (regression-based; reported) = 3.70 (95% CI: 1.50, 9.60) List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 1.00 (95% CI: 0.50, 2.02)	
Ratio of OR (crude; for T^+ reported) = NR	
Ratio of ORs (regression-based; reported) = NR	
Other reported measure = NR	

Association between test results and levels of TB exposure (origin from a high-incidence country)

IGRA (QFT-GIT)				**TST (≥5 mm)**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	4	11	15	TST +	11	15	26
IGRA -	24	153	177	TST -	18	164	182
Indeterminate	1	15	16 (excluded)	Indeterminate	0	0	0
Total	29	179	208	Total	29	179	208

Test performance parameters	
IGRA (excluding indeterminate)	**TST (excluding indeterminate)**
Sensitivity = 4/28 = 14.29%, 95% CI (5.69, 31.49)	Sensitivity = 11/29 = 37.93%, 95% CI (22.69, 56)
Specificity = 153/164 = 93.29%, 95% CI (88.39, 96.21)	Specificity = 164/179 = 91.62%, 95% CI (86.64, 94.86)
PPV = 4/15 = 26.67%, 95% CI (10.9, 51.95)	PPV = 11/26 = 42.31%, 95% CI (25.54, 61.05)
NPV = 153/177 = 86.44%, 95% CI (80.62, 90.72)	NPV = 164/182 = 90.11%, 95% CI (84.91, 93.65)
DOR (for T^+ calculated) = 2.32, 95% CI (0.68, 7.87)	DOR (for T^+ calculated) = 6.68, 95% CI (2.67, 16.73)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.35 (95% CI: 0.16, 0.76)	
Ratio of OR (crude; for T^+ reported) = NR	
Ratio of ORs (regression-based; reported) = NR	
Other reported measure = NR	

Association between test results and levels of TB exposure (history of contact with active TB)

IGRA (QFT-GIT)				**TST(≥5 mm)**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	2	13	15	TST +	4	22	26

IGRA -	8	169	177	TST -	7	175	182
Indeterminate	1	15	16	Indeterminate	0	0	0
Total	11	197	208	Total	11	197	208

Test performance parameters	
IGRA (excluding indeterminate)	**TST (excluding indeterminate)**
Sensitivity = 2/10 = 20.00%, 95% CI (5.668, 50.98)	Sensitivity = 4/11 = 36.36%, 95% CI (15.17, 64.62)
Specificity = 169/182 = 92.86%, 95% CI (88.16, 95.78)	Specificity = 175/197 = 88.83%, 95% CI (83.67, 92.51)
PPV = 2/15 = 13.33%, 95% CI (3.736, 37.88)	PPV = 4/26 = 15.38%, 95% CI (6.15, 33.53)
NPV = 169/177 = 95.48%, 95% CI (91.34, 97.69)	NPV = 175/182 = 96.15%, 95% CI (92.27, 98.12)
DOR (for T^+ calculated) = 3.25, 95% CI (0.62, 16.91)	DOR (for T^+ calculated) = 4.54, 95% CI (1.23, 16.78)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.72 (95% CI: 0.24, 2.10)	
Ratio of OR (crude; for T^+ reported) = NR	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NR	

Association between test results and levels of TB exposure (Chest x-ray indicative of LTBI)							
IGRA (QFT-GIT)				**TST(≥5 mm)**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	1	14	15	TST +	5	21	26
IGRA -	10	167	177	TST -	6	176	182
Indeterminate	0	16	16 (excluded)	Indeterminate	0	0	0
Total	11	197	208	Total	11	197	208

Test performance parameters	
IGRA (excluding indeterminate)	**TST**
Sensitivity = 1/11 = 9.09%, 95% CI (1.62, 37.74)	Sensitivity = 5/11 = 45.45%, 95% CI (21.27, 71.99)
Specificity = 167/181 = 92.27%, 95% CI (87.44, 95.34)	Specificity = 176/197 = 89.34%, 95% CI (84.25, 92.92)
PPV = 1/15 = 6.66%, 95% CI (1.18, 29.82)	PPV = 5/26 = 19.23%, 95% CI (8.50, 37.88)
NPV = 167/177 = 94.35%, 95% CI (89.91, 96.9)	NPV = 176/182 = 96.7%, 95% CI (93, 98.48)
DOR (for T^+ calculated) = 1.19, 95% CI (0.14, 10.01)	DOR (for T^+ calculated) = 6.98, 95% CI (1.96, 24.87)
OR (crude; for T^+ reported) = 1.20, 95% CI: 0.10, 6.90	OR (crude; for T^+ reported) = 6.30, 95% CI: 1.70, 22.90
OR (regression-based; reported) = 1.10, 95% CI: 0.10, 7.70 List of covariates: NR	OR (regression-based; reported) = 4.90, 95% CI: 1.10, 19.9 List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.17 (95% CI: 0.05, 0.61)	
Ratio of OR (crude; for T^+ reported) = 0.19 (95% CI: 0.05, 0.68)	
Ratio of ORs (regression-based; reported) = 0.22 (95% CI: 0.06, 0.85)	
Other reported measure = NR	

Association between test results and levels of TB exposure (IM treatment)							
IGRA (QFT-GIT)				TST(≥5 mm)			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	7	8	15	TST +	18	8	26
IGRA -	130	47	177	TST -	131	51	182
Indeterminate	12	4	16 (excluded)	Indeterminate	0	0	0
Total	149	59	208	Total	149	59	208
Test performance parameters							
IGRA (excluding indeterminate)				**TST**			
DOR (for T^+ calculated) = 0.31 (95% CI: 0.10, 0.92)				DOR (for T^+ calculated) = 0.87 (95% CI: 0.35, 2.14)			
OR (crude; for T^+ reported) = 0.30 (95% CI: 0.10, 0.90)				OR (crude; for T^+ reported) = 0.90 (95% CI: 0.40, 2.30)			
OR (regression-based; reported) = 0.30 (95% CI: 0.10, 0.90) List of covariates: NR				OR (regression-based; reported) = 0.90 (95% CI: 0.40, 2.60) List of covariates: NR			
Other reported measure =				Other reported measure =			
Association between test results and BCG status (if applicable)							
IGRA (specify)				**TST (specify)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = NR				DOR (for T+ calculated)$_{TST}$ = NR			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample							
	TST +		TST -		Total		
IGRA +	157		20		177		
IGRA -	9		6		15		
Indeterminate	0		0		0		
Total	166		26		192		
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total							
TST + threshold: ≥5 mm							
Parameters							
Kappa = 0.21, 95% CI (0.07, 0.34)							
% concordance = 163/192 = 84.90%, 95% CI (79.15, 89.27)							
% discordance = 29/192 = 15.10%, 95% CI (10.73, 20.85)							
Stratification (specify group 1)							
	TST +		TST -		Total		
IGRA +	NR		NR		NR		
IGRA -	NR		NR		NR		

Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
These authors demonstrated that there is an association of positive results from TST and IGRA with the presence of risk factors for LTBI. Additionally, their results showed that there is a negative impact of therapy with IM on IGRA results (not on TST). They further concluded that LTBI screening should be undertaken at the diagnosis of IBD, and before treatment for IM
Reviewers:
IGRA positivity rate was lower in patients on IM vs. no IM treatment; TST was not affected by IM treatment
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Ramos 2013[138] **Country:** Spain **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Outpatient infectious diseases clinic of a university hospital **Number of centres:** NR **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** Grants from Conselleria de Sanidad (051/2007), and FIS (PI08/90778)
Aim of the study
To evaluate the performance of QFG compared with the TST for the diagnosis of LTBI in patients with immune-mediated inflammatory disease (IMID) before TNF-a antagonist therapy. Additionally, the impact of immunosuppressive therapy on QFG and TST performance in different IMID was evaluated
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people (patients with IMID before TNF-a antagonist therapy)
Participants
Recruitment dates: From January 2009 to May 2011 **Total N of recruited patients:** NR **Inclusion criteria:** All adults (age C 15 years) candidates for anti-TNF-a therapy who attended the clinic **Exclusion criteria:** NR **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** 153 **Total N of patients with valid results for both IGRA and TST:** 152 **Methods of active TB diagnosis (if applicable):** NR **Outcomes (study-based) list:** Agreement; association of test positivity with exposure; influence of immunosuppressive treatment on test positivity and agreement; influence of underlying disease on test positivity **Characteristics of participants (total study sample)** Mean (range or SD) age (years): Median 52 (16–82) Women (n [%]): 73 [47.7] Race/ethnicity (n [%]): NR Geographic origin (n[%]): Born in a TB endemic area (8 [5.2]) BCG vaccination (n [%]): 29 [19] History of anti-TB treatment (n [%]): 5 [3.3] Total incidence of active TB (n [%]): NR Chest radiography (yes/no): Yes Clinical examination (yes/no): NR Morbidity (n [%]): Rheumatoid arthritis (RA) (53 [43.6]), psoriasis/psoriatic arthritis (45 [29.4]), inflammatory bowel diseases (IBD) (25 [16.3]), spondyloarthropathy (SA) (22 [14.4]), severe hidradenitis (3 [2.0]), systemic lupus erythematosus (2 [1.3]), polymyositis (1 [0.6]), sarcoidosis (1 [0.6]), and mixed connective tissue disease (1 [0.6]) Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): Immunosuppressive drug (91 [59.5]), methotrexate (57 [37.3]), corticosteroids (28 [18.3]), leflunomide (21 [13.7]), azathioprine (19 [12.4]), cyclosporine (6 [3.9])
Number of patients tested

	Total N (tested)	**Total N**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results**

		(test+)			**available)**
IGRA (QFT-GIT):	153	15	137	1	152
TST (≥5mm):	153	43	110	0	153
Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 152					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group – Born in a TB endemic area					
Non-exposed	Not born in a TB endemic area				
Exposed 1 **(specify):**	Born in a TB endemic area				
Definition of exposure group – History of contact with TB patients					
Non-exposed	No contact with TB patients				
Exposed 1 **(specify):**	Contact with TB patients				
Tests					

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	For QFG, three aliquots of 1 ml of undiluted heparinized whole blood were collected in three tubes**:** one containing TB antigens (ESAT-6, CFP-10, and TB7.7), a positive control tube containing phytohemagglutinin, and a negative control tube. Blood samples were incubated for 16–20 h at 37◦C. Plasma samples were then harvested for IFN-c quantification by a single-step sandwich-type ELISA The test was performed according to the manufacturer's instructions (Cellestis, Carnegie, Australia)	According to the instructions, the result was considered to be positive if the IFN-c level after stimulation with TB antigens minus negative control was ≥0.35 IU/ml. The test was considered negative if the IFN-c level was <0.35 IU/ml after subtraction of the negative control The test result was considered to be indeterminate if (1) the negative control was ≥8.0 IU/ml or (2) the positive control was <0.5 IU/ml Moreover, the test result was considered to be intermediate if IFN-c level was ≥0.10 IU/ml but <0.35 IU/ml	QFG and TST were performed simultaneously in a blinded fashion
TST(≥5mm)	Study participants were injected with 0.1 ml of tuberculin (2 tuberculin units of PPD) (Tuberculina PPD; Evans 2UT, UCB Pharma, S.A. Madrid, Spain) in accordance with the American Thoracic Society guidelines. The transverse skin induration diameter was measured 48–72h later	TST was deemed positive if the induration diameter was more than 5 mm	QFG and TST were performed simultaneously in a blinded fashion

Association between test results and incidence of active TB (if applicable)							
IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)							
IGRA (QFT-GIT)				TST (≥5mm)			
	Exposure level		Total		Exposure level		Total
	Born in TB endemic area	Not born in TB endemic area			Born in TB endemic area	Not born in TB endemic area	
IGRA +	4	11	15	TST +	4	39	43
IGRA -	4	133	137	TST -	4	106	110
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)	Indeterminate	0	0	0
Total	8	144	152	Total	8	145	153

Test performance parameters	
IGRA	TST
Sensitivity = 4/8 = 50.00% (95% CI: 21.52, 78.48)	Sensitivity = 4/8 = 50.00% (95% CI: 21.52, 78.48)
Specificity = 133/144 = 92.36% (95% CI: 86.84, 95.68)	Specificity = 106/145 = 73.1% (95% CI: 65.36, 79.66)
PPV = 4/15 = 26.67% (95% CI: 10.90, 51.95)	PPV = 4/43 = 9.30% (95% CI: 3.67, 21.60)
NPV = 133/137 = 97.08% (95% CI: 92.73, 98.86)	NPV = 106/110 = 96.36% (95% CI: 91.02, 98.58)
DOR (for T^+ calculated) = 12.09 (95% CI: 2.65, 55.07)	DOR (for T^+ calculated) = 2.72 (95% CI: 0.65, 11.40)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = 29.30 (95% CI: 4.60, 18.5) error	OR (regression-based; reported) = 3.10 (95% CI: 0.70, 13.70)

List of covariates: age, sex	List of covariates: age, sex
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 4.44 (95% CI: 1.53, 12.89)	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥5mm)			
	Exposure level		Total		Exposure level		Total
	Contact with TB	No contact with TB			Contact with TB	No contact with TB	
IGRA +	3	12	15	TST +	4	39	43
IGRA -	4	133	137	TST -	3	107	110
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)	Indeterminate	0	0	0
Total	7	145	152	Total	7	146	153

Test performance parameters	
IGRA	**TST**
Sensitivity = 3/7 = 42.86% (95% CI: 15.82, 74.95)	Sensitivity = 4/7 = 57.14% (95% CI: 25.05, 84.18)
Specificity = 133/145 = 91.72% (95% CI: 86.09, 95.20)	Specificity = 107/146 = 73.29% (95% CI: 65.58, 79.8)
PPV = 3/15 = 20.00% (95% CI: 7.04, 45.19)	PPV = 4/43 = 9.30% (95% CI: 3.67, 21.6)
NPV = 133/137 = 97.08% (95% CI: 92.73, 98.86)	NPV = 107/110 = 97.27% (95% CI: 92.29, 99.07)
DOR (for T^+ calculated) = 8.31 (95% CI: 1.66, 41.56)	DOR (for T^+ calculated) = 3.66 (95% CI: 0.78, 17.08)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = 8.00 (95% CI: 1.40, 47.00) List of covariates: age, sex	OR (regression-based; reported) = 3.20 (95% CI: 0.70, 15.50) List of covariates: age, sex
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 2.27 (95% CI: 0.73, 7.08)	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = 2.50 (95% CI: 0.76, 8.26)	
Other reported measure = NA	

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				TST (≥5mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	7	8	15	TST +	13	30	43
IGRA -	22	115	137	TST -	16	94	110
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)	Indeterminate	0	0	0
Total	29	123	152	Total	29	124	153

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = 4.57 (95% CI: 1.50, 13.91)	DOR (for T+ calculated)$_{TST}$ = 2.54 (95% CI: 1.10, 5.89)

OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = 5.10 (95% CI: 1.50, 17.50) List of covariates: Age, sex	OR (regression-based; reported) $_{TST}$ = 2.40 (95% CI: 1.01, 5.80) List of covariates: Age, sex
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + (≥5mm)	TST -	Total
IGRA (QFT-GIT) +	13	2	15
IGRA (QFT-GIT) -	30	107	137
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)
Total	43	109	152

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥5mm

Parameters

Kappa = 0.35 (95% CI: 0.22, 0.48)

% concordance = 120/152 = 78.95% (95% CI: 71.79, 84.67)

% discordance = 32/152 = 21.05% (95% CI: 15.33, 28.21)

Between-test agreement, concordance, and discordance (if applicable)
Patients not receiving immunosuppressant

Total sample

	TST + (≥5mm)	TST -	Total
IGRA (QFT-GIT) +	11	0	11
IGRA (QFT-GIT) -	10	41	51
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)
Total	21	41	62

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Patients not receiving immunosuppressant

TST + threshold: ≥5mm

Parameters

Kappa = 0.59 (95% CI: 0.36, 0.82)

% concordance = 52/62 = 83.87% (95% CI: 72.79, 91.00)

% discordance = 10/62 = 16.13% (95% CI: 9.00, 27.21)

Between-test agreement, concordance, and discordance (if applicable)
Patients receiving immunosuppressant

Total sample

	TST + (≥5mm)	TST -	Total
IGRA (QFT-GIT) +	2	2	4
IGRA (QFT-GIT) -	20	66	86
Indeterminate	NR (excluded)	NR (excluded)	1 (excluded)
Total	22	68	90

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Patients receiving immunosuppressant

TST + threshold: ≥5mm

Parameters

Kappa = 0.08 (95% CI: -0.05, 0.22)

% concordance = 68/90 = 75.56% (95% CI: 65.75, 83.27)

% discordance = 22/90 = 24.44% (95% CI: 16.73, 34.25)

Other outcomes

Test and cut-off (if applicable)	Adverse events n/N (%) (specify)	Health related quality of life mean score (SD) (specify)
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
Test positivity odds for QFT was decreased in immunosuppressant recipients vs. those not on immunosuppressant (OR = 0.20, 95% CI: 0.06, 0.80). In contrast, test positivity odds for TST between these groups was similar (OR = 0.70, 95% CI: 0.30, 1.40). Therefore, immunosuppressant therapy impaired preferentially the sensitivity of the QFG test, since the rate of positive results was significantly lower in patients on immunosuppressive therapy We observed a worse agreement between TST and QFG in patients on immunosuppressive therapy. The TST positive and QFG-negative results in immunosuppressive patients may be explained due to a false positivity of TST related to atypical mycobacteria In patients with IMID, QFG may have a limited role for screening of LTBI. We found a negative effect of immunosuppressive therapy on QFG performance (sensitivity)		
Reviewers:		
QFT performed better than TST in correctly identifying LTBI with better specificity (stronger associations with exposures: born in endemic area; contact with TB case); however, QFT test positivity rate (not necessarily sensitivity) was influenced by immunosuppressant therapy, i.e., it was lower in patients on this therapy vs. patients without the therapy. This influence was not observed for TST BCG vaccination influenced both QFT and TST positivity odds similarly (increased positivity odds in vaccinated vs. not vaccinated for both tests) Agreement was lower in patients on immunosuppressant therapy vs. without the therapy due to lower specificity of TST vs. QFT		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; IBD = inflammatory bowel diseases; PPV = positive predictive value; NPV = negative predictive value; RA = rheumatoid arthritis; SA = spondyloarthropathy; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details
First author surname year of publication: Seyhan 2010[139] **Country:** Turkey **Study design:** Retrospective cohort/cross-sectional study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** NR **Number of centres:** NR **Total length of follow up (if applicable):** NA **Funding** (government/private/manufacturer/other - specify)**:** None
Aim of the study
To compare the results of QFT-G with TST for detecting LTBI in hemodialysis patients
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Hemodialysis patients
Participants
Recruitment dates: Between November 2008 and December 2008 **Total N of recruited patients:** NR **Inclusion criteria:** Hemodialysis patients **Exclusion criteria:** Suspicion of active TB infection, use of immunosuppressive drugs, and other known immunodeficiency status (human immunodeficiency virus [HIV], malignancy, etc **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** NR **Total N of patients with valid results for both IGRA and TST:** 100 **Methods of active TB diagnosis (if applicable):** **Outcomes (study-based) list:** Test results, TST or QFT-G and risk factors, concordance between TST and QFT-G test **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 56.2±15.3 Women (n [%]): 53 [53] Race/ethnicity (n [%]): NR Geographic origin (n[%]): NR BCG vaccination (n [%]): 72 [72] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): NR Chest radiography (yes/no): Yes Clinical examination (yes/no): NR Morbidity (n [%]): NR Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (QFT-G):	100	43	57	0	100
TST (≥10mm):	100	34	66	0	100
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 100

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group-1	
Non-exposed	No prior history of active TB
Exposed 1 **(specify):**	Prior history of active TB
Definition of exposure group-2	
Non-exposed	No previous contact of the patient with TB cases

Exposed 1 **(specify):**	Previous contact of the patient with TB cases (details of any contact with a person having TB, individuals who had household contact with or who had worked in the same rooms as patients with smear-positive pulmonary TB, and elapsed time after the contact)
Definition of exposure group-3	
Non-exposed	No chest radiograph changes consistent with old TB
Exposed 1 **(specify):**	Chest radiograph changes consistent with old TB

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-G, not reported	≥0.35 IU/mL of IFN-γ in the TB antigen tube minus the negative control tube was considered to be a positive test result	Blood was collected before TST placement.
TST≥ 10mm	Mantoux method was performed intradermally on the volar surface of the forearm with 0.1 mL (5TU) of PPD material (Intervax Biologicals, Markham, Ontario, Canada), induration was measured 48-72 hours after TST placement	≥ 10mm induration was considered to be a positive test result	People with an initial induration of less than 10mm were administered a second TST one week later to cause a potential booster response. Results from the two-step testing were used in all further analyses

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA

Other reported measure = NR							
Association between test results and levels of TB exposure (Previous TB disease)							
IGRA (QFT-GIT)				**TST≥ 10mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	6	37	43	TST +	3	31	34
IGRA -	2	55	57	TST -	5	61	66
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	8	92	100	Total	8	92	100
Test performance parameters							
IGRA				**TST**			
Sensitivity = 6/8 = 75%, 95% CI (40.93, 92.85)				Sensitivity = 3/8 = 37.5%, 95% CI (13.68, 69.43)			
Specificity = 55/92 = 59.78%, 95% CI (49.57, 69.22)				Specificity = 61/92 = 66.3%, 95% CI (56.17, 75.14)			
PPV = 6/43 = 13.95%, 95% CI (6.556, 27.26)				PPV = 3/34 = 8.824%, 95% CI (3.047, 22.96)			
NPV = 55/57 = 96.49%, 95% CI (88.08, 99.03)				NPV = 61/66 = 92.42%, 95% CI (83.46, 96.72)			
DOR (for T^+ calculated) = 4.46, 95% CI (0.85, 23.31)				DOR (for T^+ calculated) = 1.18, 95% CI (0.26, 5.26)			
OR (crude; for T^+ reported) = NR				OR (crude; for T^+ reported) = NR (NS)			
OR (regression-based; reported) = 2.06, 95% CI (0.30, 12.80) List of covariates: NR				OR (regression-based; reported) = NR (NS) List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 3.78 (95% CI: 1.21, 11.83)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NR							
Association between test results and levels of TB exposure (Previous contact with TB)							
IGRA (QFT-GIT)				**TST (≥10mm)**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	10	33	43	TST +	6	28	34
IGRA -	3	54	57	TST -	7	59	66
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	13	87	100	Total	13	87	100
Test performance parameters							
IGRA				**TST**			
Sensitivity = 10/13 = 76.92%, 95% CI (49.74, 91.82)				Sensitivity = 6/13 = 46.15%, 95% CI (23.21, 70.86)			
Specificity = 54/87 = 62.07%, 95% CI (51.57, 71.55)				Specificity = 59/87 = 67.82%, 95% CI (57.43, 76.7)			
PPV = 10/43 = 23.26%, 95% CI (13.15, 37.74)				PPV = 6/34 = 17.65%, 95% CI (8.349, 33.51)			
NPV = 54/57 = 94.74%, 95% CI (85.63, 98.19)				NPV = 59/66 = 89.39%, 95% CI (79.69, 94.77)			
DOR (for T^+ calculated) = 5.45, 95% CI (1.40, 21.27)				DOR (for T^+ calculated) = 1.81, 95% CI (0.55, 5.87)			

OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR (NS)
OR (regression-based; reported) = 5.08, 95% CI (1.20, 21.20) List of covariates: NR	OR (regression-based; reported) = NR (NS) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 3.01 (95% CI: 1.20, 7.56)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and levels of TB exposure (Chest X-ray with changes)

IGRA (QFT-GIT)				**TST≥10mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	11	32	43	TST +	4	30	34
IGRA -	5	52	57	TST -	12	54	66
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	16	84	100	Total	16	84	100

Test performance parameters	
IGRA	**TST**
Sensitivity = 11/16 = 68.75%, 95% CI (44.40, 85.84)	Sensitivity = 4/16 = 25.00%, 95% CI (10.18, 49.50)
Specificity = 52/84 = 61.90%, 95% CI (51.22, 71.55)	Specificity = 54/84 = 64.29%, 95% CI (53.62, 73.70)
PPV = 11/43 = 25.58%, 95% CI (14.93, 40.24)	PPV = 4/34 = 11.76%, 95% CI (4.67, 26.62)
NPV = 52/57 = 91.23%, 95% CI (81.05, 96.19)	NPV = 54/66 = 81.82%, 95% CI (70.85, 89.28)
DOR (for T^+ calculated) = 3.57, 95% CI (1.14, 11.24)	DOR (for T^+ calculated) = 0.60, 95% CI (0.18, 2.02)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR (NS)
OR (regression-based; reported) = 3.06, 95% CI (2.10, 11.90) List of covariates: NR	OR (regression-based; reported) = NR (NS) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 5.95 (95% CI: 2.54, 13.91)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				**TST ≥10mm**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	34	9	43	TST +	30	4	34
IGRA -	38	19	57	TST -	42	24	66
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	72	28	100	Total	72	28	100

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{QFT}$ = 1.89 (95% CI: 0.75, 4.73)	DOR $_{TST}$ (for T+ calculated) = 4.28 (95% CI: 1.35, 13.64)

OR (crude; for T^+ reported) = NR (NS)	OR (crude; for T+ reported) = NR (SS)
OR (regression-based; reported)$_{QFT}$ = NR (NS) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 4.10 (1.30, 13.90) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	21	22	43
IGRA -	13	44	57
Indeterminate	0	0	0
Total	34	66	100

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Total

TST + threshold: ≥ 10mm

Parameters

Kappa = 0.27, 95% CI (95% CI: 0.07, 0.46)

% concordance = 65/100 = 65.00%, 95% CI (55.25, 73.64)

% discordance = 35/100 = 35.00%, 95% CI (26.36, 44.75)

Stratification (BCG vaccinated)

	TST +	TST -	Total
IGRA +	17	17	34
IGRA -	13	25	38
Indeterminate	0	0	0
Total	30	42	72

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG

TST + threshold: ≥ 10mm

Parameters

Kappa = 0.16, 95% CI (-0.07, 0.39)

% concordance = 42/72 = 58.33%, 95% CI (46.81, 69.01)

% discordance = 30/72 = 41.67%, 95% CI (30.99, 53.19)

Stratification (non-BCG vaccinated)

	TST +	TST -	Total
IGRA +	4	5	9
IGRA -	0	19	19
Indeterminate	0	0	0
Total	4	24	28

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Unvaccinated

TST + threshold: ≥ 10mm

Parameters

Kappa = 0.52, 95% CI (0.19, 0.84)

% concordance = 23/28 = 82.14%, 95% CI (64.41, 92.12)

% discordance = 5/28 = 17.86%, 95% CI (7.878, 35.59)

Other outcomes

Test and cut-off (if applicable)	Adverse events n/N (%) (specify)	Health related quality of life mean score (SD) (specify)
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
These authors concluded that there was poor agreement between TST and QFT-G for LTBI in HD patients. Additionally, unlike the TST, the QFT-G results were significantly related to LTBI risk factors, but not related to the BCG status. They further concluded that QFT-G was a superior to the TST test for detecting LTBI in HD patients
Reviewers:
QFT-GIT performed better than TST in identifying LTBI correctly showing stronger associations between test positivity odds and the exposures. Also, IGRA was not dependent on BCG vaccination unlike TST positivity. Agreement was higher in BCG non vaccinated patients
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Shen 2012[140]
Country: China
Study design: Retrospective study
Study setting (e.g., outbreak investigation, community-based - specify)**:** University hospital
Number of centres: 1
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** None

Aim of the study

To evaluated the diagnostic value of an enzyme-linked immunosorbent spot (ELISPOT) assay measuring interferon-Y in hepatitis C patients with LTBI

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Hepatitis C patients

Participants

Recruitment dates: From January 2009 to December 2010
Total N of recruited patients: NR
Inclusion criteria: Hepatitis patients with (TB exposure group-patients who had history of exposure to TB and did not do clinical diagnosis of TB, with obvious clinical symptoms; non-TB exposure group- patients who had no history of exposure to TB and no clinical symptoms; TB group-patients who were clinically diagnosed with TB and with apparent clinical symptoms)
This review focuses on 70 patients (TB exposure group-patients), n = 31 (suspected LTBI; excluding 9 TB patients) and n = 39 non-exposed patients (no history of exposure to TB and no clinical symptoms)
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 160 (TST and ELISPOT)
Total N of patients with valid results for both IGRA and TST: 160 (TST and ELISPOT)
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Test results, sensitivity and specificity of TST and ELISPOT
Characteristics of participants (total study sample)
Mean (range or SD) age (years): TB exposure group n = 40 (42.9 ± 18.6); No TB exposure group (n = 39) 37.8 ±17.6
Women (n [%]): TB exposure (37 [47]); No TB exposure (17 [45])
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]):NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): Hepatitis C
Co-morbidity (n [%]): Heart disease, diabetes, liver cirrhosis, solid tumor, chronic renal failure
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT): ELISPOT	70	26	44	0	70
TST (≥5 mm):	70	34	36	0	70
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST:	
Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group	
Non-exposed	No history of TB exposure and no clinical symptoms (n = 39)
Exposed 1 **(specify):**	History of exposure to tuberculosis (suspected having TB, but no symptoms of TB, n = 31)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	IFN-γ ELISPOT assay (Beijing Gaoke Life and Technology Inc., China) was performed according to the manufacturer's recommendations	Not stated	NA
TST≥5 mm	TST was performed by intradermal injection (Mantoux method) of 0.1 mL (5U) of PPD according to current recommendations. The induration was measured with a ruler by a trained physician 72 hours after the injection	TST was considered positive when the transverse diameter of induration was ≥5 mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (Suspected TB disease)

IGRA (TSPOT)			**TST≥5mm**		
	Exposure level	Total		Exposure level	Total

	Yes	No			Yes	No	
IGRA +	22	4	26	TST +	19	15	34
IGRA -	9	35	44	TST -	12	24	36
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	31	39	70	Total	31	39	70

Test performance parameters	
IGRA	**TST**
Sensitivity = 22/31 = 70.97%, 95% CI (53.41, 83.9)	Sensitivity = 19/31 = 61.29%, 95% CI (43.82, 76.27)
Specificity = 35/39 = 89.74% (95% CI: 76.42, 95.94)	Specificity = 24/39 = 61.54% (95% CI: 45.9, 75.11)
PPV = 22/26 = 84.62% (95% CI: 66.47, 93.85)	PPV = 19/34 = 55.88% (95% CI: 39.45, 71.12)
NPV = 35/44 = 79.55% (95% CI: 65.5, 88.85)	NPV = 24/36 = 66.67% (95% CI: 50.33, 79.79)
DOR (for T^+ calculated) = 21.39 (95% CI: 5.87, 77.93)	DOR (for T^+ calculated) = 2.53 (95% CI: 0.96, 6.67)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = 8.45 (95% CI: 3.71, 19.28)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT/QFT)				**TST (>5 mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA (TSPOT/QFT)	**TST (>5 mm)**
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NR	DOR $_{TST}$ (for T+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported)$_{QFT}$ = NR OR (regression-based; reported)$_{TSPOT}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR
TST + threshold: NR
Parameters

Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
Based on the results from this study the ELISPOT assay had a high diagnostic sensitivity and a low false positive rate in the diagnosis of LTBI. They concluded that the use of this assay may be effective in diagnosing LTBI in this patient group to prevent LTBI developing into active TB			
Reviewers:			
IGRA performed better than TST for LTBI identification (on all parameters)			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Souza 2014[153] **Country**: Brazil **Study design**: cross-sectional/retrospective cohort study **Study setting** (e.g., outbreak investigation, community-based - specify): outpatient clinics **Number of centres**: 8 **Total length of follow up (if applicable)**: NA **Funding** (government/private/manufacturer/other - specify): This research was supported by Fundacao de Apoio `a Pesquisa do Distrito Federal, FAPDF funded by SUS-PPSUS Grant no. 193.000.353/2010.
Aim of the study
To evaluate the added value of QFT-GIT over the TST for detecting LTBI among persons living with HIV/AIDS (PLWHA); also to explore the factors associated with a positive QFT-GIT and with discordant QFT-GIT/TST results
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised (HIV/AIDS)
Participants
Recruitment dates: between May 2011 and March 2013 **Total N of recruited patients**: NR **Inclusion criteria**: People with HIV/AIDS over 17 years who were not submitted to TST in the previous five weeks **Exclusion criteria**: Patients with history of other immunosuppression conditions (severe AIDS-related opportunistic infections, acute viral infections, those submitted to any vaccination in the previous two months, and those using immunosuppressive drugs), patients with present or past active TB and those with a history of a previous positive TST **Total N of excluded patients:** NR **Total N of patients tested with both IGRA and TST:** NR **Total N of patients with valid results for both IGRA and TST:** 299 **Methods of active TB diagnosis (if applicable):** NA **Outcomes (study-based) list:** between test agreement, association between factors and test results (positive, discordant tests) **Characteristics of participants (total study sample)** Mean (range or SD) age (years): median 40 (IQR = 32–46) years Women (n [%]): 85 [28.3] Race/ethnicity (n [%]): NR Geographic origin (n[%]): NR BCG vaccination (n [%]): 228 [76.0] History of anti-TB treatment (n [%]): NR Total incidence of active TB (n [%]): NA Chest radiography (yes/no): NR Clinical examination (yes/no): NR Morbidity (n [%]): HIV/AIDS Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT)	300	14	285	1	299
TST: **≥5mm**	300	10	290	0	300

Test 3 (specify)					
Total N of patients with valid results for both IGRA and TST: 299					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group – History of contact with index case					
Non-exposed	No				
Exposed 1 **(specify)**:	Yes				
Exposed 2 **(specify)**:	NR				
Exposed 3 **(specify)**:	NR				
Exposed 4 **(specify)**:	NR				

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT was performed according to the manufacturer's instruction	Positive result was considered if the difference between interferon response to TB antigens and negative control was ≥0.35 UI/mL and interferon response to TB antigens was ≥25% compared to the negative control response QFT-GIT was considered to be indeterminate if the interferon response to the negative control was ≥8UI/mL or <0.5UI/mL compared to the positive control	
TST≥5mm	Participants were submitted to TST using 0.1mL of PPD-RT 23 (2 units of tuberculin)	Injection and reading of induration 72 to 96 hours after injection were performed by a trained HCW Positive result was TST induration was ≥5mm	

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA
NPV= NA	NPV= NA

Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$= NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$= NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥5mm)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	0	13	13	TST +	1	8	9
IGRA -	35	245	280	TST -	34	251	285
indeterminate	NR	NR	1	indeterminate	0	0	0
Total	35	258	293	Total	35	259	294

Test performance parameters

IGRA	TST
Sensitivity = 0/35=0.00% (95% CI: 0.0, 9.89)	Sensitivity = 1/35=2.86% (95% CI: 0.50, 14.53)
Specificity = 245/258=94.96% (95% CI: 91.57, 97.03)	Specificity =251/259=96.91% (95% CI: 94.02, 98.43)
PPV= 0/13=0.00% (95% CI: 0.0, 22.81)	PPV=1/9= 11.11% (95% CI: 1.99, 43.5)
NPV= 245/280=87.5% (95% CI: 83.11, 90.87)	NPV=251/285=88.07% (95% CI: 83.79, 91.34)
DOR (for T^+ calculated)= 0.50 (95% CI: 0.06, 4.24)	DOR (for T^+ calculated)= 0.93 (95% CI: 0.11, 7.61)
OR (crude; for T^+ reported)= 0.49 (95% CI: 0.06, 3.82)	OR (crude; for T^+ reported)= 0.92 (95% CI: 0.11, 7.61)
OR (regression-based; reported)= NR List of covariates: NR	OR (regression-based; reported)= 1.21 (95% CI: 0.13, 11.16) List of covariates: NR
Other reported measure = NR	Other reported measure =NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 0.54 (95% CI: 0.12, 2.49)
Ratio of OR (crude; for T^+ reported) = 0.53 (95% CI: 0.12, 2.42)
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (specify)				TST (specify)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported) $_{IGRA}$ = NA	OR (regression-based; reported) $_{TST}$ = NA

List of covariates: NA		List of covariates: NA	
Other reported measure = NA		Other reported measure = NA	
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST +(≥5mm)	TST -	Total
IGRA +	6	8	14
IGRA -	4	281	285
indeterminate	0	1	1
Total	10	289	299
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥5mm			
Parameters			
Kappa = 0.48 (95% CI: 0.37, 0.59)			
% concordance = 287/299 = 96.00% (95% CI: 93.12, 97.69)			
% discordance = 12/299 = 4.01% (95% CI: 2.31, 6.88)			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Conclusions			
Authors:			
QFT-GIT alone was more effective to detect LTBI than TST (QFT yielded more positives), assuming that any test is a marker of LTBI			
Reviewers:			
The authors used invalid assumption of test positivity as a marker of LTBI; the results are inconclusive regarding the strength of association between test positivity and prior exposure to index			

case (ORs and 95% CIs are too wide)
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details

First author surname year of publication: Takeda 2011[141]
Country: Japan
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Hospital based
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Ministry of Health, Labor, and Welfare

Aim of the study

To evaluate whether QFT-GIT is useful in detecting LTBI in systemic lupus erythematosus (SLE) patients

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (patients with SLE)

Participants

Recruitment dates: July 2006 to September 2008
Total N of recruited patients: NR
Inclusion criteria: Systemic lupus erythematosus (SLE) patients; non-SLE connective tissue disease (rheumatoid arthritis, myositis, vasculitides, systemicscleroderma, Sjoegren's syndrome, Behcet's disease, adult-onset Still's disease)
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 71 (IGRA) and 43 (TST)
Total N of patients with valid results for both IGRA and TST: NR
Methods of active TB diagnosis (if applicable): Positive culture for MTB or a positive result on a polymerase chain reaction test for MTB DNA in any clinical specimen associated with compatible TB symptoms and radiographic findings
Outcomes (study-based) list: Association of test positivity and risk for LTBI, factors influencing indeterminate QFT results
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 38.3 (15.2)
Women (n [%]): 58 [81.7]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): SLE
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Corticosteroids (37 [52.1]), immunosuppressive drugs (19 [26.8]), prednisolone pulse therapy (2 [2.8]), NSAIDs or no therapy (13 [18.3])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-2G):	71	2	46	23	71
TST (≥10 mm):	43	3	40	0	43
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: Unclear

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group	
Non-exposed	Without risk of LTBI
Exposed 1 **(specify):**	With risk factors for LTBI (history of household TB contact; chest X ray suggestive of previous TB showing nodules, fibrotic scars, calcified granulomas, basal thickening; history of active TB)
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Quantiferon-TB Gold (QFT-2G), Cellestis, Carnegie, Australia	≥ 0.35 IU/mL	Negative result if the IFN-γ level in the antigen stimulated wells was <0.35 IU/mL and in the mitogen wells was ≥0.5 IU/mL. Results were considered indeterminate if the IFN-γ level in the antigen stimulated wells was <0.5 IU/mL, or if the IFN-γ level in the antigen-stimulated wells was below half of the level of the negative control was > 0.7 IU/mL
TST≥10 mm	0.1 mL of tuberculin purified protein derivative (PPD) (approximately 3 tuberculin units of PPD-S), Nippon BCG Manufacturing, Tokyo, Japan) into the venral surface of the forearm. The induration was measured 48 hours later	≥10 mm, according to the usual criterion of the TST in Japan	NA

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA

Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (risk for LTBI)

IGRA				TST			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	2	0	2	TST +	1	2	3
IGRA -	16	30	46	TST -	13	27	40
Indeterminate	8	15	23	Indeterminate	0	0	0
Total	26	45	71	Total	14	29	43

Test performance parameters

IGRA	TST
Including indeterminate-as test negative Sensitivity = 2/26 = 7.70% (95% CI: 2.13, 24.14) **Excluding indeterminate** Sensitivity = 2/18 = 11.11% (95% CI: 3.10, 32.80)	Sensitivity = 1/14 = 7.14%, 95% CI (1.27, 31.47)
Including indeterminate-as test negative Specificity = 45/45 = 100.00% (95% CI: 92.13, 100.00) **Excluding indeterminate** Specificity = 30/30 = 100.00% (95% CI: 88.65, 100.00)	Specificity = 27/29 = 93.10%, 95% CI (78.04, 98.09)
PPV = 2/2 = 100.00%, 95% CI (34.24, 100.00)	PPV = 1/3 = 33.33%, 95% CI (6.15, 79.23)
Including indeterminate-as test negative NPV = 45/69 = 65.22% (95% CI: 53.45, 75.38) **Excluding indeterminate** NPV = 30/46 = 65.22% (95% CI: 50.77, 77.32)	NPV = 27/40 = 67.50%, 95% CI (52.02, 79.92)
DOR (for T^+ calculated) = 3.75 (95% CI: 0.31, 44.6)	DOR (for T^+ calculated) = 1.04, 95% CI (0.08, 12.53)
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 3.61 (95% CI: 0.59, 21.99)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (TSPOT/QFT)				TST (>5 mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA (TSPOT/QFT)	**TST (>5 mm)**
DOR (for T^+ calculated)$_{TSPOT/QFT}$ = NA	DOR $_{TST}$ (for T+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported)$_{QFT}$ = NA OR (regression-based; reported)$_{TSPOT}$ = NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**

IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
The authors concluded that the QFT-2G test may have more potential to assist in the diagnosis of active MTB infection and LTBI than TST in people who have systemic lupus. Additionally, the authors suggested that the results should be taken in caution in this patient group because one-third of the patients had an indeterminate test result, and care should be taken especially for those patients who have parallel or subsequent flares of the disease		
Reviewers:		
The authors did not report on the number of people who had valid results for both the IGRA and TST. TST was done on a subsample of 71 patients		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Vassilopolous 2011[142]
Country: Greece
Study design: Retrospective cohort study/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Outpatient rheumatology clinic of Hippokration general hospital
Number of centres: One
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Supported in part by research grants from the Hellenic Society for Rheumatology and the Special Account for Research Grants (SARG), National and Kapodistrian University of Athens, Athens, Greece

Aim of the study

To compare the latest IGRAs (QFT-GIT and T-SPOT.TB assays) and TST for LTBI diagnosis in rheumatic patients starting anti –TNF treatment

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Rheumatic patients starting anti-TNF therapies

Participants

Recruitment dates: Between September 2008 and September 2010
Total N of recruited patients: 157
Inclusion criteria: Patients with various rheumatic diseases who were seen at the Outpatient Rheumatology Clinic of Hippokration General Hospital (2nd Department of Medicine, Athens University School of Medicine, Athens, Greece) and scheduled for anti-TNF treatment
Exclusion criteria: Patients with active TB, a history of treatment with anti-TB agents, including isoniazid (INH) for LTBI, or a history of previous treatment with anti-TNF agents or other biologics
Total N of excluded patients: 2 (indeterminate QFT-GIT results from the analysis: spondyloarthropathy related to UC on high dose methylprednisolone)
Total N of patients tested with both IGRA and TST: 157
Total N of patients with valid results for both IGRA and TST: 155
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Test results, concordance of agreement between two assays
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 52 ±16
Women (n [%]): 90 [58]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]):NR
BCG vaccination (n [%]): 81 [76]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): NR
Co-morbidity (n [%]): 15 [21.4]
Type of during-study treatment (n [%]): Immunosuppressive therapy (DMARDs/steroids (98 [63]); DMARDs (80 [52]) steroids (66 [43])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	157	32	123	2	155
IGRA (T-SPOT.TB):	157	39	116	2	155

TST (≥ 5mm):	157	58	97	2	155

Total N of patients with valid results for both IGRA and TST: 155

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	No history of previous TB contact
Exposed 1 **(specify):**	History of previous TB contact
Definition of exposure group	
Non-exposed	Chest x-ray without signs suggestive of old TB
Exposed 2 **(specify):**	Chest x-ray suggestive of old TB
Definition of exposure group	
Non-exposed	No risk factor for TB (≥ 1)
Exposed 3 **(specify):**	Any risk factor for TB (≥ 1) including: age >50 years, chest X-ray suggestive of old/healed TB, contact with a person with TB, and birth or residence in a country with a high TB prevalence (non-Greek nationality)

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT was performed according to the manufacturer's instructions	NR	The blood draw for both IGRAs was performed just prior to TST application in order to avoid potential interference with the IGRA results
IGRA (TSPOT)	The T-SPOT.TB assay was performed as previously described	NR	The blood draw for both IGRAs was performed just prior to TST application in order to avoid potential interference with the IGRA results
TST≥ 5mm	Mantoux method of 0.1 mL (2 IU) of purified protein derivative (PPD) RT 23; Statens Serum Institute, Copenhagen, Denmark)	A TST was considered positive when the diameter of transverse induration was ≥ 5mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA

Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NR

Association between test results and levels of TB exposure (TB exposure)

IGRA (T-SPOT.TB)				TST≥ 5mm			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	5	34	39	TST +	10	48	58
IGRA -	15	101	116	TST -	10	87	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	20	135	155	Total	20	135	155

Test performance parameters

IGRA	TST
Sensitivity = 5/20 = 25.00%, 95% CI (11.19, 46.87)	Sensitivity = 10/20 = 50.00%, 95% CI (29.93, 70.07)
Specificity = 101/135 = 74.81%, 95% CI (66.88, 81.38)	Specificity = 87/135 = 64.44%, 95% CI (56.07, 72.02)
PPV = 5/39 = 12.82%, 95% CI (5.60, 26.71)	PPV = 10/58 = 17.24%, 95% CI (9.64, 28.91)
NPV = 101/116 = 87.07%, 95% CI (79.76, 92.00)	NPV = 87/97 = 89.69%, 95% CI (82.05, 94.3)
DOR (for T^+ calculated) = 0.99, 95% CI (0.33, 2.92)	DOR (for T^+ calculated) = 1.81, 95% CI (0.70, 4.66)
OR (crude; for T^+ reported) = 0.99, 95% CI (NR; p = 0.99)	OR (crude; for T^+ reported) = 1.81, 95% CI (NR; p = 0.22)
OR (regression-based; reported) = 0.89, 95% CI (NR; p = 0.86) List of covariates: NR	OR (regression-based; reported) = 1.73, 95% CI (NR; p = 0.30) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = 0.55 (95% CI: 0.26, 1.14)
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Association between test results and levels of TB exposure (TB exposure)

IGRA (QFT-GIT)				TST≥ 5mm			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	3	29	32	TST +	10	48	58
IGRA -	17	106	123	TST -	10	87	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	20	135	155	Total	20	135	155

Test performance parameters

IGRA	TST
Sensitivity = 3/20 = 15.00%, 95% CI (5.23, 36.04)	Sensitivity = 10/20 = 50.00%, 95% CI (29.93, 70.07)
Specificity = 106/135 = 78.52%, 95% CI (70.85, 84.61)	Specificity = 87/135 = 64.44%, 95% CI (56.07, 72.02)

PPV = 3/32 = 9.37%, 95% CI (3.24, 24.22)	PPV = 10/58 = 17.24%, 95% CI (9.64, 28.91)
NPV = 106/123 = 86.18%, 95% CI (78.98, 91.19)	NPV = 87/97 = 89.69%, 95% CI (82.05, 94.3)
DOR (for T^+ calculated) = 0.64, 95% CI (0.17, 2.35)	DOR (for T^+ calculated) = 1.81, 95% CI (0.70, 4.66)
OR (crude; for T^+ reported) = 0.64, 95% CI (NR; p = 0.5)	OR (crude; for T^+ reported) = 1.81, 95% CI (NR; p = 0.22)
OR (regression-based; reported) = 0.55, 95% CI (NR; p = 0.41) List of covariates: NR	OR (regression-based; reported) = 1.73, 95% CI (NR; p = 0.30) List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.35 (95% CI: 0.15, 0.81)	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NR	
Association between test results and levels of TB exposure (Chest x-ray suggestive of old TB)	

IGRA (T-SPOT.TB)				**TST≥ 5mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	4	35	39	TST +	9	49	58
IGRA -	10	106	116	TST -	5	92	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	14	141	155	Total	14	141	155

Test performance parameters	
IGRA	**TST**
Sensitivity = 4/14 = 28.57%, 95% CI (11.72, 54.65)	Sensitivity = 9/14 = 64.29%, 95% CI (38.76, 83.66)
Specificity = 106/141 = 75.18%, 95% CI (67.44, 81.58)	Specificity = 92/141 = 65.25%, 95% CI (57.08, 72.61)
PPV = 4/39 = 10.26%, 95% CI (4.06, 23.58)	PPV = 9/58 = 15.52%, 95% CI (8.38, 26.93)
NPV = 106/116 = 91.38%, 95% CI (84.86, 95.25)	NPV = 92/97 = 94.85%, 95% CI (88.5, 97.78)
DOR (for T^+ calculated) = 2.21, 95% CI (0.35, 4.10)	DOR (for T^+ calculated) = 3.38, 95% CI (1.07, 10.64)
OR (crude; for T^+ reported) = 2.21, 95% CI (NR; p = 0.76)	OR (crude; for T^+ reported) = 3.38, 95% CI (NR; p = 0.04)
OR (regression-based; reported) = 0.48, 95% CI (NR; p = 0.31) List of covariates: NR	OR (regression-based; reported) = 3.50, 95% CI (NR; p = 0.05) List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.65 (95% CI: 0.28, 1.54)	
Ratio of OR (crude; for T^+ reported) = NA	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NR	
Association between test results and levels of TB exposure (Chest x-ray suggestive of old TB)	

IGRA (QFT-GIT)				**TST≥ 5mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	14	28	32	TST +	9	49	58
IGRA -	10	113	123	TST -	5	92	97
Indeterminate	0	0	0	Indeterminate	0	0	0

Total	24	141	155	Total	14	141	155
Test performance parameters							
IGRA				**TST**			
Sensitivity = 58.33% (95% CI: 38.83, 75.53)				Sensitivity = 9/14 = 64.29%, 95% CI (38.76, 83.66)			
Specificity = 80.14% (95% CI: 72.8, 85.89)				Specificity = 92/141 = 65.25%, 95% CI (57.08, 72.61)			
PPV = 33.33% (95% CI: 21.01, 48.45)				PPV = 9/58 = 15.52%, 95% CI (8.38, 26.93)			
NPV = 91.87% (95% CI: 85.68, 95.52)				NPV = 92/97 = 94.85%, 95% CI (88.5, 97.78)			
DOR (for T^+ calculated) = 5.65 (95% CI: 2.27, 14.05)				DOR (for T^+ calculated) = 3.38, 95% CI (1.07, 10.64)			
OR (crude; for T^+ reported) = 1.61, 95% CI (NR; p = 0.44)				OR (crude; for T^+ reported) = 3.38, 95% CI (NR; p = 0.04)			
OR (regression-based; reported) = 1.29, 95% CI (NR; p = 0.72) List of covariates: NR				OR (regression-based; reported) = 3.50, 95% CI (NR; p = 0.05) List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 1.67 (95% CI: 0.79, 3.53)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NR							
Association between test results and levels of TB exposure (any risk factor for TB ≥ 1)							
IGRA (T-SPOT.TB)				**TST≥ 5mm**			
	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	34	5	39	TST +	42	16	58
IGRA -	68	48	116	TST -	60	37	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	102	53	155	Total	102	53	155
Test performance parameters							
IGRA				**TST**			
Sensitivity = 34/102 = 33.33%, 95% CI (24.94, 42.94)				Sensitivity = 42/102 = 41.18%, 95% CI (32.12, 50.88)			
Specificity = 48/53 = 90.57%, 95% (79.75, 95.9)				Specificity = 37/53 = 69.81%, 95% CI (56.46, 80.48)			
PPV = 34/39 = 87.18%, 95% CI (73.29, 94.4)				PPV = 42/58 = 72.41%, 95% CI (59.80, 82.25)			
NPV = 48/116 = 41.38%, 95% CI (32.83, 50.48)				NPV = 37/97 = 38.14%, 95% CI (29.10, 48.09)			
DOR (for T^+ calculated) = 4.80, 95% CI (1.75, 13.16)				DOR (for T^+ calculated) = 1.61, 95% CI (0.79, 3.28)			
OR (crude; for T^+ reported) = 4.80, 95% CI (NR; p = 0.02)				OR (crude; for T^+ reported) = 1.60, 95% CI (NR; p = 0.12)			
OR (regression-based; reported) = NR List of covariates: NR				OR (regression-based; reported) = NR List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 2.98 (95% CI: 1.59, 5.60)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NR							
Association between test results and levels of TB exposure (any risk factor for TB ≥ 1)							
IGRA (QFT-GIT)				**TST≥ 5mm**			

	Exposure level		Total		Exposure level		Total
	Yes	No			Yes	No	
IGRA +	26	6	32	TST +	42	16	58
IGRA -	76	47	123	TST -	60	37	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	102	53	155	Total	102	53	155
Test performance parameters							
IGRA				**TST**			
Sensitivity = 26/102 = 25.49%, 95% (18.03, 34.73)				Sensitivity = 42/102 = 41.18%, 95% CI (32.12, 50.88)			
Specificity = 47/53 = 88.68%, 95% CI (77.42, 94.71)				Specificity = 37/53 = 69.81%, 95% CI (56.46, 80.48)			
PPV = 26/32 = 81.25%, 95% CI (64.69, 91.11)				PPV = 42/58 = 72.41%, 95% CI (59.80, 82.25)			
NPV = 47/123 = 38.21%, 95% CI (30.10, 47.03)				NPV = 37/97 = 38.14%, 95% CI (29.10, 48.09)			
DOR (for T^+ calculated) = 2.68, 95% CI (1.02, 6.99)				DOR (for T^+ calculated) = 1.61, 95% CI (0.79, 3.28)			
OR (crude; for T^+ reported) = 2.68, 95% CI (NR; p = 0.04)				OR (crude; for T^+ reported) = 1.60, 95% CI (NR; p = 0.12)			
OR (regression-based; reported) = NR List of covariates: NR				OR (regression-based; reported) = NR List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = 1.66 (95% CI: 0.90, 3.07)							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NR							
Association between test results and BCG status (if applicable)							
IGRA (T-SPOT.TB)				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	24	15	39	TST +	41	17	58
IGRA -	79	37	116	TST -	62	35	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	93	52	155	Total	103	52	155
Test performance parameters							
IGRA (T-SPOT.TB)				**TST (>5 mm)**			
DOR (for T^+ calculated)$_{TSPOT}$ = 0.74, 95% CI (0.35, 1.59)				DOR $_{TST}$ (for T+ calculated) = 1.36, 95% CI (0.67, 2.74)			
OR (crude; for T^+ reported) = 0.75, 95% CI (NR; p = 0.45)				OR (crude; for T+ reported) = 1.36, 95% CI (NR; p = 0.39)			
OR (regression-based; reported)$_{TSPOT}$ = 0.51, 95% CI (NR; p = 0.17) List of covariates: NR				OR (regression-based; reported) $_{TST}$ = 1.43, 95% CI (NR; p = 0.34) List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Association between test results and BCG status (if applicable)							
IGRA (QFT-GIT)				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	22	10	32	TST +	41	17	58
IGRA -	81	42	123	TST -	62	35	97
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	103	52	155	Total	103	52	155

Test performance parameters	
IGRA (QFT-GIT)	**TST (>5 mm)**
DOR (for T^+ calculated)$_{QFT}$ = 1.14, 95% CI (0.49, 2.63)	DOR $_{TST}$ (for T+ calculated) = 1.36, 95% CI (0.67, 2.74)
OR (crude; for T^+ reported) = 1.14, 95% CI (NR; p = 0.76)	OR (crude; for T+ reported) = 1.36, 95% CI (NR; p = 0.39)
OR (regression-based; reported)$_{QFT}$ = 1.05, 95% CI (NR; p = 0.90) List of covariates: NR	OR (regression-based; reported) $_{TST}$ = 1.43, 95% CI (NR; p = 0.34) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +≥5mm	TST -	Total
IGRA + (TSPOT)	26	13	39
IGRA -	32	84	116
Indeterminate	0	0	0
Total	58	97	155

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify):

TST + threshold: ≥5mm

Parameters

Kappa = 0.34 (95% CI: 0.17, 0.50)

% concordance = 110/155 = 71.0% (95% CI: 63.38, 77.54)

% discordance = 45/155 = 29.03% (95% CI: 22.46, 36.62)

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +≥5mm	TST -	Total
IGRA + (QFT-GIT)	17	15	32
IGRA -	41	82	123
Indeterminate	0	0	0
Total	58	97	155

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥5mm

Parameters

Kappa = 0.15 (95% CI: 0.01, 0.29)

% concordance = 99/155 = 63.87% (95% CI: 56.06, 71.01)

% discordance = 56/155 = 36.13% (95% CI: 28.99, 43.94)

Other outcomes

Test and cut-off (if applicable)	Adverse events n/N (%) (specify)	Health related quality of life mean score (SD) (specify)
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions

Authors:

These authors demonstrated that IGRAs appeared to be correlated better with TB risk than TST and should be included in LTBI screening of patients who are about to commence anti-TNF therapies. Furthermore, they suggested that in view of the high risk of TB in this patient group, a combination of one IGRA and TST is probably more appropriate for LTBI

Reviewers:
Steroid use was negatively associated with a positive QFT-GIT assay
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details

First author surname year of publication: Anibarro 2012[117]
Country: Spain
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Outbreak investigation
Number of centres: One
Total length of follow up (if applicable): 18 months
Funding (government/private/manufacturer/other - specify)**:** University of Vigo and SUDOE-FEDER (IMMUNONET-SOE1/P1/E014)

Aim of the study

To compare the results of an IGRA with those for the TST in patients with early stage renal disease (ESRD) after a TB outbreak at a dialysis centre

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised (people undergoing haemodialysis treatment)

Participants

Recruitment dates: NR
Total N of recruited patients: 58
Inclusion criteria: All patients who attended the dialysis unit while index case was on duty
Exclusion criteria: Patients who had a previous +ve TST test
Total N of excluded patients: 6
Total N of patients tested with both IGRA and TST: 52
Total N of patients with valid results for both IGRA and TST: 52
Methods of active TB diagnosis (if applicable): Microscopic examination of sputum and sputum culture
Outcomes (study-based) list: Test results, relationship between TST and erythema, concordance between diagnostic tests
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 62 (16.8)
Women (n [%]): 21 [40.4]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 7 [13.5]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): None
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): End stage renal disease (58 [100])
Co-morbidity (n [%]): Diabetes mellitus (8 [15.4])
Type of during-study treatment (n [%]): Immunosuppressive therapy (8[15.3])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (specify): QFT-GIT	52	18	34	0	52
TST: (≥5 mm)	52	11	41	0	52
Test 3 (specify):					

Total N of patients with valid results for both IGRA and TST: 52

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group

Non-exposed	
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA	QFT-GIT, one ml of whole blood, blood collected immediately before TST, Cellestic Ltd, Carnegie, Australia	0.35 IU/mL	
TST (one and two-step)	Mantoux method, 0.1ml (2 TU) of PPD injected intradermally to the volar surface of the forearm, TST results read 72h after testing, Statens serum Institute, Copenhagen, Denmark	TST ≥ 5mm, a second test was performed five days later if the first TST-1 was <5 mm	Study does not mention how soon after the result will be read for the second TST

Association between test results and incidence of active TB (if applicable)

IGRA				**TST≥5mm (two-step)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	N/A	N/A	11 LTBI treated	TST +	N/A	N/A	11 LTBI treated
IGRA -	0	32	32	TST -	0	32	32
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	0	32	32	Total	0	32	32

Test performance parameters

IGRA	**TST**
Sensitivity = N/A	Sensitivity = N/A
Specificity = N/A	Specificity = N/A
PPV = N/A	PPV = N/A
NPV = 100%, 95% CI (89.28, 100.00)	NPV = 100%, 95% CI (89.28, 100.00)
Cumulative Incidence $_{IGRA+}$ = N/A	Cumulative Incidence $_{TST+}$ = N/A
Cumulative Incidence $_{IGRA-}$ = 0/32 = 0	Cumulative Incidence $_{TST-}$ = 0/32 = 0
Cumulative Incidence Ratio $_{IGRA}$ = N/A	Cumulative Incidence Ratio $_{TST}$ = N/A
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence = NA
Ratio of incidence density rate ratios = NR
Other reported measure = NR

Association between test results and levels of TB exposure (if applicable)

IGRA				TST			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	3	15	18
IGRA -	0	34	34
Indeterminate	0	0	0
Total	3	49	52
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total (One-step TST)			
TST + threshold: ≥ 5mm induration			
Parameters			
Kappa = 0.21, 95% CI: 0.04, 0.37			
% concordance = 37/52 = 71.15% (95% CI: 57.73, 81.67)			
% discordance = 15/52 = 28.85% (95% CI: 18.33, 42.27)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	9	9	18
IGRA -	2	32	34
Indeterminate	0	0	0
Total	11	41	52
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total (Two-step test)			
TST + threshold: ≥ 5mm induration			
Parameters			
Kappa = 0.49, 95% CI: 0.22, 0.74)			
% concordance = 41/52 = 78.85% (95% CI: 65.97, 87.76)			
% discordance = 11/52 = 21.15% (95% CI: 12.24, 34.03)			
Stratification (specify group 2)			
	TST +	TST -	Total

IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NR		NR
Conclusions			
Authors:			
This study demonstrated that QFT-GIT had a better sensitivity than TST in detecting latent TB in haemodialysis patients, after exposure to Mycobacterium tuberculosis. TST administered a second time can be performed to increase the sensitivity			
Reviewers:			
Authors have not presented results stratified by the level of exposure to TB.			
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation			

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Chang 2011[119]
Country: South Korea
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Hospital-based
Number of centres: One
Total length of follow up (if applicable): 18 mo (median)
Funding (government/private/manufacturer/other - specify)**:** IN-SUNG Foundation for Medical Research (CA98051)

Aim of the study

To evaluate the usefulness of IGRA for the diagnosis of LTBI in arthritis patients who received TNF antagonists in South Korea where the incidence of tuberculosis is intermediate (70–90/105 per year) and BCG vaccination is mandatory at birth

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people**:** Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) before starting TNF antagonist

Participants

Recruitment dates: August 2007–July 2009
Total N of recruited patients: 108
Inclusion criteria: Inflammatory arthritis including RA and AS who visited our facility to evaluate LTBI before starting TNF antagonist
Exclusion criteria: Active TB
Total N of excluded patients: 1
Total N of patients tested with both IGRA and TST: 107
Total N of patients with valid results for both IGRA and TST: 100
Methods of active TB diagnosis (if applicable): Medical history (current symptoms, prior history of treatment for tuberculosis, and recent history of contact with a case of active TB) and TST (according to the recommendation of the Korea Food and Drug Administration)
Outcomes (study-based) list: Test results, concordance/discordance, incidence of active TB, prognostic test accuracy indices (sensitivity, specificity, predictive values, false negative/false positive rates)
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 39 (median)
Women (n [%]): 44 [41]
Race/ethnicity (n [%]): Asian
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 63 [59]
History of anti-TB treatment (n [%]): 4 [3.8]
Total incidence of active TB (n [%]): 1 [0.9%]
Chest radiography (yes/no): NR
Clinical examination (yes/no): Yes
Morbidity (n [%]): RA (46 [43]) and AS (61 [57])
Co-morbidity (n [%]): NR
Type of during-study treatment: RA (Glucocorticoid: 31/46, Methotrexate: 39/46), AS (Glucocorticoid: 6/61, Methotrexate: 3/61)

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-IT):	107	36	64	7	100

TST:	107	36	71	0	107
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 100

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NA
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-IT)	The QuantiFERON-TB Gold In-Tube test (QFT-GIT test; Cellestis Ltd., Carnegie, Australia) performed according to the manufacturer instructions	Positive test result was defined as ≥0.35 IU/mL	Both the TST and QFT-IT were performed on the same day as the screening examination in all patients before initiating TNF antagonists
TST	The TST was performed on the volar side of the forearm using the Mantoux method with 2 tuberculin units (TU) of purified protein derivative RT23 (Statens Serum Institut; Copenhagen, Denmark). This dose is approximately equivalent to the international standard of 5 TU tuberculin PPD-S	Induration size was measured after 48–72h, and we used a 10-mm induration as a positive cut-off value for the TST	

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	37 LTBI treated	TST +	0	16	16
IGRA -	0	64	64	TST -	0	54	54
Indeterminate	0	6	6	Indeterminate	0	0	
Total	0	70	70	Total	0	70	70

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = 70/70 = 100% (95% CI: 94.8, 100)	Specificity = 54/70 = 77.14 (95% CI: 66.05, 85.41)
PPV = NA	PPV = 0/16 = 0
NPV = 64/64 = 100% (95% CI: 94.8, 100)	NPV = 54/54 = 100% (95% CI: 93.4, 100)
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = 0/16 = 0
Cumulative Incidence $_{IGRA-}$ = 0/64 = 0	Cumulative Incidence $_{TST-}$ = 0/54 = 0
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA							
Ratio of incidence density rate ratios = NR							
Other reported measure = NR							
Association between test results and levels of TB exposure (if applicable)							
IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA
Test performance parameters							
IGRA				**TST**			
Sensitivity = NA				Sensitivity = NA			
Specificity = NA				Specificity = NA			
PPV = NA				PPV = NA			
NPV = NA				NPV = NA			
DOR (for T^+ calculated) = NA				DOR (for T^+ calculated) = NA			
OR (crude; for T^+ reported) = NA				OR (crude; for T^+ reported) = NA			
OR (regression-based; reported) = NA List of covariates: NA				OR (regression-based; reported) = NA List of covariates: NA			
Other reported measure = NA				Other reported measure = NA			
Comparison between tests (IGRA vs. TST)							
Ratio of DORs (for T^+ calculated) = NA							
Ratio of OR (crude; for T^+ reported) = NA							
Ratio of ORs (regression-based; reported) = NA							
Other reported measure = NR							
Association between test results and BCG status (if applicable)							
IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = NR				DOR (for T+ calculated)$_{TST}$ = NR			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample							
	TST +			TST -			Total
IGRA +	19			17			36
IGRA -	16			48			64
Indeterminate	1			6			7
Total	36			71			107
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): total							
TST + threshold: > 10mm							

Parameters			
Kappa = 0.26, 95% CI: 0.07, 0.45			
% concordance = 67/100 = 67.0%, 95% CI: 57.31, 75.44			
% discordance = 33/100 = 33.0%, 95% CI: 24.56, 42.69			
Rheumatoid arthritis (RA)			
	TST +	TST -	Total
IGRA +	8	9	17
IGRA -	1	24	25
Indeterminate	NR	NR	NR
Total	9	33	42
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): RA			
TST + threshold: > 10mm			
Parameters			
Kappa = 0.46, 95% CI: 0.21, 0.72			
% concordance = 32/42 = 76.20%, 95% CI: 61.47, 86.52			
% discordance = 10/42 = 23.80%, 95% CI: 13.48, 38.53			
Ankylosing spondylitis (AS)			
	TST +	TST -	Total
IGRA +	11	8	19
IGRA -	15	24	39
Indeterminate	NR	NR	NR
Total	26	32	58
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Ankylosing spondylitis			
TST + threshold: > 10mm			
Parameters			
Kappa = 0.14, 95% CI: -0.10, 0.39			
% concordance = 35/58 = 60.34%, 95% CI: 47.49, 71.91			
% discordance = 23/58 = 39.66%, 95% CI: 28.09, 52.51			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
IGRA performed better in terms of specificity than TST, but several observations of IGRA were indeterminate; in general, the agreement between IGRA and TST was low; better agreement was observed for rheumatoid arthritis and ankylosing spondylitis
Reviewers:
See above
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Elzi 2011[114]
Country: Switzerland
Study design: Retrospective case only study (no control group)
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community-based cohort
Number of centres: One
Total length of follow up (if applicable): 2 years
Funding (government/private/manufacturer/other - specify)**:** Grants/honoraria received from private manufacturers (Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche. M. Hoffmann, Janssen, Pfizer)

Aim of the study

To evaluate the sensitivity of T-SPOT.TB in comparison to TST to identify HIV-infected individuals with latent TB, who therefore qualify for preventive treatment

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised people (HIV)

Participants

Recruitment dates: 1993 to 2005
Total N of recruited patients: 64
Inclusion criteria: NR
Exclusion criteria: NR
Total N of excluded patients: None
Total N of patients tested with both IGRA and TST: 64
Total N of patients with valid results for both IGRA and TST: 44
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Sensitivity, agreement, influence of age, CD count and other covariates on test positivity
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median of 33 (IQR: 31-42) yrs
Women (n [%]): 20/64 [31]
Race/ethnicity (n [%]): White 29/64 [45.3]
Geographic origin (n[%]): NR
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): NR
Clinical examination (yes/no): NR
Morbidity (n [%]): HIV
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (T-SPOT.TB):	64	25	18	21	43
TST: Mantoux	44	22	22	0	44
Test 3 (specify):					

Total N of patients with valid results for both IGRA and TST: 44

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group

Non-exposed	
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (T-SPOT.TB)	T-SPOT.TB was retrospectively performed using frozen viable lymphocytes of HIV-infected individuals stored within 6 months before culture-confirmed TB occurred T-SPOT.TB was performed by using a commercial kit according to the manufacturer's instructions. Each patient test required 4 wells: 2 for the negative (containing no antigen control) and positive controls and 2for the MTB antigens, Panel A (ESAT-6) and B (CFP-10) Evaluating the number of spots obtained provided a measurement of the frequency of MTB tuberculosis sensitive cells	The test result was considered "positive" if the number of spots per test well was ≥ 6 in either of both Panel A and B. The test result was considered "negative" if both Panel A and B showed < 6 spots. Where the positive control was < 20 spots, or the negative control ≥ 10 spots, the test was scored as "indeterminate"	NR
TST	NR	≥ 5mm for positivity	NR

Association between test results and incidence of active TB (if applicable)

IGRA (T-SPOT.TB)				**TST (≥ 5mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	25	NA		TST +	22	NA	
IGRA -	18	NA		TST -	22	NA	
Indeterminate	21	NA		Indeterminate	0	NA	
Total	64	NA		Total	44	NA	

Test performance parameters	
IGRA	**TST (≥ 5mm)**
indeterminate excluded Sensitivity = 25/43 = 58.14% (95% CI: 43.33, 71.62) **indeterminate included** Sensitivity = 25/64 = 39.06% (95% CI: 28.06, 51.31)	Sensitivity = 22/44 = 50.00% (95% CI: 35.83, 64.17)
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR

Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NR
Other reported measure = NR

Association between test results and incidence of active TB (if applicable)

TST (≥ 5mm) and IGRA combined (at least one test positive)

	Incidence of active TB		Total
	Yes	No	
TST or IGRA +	29	NA	NA
TST and IGRA -	15	NA	NA
Indeterminate	0	NA	NA
Total	44	NA	NA

Test performance parameters (TST and IGRA combined)

Sensitivity = 29/44 = 65.91% (95% CI: 51.14, 78.12)
Specificity, PPV, NPV, others = NA

Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR

IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + (≥ 5mm)	TST -	Total
IGRA +	10	7	17
IGRA -	7	8	15
Indeterminate	5	7	12
Total	22	22	44

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total

TST + threshold: ≥ 5mm

Parameters

Indeterminate excluded
Kappa = 0.12 (95% CI: -0.22, - 0.46)
% concordance = 18/32 = 56.25% (95% CI: 39.33, 71.83)
% discordance = 14/32 = 43.75% (95% CI: 28.17, 60.67)

Indeterminate included
Kappa = 0.14 (95% CI: -0.15, - 0.42)
% concordance = 25/44 = 57.00% (95% CI: 42.22, 70.32)
% discordance = 19/44 = 43.20% (95% CI: 29.68, 57.78)

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR

% discordance = NR

Stratification (specify group 2)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR		
Parameters		
Kappa = NR		
% concordance = NR		
% discordance = NR		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
T-SPOT.TB has a similar sensitivity to TST to detect latent TB in HIV infected individuals. There was poor agreement between T-SPOT.TB and TST results. The combination of TST and TSPOT. TB (at least one test positive) resulted in improved sensitivity over TST or IGRA alone		
Reviewers:		
This is a retrospective case only study which does not allow to estimate incidence of active TB between test positive vs. negative groups from baseline (no denominators provided). Likewise, no specificity and predictive values could be estimated; the sample (64 out of 242) may have been highly selected, thus prone to selection bias and limitation in regards to applicability of its results; moreover, for IGRA frozen blood samples were analysed		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Kim 2011[116] **Country:** Korea **Study design:** Prospective cohort study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Tertiary-care hospital **Number of centres:** One **Total length of follow up (if applicable):** median 14 mo (IQR: 8-19) **Funding** (government/private/manufacturer/other - specify)**:** Basic Science Research Program through National Research Foundation (NRF) funded by the Ministry of Education, Science and Technology (MEST) (grant 2008-E00136
Aim of the study
To assess whether an enzyme-linked immunosorbent spot (ELISPOT) assay is capable of predicting active TB development in kidney transplant (KT) recipients with negative TST results and without LTBI risk factors
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Immunocompromised people (kidney transplant [KT] recipients)
Participants
Recruitment dates: June 2008 and December 2009 **Total N of recruited patients:** 324 **Inclusion criteria:** KT patients (age≥16 yrs) with TST – (<10mm) and without TB risk factors (history of close contact with TB case, abnormal CXR, history of untreated or inadequately treated TB, newly infected persons) **Exclusion criteria:** Refusal of informed consent, presence of active TB, presence of skin disease that precluded TST, pediatric renal transplant candidates (<16 years old), TB risk factors, and presence of any contraindication for KT (e.g. malignancy) **Total N of excluded patients:** 28 (n = 12 refusal, pediatric, pancreas transplants, transplantation not done, donor kidney problem; n = 16 LTBI risk factors who received anti-TB preventive therapy) **Total N of patients tested with both IGRA and TST:** 272 (out of 296, 24 with TST + [≥10mm] received anti-TB preventive therapy before KT, leaving 272 KT patients with TST-[<10mm] also tested with IGRA who did not receive anti-TB preventive therapy) **Total N of patients with valid results for both IGRA and TST:** 242 (out of 272 patients, 30 had indeterminate IGRA results) **Methods of active TB diagnosis (if applicable):** Symptoms/signs, sputum AFB smear, and a CT scan **Outcomes (study-based) list:** Development of TB, mortality, KT rejection **Characteristics of participants (total study sample):** 272 patients Mean (range or SD) age (years): Mean age range (40.4-46.0 yrs) Women (n [%]): 126 (46.3) Race/ethnicity (n [%]): NR Geographic origin (n[%]): NR BCG vaccination (n [%]): 215 [79.0] History of anti-TB treatment (n [%]): None Total incidence of active TB (n [%]): 4/272 [1.47] (incidence rate: 0.83 per person-years, 95% CI: 0.23, 2.12) Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): Glomerulonephritis 72 [26.5], hypertension 65 [23.9], diabetes mellitus 48 [17.6], unknown 58 [21.3], polycystic kidney 12 [4.4], other 11 [4.0] Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): anti-IL-2 receptor antibodies (238 [87.5]), antithymocyte antibodies (21 [7.7]), rituximab (11 [4.0])

Number of patients tested					
	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**
IGRA (T-SPOT.TB):	272	71	171	30	242
TST (Mantoux):	272	0 (≥10mm)	272 (<10mm)	0	272
Test 3 (specify):	Nr	NR	NR	NR	NR
Total N of patients with valid results for both IGRA and TST: 242					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group					
Non-exposed	NA				
Exposed 1 **(specify):**	NA				
Exposed 2 **(specify):**	NA				
Exposed 3 **(specify):**	NA				
Exposed 4 **(specify):**	NA				

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (T-SPOT.TB)	A peripheral venous blood sample was collected from each patient for an ELISPOT assay for the IFN-c - producing T-cell response (i.e. T-SPOT.TB, Oxford Immunotec, Abingdon, UK) All blood samples were collected prior to TST to avoid a possible boosting effect of TST on the ELISPOT assay	NR	The development of TB after KT was observed by attending surgeons, nephrologists and infectious diseases specialists blind to the results of ELISPOT assays, to avoid a verification bias
TST (Mantoux)	The TST was performed by the Mantoux technique, injecting a 2-TU (tuberculin unit) dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm	The positive criterion for TST was 10 mm or greater size of induration 48–72 h after injection, and in accordance with Korea Centers for Diseases Control and Prevention guidelines	NR

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST (≥10mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	4	67	71	TST +	NA	NA	NA

IGRA -	0	171	171	TST -	4	268	272
Indeterminate	0	30	30	Indeterminate	0	0	0
Total	4	268	272	Total	4	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = 4/4 = 100.00% (95% CI: 51.01, 100.00)	Sensitivity = NA
Indeterminate excluded Specificity = 171/238 = 71.84% (95% CI: 65.82, 77.18) **Indeterminate included** Specificity = 201/268 = 75.00% (95% CI: 69.49, 79.81)	Specificity = NA
PPV = 4/71 = 5.63% (95% CI: 2.21, 13.61)	PPV = NA
Indeterminate excluded NPV = 171/171 = 100.00% (95% CI: 97.80, 100.00) **Indeterminate included** NPV = 201/201 = 100.00% (95% CI: 98.12, 100.00)	NPV = 268/272 = 98.53% (95% CI: 96.28, 99.43)
Cumulative Incidence $_{IGRA+}$ = 4/71 = 5.63% (95% CI: 2.21, 13.61)	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = 0/171 = X	Cumulative Incidence $_{TST-}$ = 4/272 = 1.47% (95% CI: 0.43, 3.85)
Cumulative Incidence Ratio $_{IGRA}$ = X	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = 4/122.10 p-yrs = 0.0328 p-yrs = 3.28/100 p-yrs (95% CI: 0.89, 8.39)	Incidence density rate $_{TST+}$ = NA
Indeterminate excluded Incidence density rate $_{IGRA-}$ = 0/307.83 p-yrs = 0.00/100 p-yrs **Indeterminate included** Incidence density rate $_{IGRA-}$ = 0/361.16 p-yrs = 0.00/100 p-yrs	Incidence density rate $_{TST-}$ = 4/483.25 p-yrs = 0.0083 p-yrs = 0.83/100 p-yrs (95% CI: 0.23, 2.12)
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = **Indeterminate excluded** Incidence density rate difference $_{IGRA}$ = 3.3/100 p-yrs (95% CI: 1.3, 5.3) **Indeterminate included** Incidence density rate difference $_{IGRA}$ = 3.3/100 p-yrs (95% CI: 1.4, 5.1)	Other reported measure $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NR
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = NR
Other reported measure =

Association between test results and BCG status (if applicable)							
IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
Positive ELISPOT results predict subsequent development of TB in KT recipients in whom LTBI cannot be detected by TST or who lack clinical risk factors for LTBI
Reviewers:
The available data did not allow the proper direct comparison between IGAA and TST (no relevant data for TST positives); however, IGRA correctly identified the incidence of 4 TB cases as opposed to TST which was negative in all 4 TB cases
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Peter Auguste
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Lee 2009[118]
Country: Taiwan
Study design: Prospective, matched, double cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** NR
Number of centres: One
Total length of follow up (if applicable): 2 yrs follow-up
Funding (government/private/manufacturer/other - specify)**:** National health research institutes, Department of Health, Executive Yuan, republic of China (NHRI-CN-CL-094-PP13) and Kaohsiung Veterans General Hospital, Kaohsuing, Taiwan (VGHKS95-012)

Aim of the study

To compare QFT-G, T-SPOT.TB, and TST in terms of their ability to diagnose LTBI in end stage renal disease(ESRD) patients, and to determine the prevalence of LTBI in ESRD patients compared with healthy controls, the risk factors for QFT-G and TST positivity, and the predictive value of a positive QFT-G, ELISPOT, or TST for active TB disease over a two-year period

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised (ESRD)

Participants

Recruitment dates: September 2005
Total N of recruited patients: 64 patients
Inclusion criteria: Patients with ESRD
Exclusion criteria: NR
Total N of excluded patients: None
Total N of patients tested with both IGRA and TST: 32
Total N of patients with valid results for both IGRA and TST: 32
Methods of active TB diagnosis (if applicable): Asymptomatic cases are diagnosed with a chest x-ray, and symptomatic cases are diagnosed with a sputum TB smear, culture and chest radiography
Outcomes (study-based) list: Primary outcome was LTBI and secondary outcomes was development of active TB, concordance between tests, risk factors for a positive result
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 53.8 (34.4-77.7)
Women (n [%]): 24 [37.5]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Kaohsiung
BCG vaccination (n [%]): 53 [82.8]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): End stage renal dialysis
Co-morbidity (n [%]): Diabetes mellitus (7 [10.9])
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-G):	32	12	18	2	30
IGRA (ELISPOT):	32	15	17	0	32
TST (≥ 10mm):	32	20	12	0	32
Total N of patients with valid results for both IGRA and TST:					

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group	
Non-exposed	NR
Exposed 1 **(specify):**	NR
Exposed 2 **(specify):**	NR
Exposed 3 **(specify):**	NR
Exposed 4 **(specify):**	NR

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Whole blood was drawn prior to carrying out the TST. The QFT-G was performed according to the respective manufacturer's instructions	A QFT-G analysis software, available for download from the Cellestis Ltd website, was used for quality control assessment and to calculate the test results	NA
TSPOT	Whole blood was drawn prior to carrying out the TST. The T-SPOT.TB was performed according to the respective manufacturer's instructions	NR	NA
TST (two step; ≥ 10mm)	A two-step TST using the Mantoux method with two tuberculin units of tuberculin RT-23 (PPD RT 23 SSI; Statens Serum Institut, Copenhagen, Denmark) was performed according to standard protocol. The reactions were read after 48–72 h. Second TST test was performed 1-3 weeks later for initial negative TST result	≥ 10mm induration for ESRD patients and BCG-unvaccinated individuals, ≥ 15mm induration for BCG-vaccinated, healthy individuals	NA

Association between test results and incidence of active TB (if applicable)

IGRA (QFT-G)				**TST (two-step; ≥10mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	1	11	12	TST +	1	19	20
IGRA -	0	18	18	TST -	1	11	12
Indeterminate	1	1	2 (excluded)	Indeterminate			
Total	2	30	32	Total	2	30	32

Test performance parameters	
IGRA (exclude indeterminate)	**TST**
Sensitivity = 1/1 = 100.00%, 95% CI: 20.65, 100.00	Sensitivity = 1/2 = 50.00% (95% CI: 9.45, 90.55)
Specificity = 18/30 = 60.00%, 95% CI: 44.00, 77.31	Specificity = 11/30 = 36.67%, 95% CI: 21.87, 54.49
PPV = 1/12 = 8.33%, 95% CI: 1.49, 35.39	PPV = 1/20 = 5.00%, 95% CI: 0.89, 23.61
NPV = 18/18 = 100.00%, 95% CI: 82.41, 100.00	NPV = 11/11 = 100.00%, 95% CI:74.12, 100.00
Cumulative Incidence $_{IGRA+}$ = 1/12 = 8.33%, 95% CI (1.49, 35.39)	Cumulative Incidence $_{TST+}$ = 1/20 = 5.00%, 95% CI (0.89, 23.61)
Cumulative Incidence $_{IGRA-}$ = 0/18 = 5.56% (95%	Cumulative Incidence $_{TST-}$ = 0/11 = 9.09% (95%

CI: 5.40, 27.29)	CI: 0.23, 41.3)
Cumulative Incidence Ratio $_{IGRA}$ = 1.55% (95% CI: 0.02, 124.2)	Cumulative Incidence Ratio $_{TST}$ = 0.55% (95% CI: 0.01, 47.06)
Incidence density rate $_{IGRA+}$ = 3.40 per 100 PYS	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence = 2.82% (95% CI: 0.13, 62.64)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and incidence of active TB (if applicable)	

IGRA (TSPOT)				**TST (two-step; ≥10mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	0	15	15	TST +	1	19	20
IGRA -	2	15	17	TST -	1	11	12
Indeterminate	0	0	0	Indeterminate	0	0	0
Total	2	30	32	Total	2	30	32

Test performance parameters	
IGRA	**TST**
Sensitivity = 0/2 = 0.00% (95% CI: 0.00, 65.76)	Sensitivity = 1/2 = 50.00% (95% CI: 9.45, 90.55)
Specificity = 15/30 = 50.00% (95% CI: 33.15, 66.85)	Specificity = 11/30 = 36.67%, 95% CI: 21.87, 54.49
PPV = 0/15 = 0.00% (95% CI: 0.00, 20.39)	PPV = 1/20 = 5.00%, 95% CI: 0.89, 23.61
NPV = 15/17 = 88.24% (95% CI: 65.66, 96.71)	NPV = 11/11 = 100.00%, 95% CI:74.12, 100.00
Cumulative Incidence $_{IGRA+}$ = 0/15 = 6.67% (95% CI: 0.17, 31.9)	Cumulative Incidence $_{TST+}$ = 1/20 = 5.00%, 95% CI (0.89, 23.61)
Cumulative Incidence $_{IGRA-}$ = 2/17 = 11.76% (95% CI: 2.03, 35.59)	Cumulative Incidence $_{TST-}$ = 0/11 = 9.09% (95% CI: 0.23, 41.3)
Cumulative Incidence Ratio $_{IGRA}$ = 0.57% (95% CI: 0.01, 12.1)	Cumulative Incidence Ratio $_{TST}$ = 0.55% (95% CI: 0.01, 47.06)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence = 1.04% (95% CI: 0.06, 17.34)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and levels of TB exposure (if applicable)	

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA

Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA (QFT-G) +	NR	NR	12
IGRA (QFT-G) -	NR	NR	18
Indeterminate	NR	NR	2
Total	20	12	32
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total			
TST + threshold: ≥ 10mm induration for ESRD patients and BCG-unvaccinated patients			
Parameters			
Kappa = 0.25, 95% CI (-0.06,- 0.56)			
% concordance = 60.0%			
% discordance = NR (40.0%)			
Stratification (ESRD on hemodialysis)			
	TST +	TST -	Total
IGRA (ELISPOT) +	NR	NR	15
IGRA (ELISPOT)-	NR	NR	17
Indeterminate	NR	NR	0
Total	20	12	32
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): ESRD on hemodialysis			
TST + threshold: ≥ 10mm induration for ESRD patients and BCG-unvaccinated patients			
Parameters			
Kappa = 0.32 95% CI (-0.01, -0.65)			
% concordance = 65.6%			
% discordance = NR (34.4%)			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
Indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			

% discordance = NA		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
This pilot study compared test results of TST, QFT-G, and ELISPOT and showed that there was moderate agreement between QFT-G and ELISPOT, but fair agreement between TST and either QFT-G or ELISPOT		
Reviewers:		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Lee 2014[149] **Country**: South Korea **Study design**: Prospective longitudinal study **Study setting** (e.g., outbreak investigation, community-based - specify): tertiary hospital-based **Number of centres**: One **Total length of follow up (if applicable)**: 391 patients followed up for 581.7 person –years; median duration 1.3 years (IQR 0.6-2.3) **Funding** (government/private/manufacturer/other - specify): supported by grant from the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning
Aim of the study
To test the hypothesis that hematopoietic stem cell transplant (HCT) recipients who are QFT-TB positive develop active TB more frequently than QFT-TB negative or indeterminate patients; to evaluate whether the QFT-TB assay can predict active TB development in HCT recipients without any clinical risk factors for LTBI
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Hematopoietic stem cell transplant (HCT) recipients
Participants
Recruitment dates: January 2010 and December 2012. Resulting cohort observed until June 2013. **Total N of recruited patients**: 409 **Inclusion criteria**: adult patients admitted for allogeneic HCT **Exclusion criteria**: patients with history of close contact with active TB, history of untreated or inadequate treated TB, and the radiograph evidence of old TB. Patients who refused informed consent, presence of active TB, presence of skin disease that precluded the TST (between January 2010 and December 2011), and pediatric HCT candidates (<16 years old) **Total N of excluded patients:** 18 **Total N of patients tested with both IGRA and TST:** 169 **Total N of patients with valid results for both IGRA and TST:** 159 **Methods of active TB diagnosis (if applicable):** chest x-ray, a sputum AFB smear and CT scan (pulmonary TB) **Outcomes (study-based) list:** development of active TB **Characteristics of participants (total study sample)** Mean (range or SD) age (years): 42.3 [13.8] Women (n [%]): 183 [46.8%] Race/ethnicity (n [%]): Korean 409 [100%] Geographic origin (n[%]): NR BCG vaccination (n [%]): History of scars (353 [90.7%]) History of anti-TB treatment (n [%]): None Total incidence of active TB (n [%]): 8/391 [2.04%] Chest radiography (yes/no): Yes Clinical examination (yes/no): NR Morbidity (n [%]): HCT Co-morbidity (n [%]): Acute or chronic graft-versus-host disease (151 [38.6%]); diabetes mellitus (32 [8.2%]); liver cirrhosis (4[1.0%]); Solid organ transplant (2[0.5%]); HIV (0) Type of during-study treatment (n [%]): isoniazid prophylaxis to 5/409 [1.22%] patients with clinical risk factors for LBTI (who were excluded from the analyses)
Number of patients tested

	Total N (tested)	**Total N (test+)**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results available)**

IGRA (QFT-GIT) 1st year enrollment cohort:	391	45	315	31	360
IGRA (QFT-GIT): 2nd year enrollment cohort:	169	26	133	10	159
TST (>5mm): 2nd year enrollment cohort:	169	19	150	0	169
TST (>10mm): 2nd year enrollment cohort:	169	12	157	0	169
Total N of patients with valid results for both IGRA and TST: 159					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group					
Non-exposed	NA				
Exposed 1 **(specify)**:	NA				
Exposed 2 **(specify)**:	NA				
Exposed 3 **(specify)**:	NA				
Exposed 4 **(specify)**:	NA				

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA (QFT-GIT)	A peripheral venous blood sample was collected from each patient for the QFT-TB assay (Cellestis, Carnegie, Victoria, Australia), and placed directly into three 1 mL tubes containing, respectively, Mycobacterium tuberculosis early secreted antigenic target of 6 kDa (ESAT)-6, culture filtrate protein (CFP)-10 and TB 7.7, phytohemagglutinin (a mitogen used as a positive control), and (3) saline (Nil used as a negative control). The samples were incubated at 37°C for 16-18 h, then processed and tested for quantitative interferon-g levels (IU/mL). The assay was interpreted according to the manufacturer's instructions. All blood samples were collected prior to the TST to avoid a possible boosting effect of the TST on the QFT-TB assay	NR	
TST≥5mm ≥10mm	The TST was performed by the Mantoux technique, injecting a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm	The positive criterion for the TST was a 5mm or greater in duration 48-72h after injection	The results of TSTs were measured by the trained nurse

Association between test results and incidence of active TB (if applicable)

IGRA [QFT-GIT]				TST (≥5mm)			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	3	23	26	TST +	0	19	19

IGRA -	2	131	133	TST -	5	145	150
indeterminate	0	10	10	indeterminate	0	0	0
Total	5	154	159	Total	5	164	169

Test performance parameters	
IGRA (QFT-GIT)	**TST≥5mm**
Sensitivity = 3/5= 60.00% (95% CI: 23.07, 88.24)	Sensitivity = 0/5=0.0% (95% CI: 0.0, 43.45)
Specificity =131/154= 85.06% (95% CI: 78.59, 89.84)	Specificity = 145/164=88.41% (95% CI: 82.61, 92.46)
PPV= 3/26=11.54% (95% CI: 4.00, 28.98)	PPV= 0/19=0.0% (95% CI: 0.0, 16.82)
NPV= 131/133=98.5% (95% CI: 94.68, 99.59)	NPV=145/150=96.67% (95% CI: 92.43, 98.57)
Cumulative Incidence $_{IGRA+}$ = 3/26=11.54% (95% CI: 3.17, 29.80)	Cumulative Incidence $_{TST+}$ = 0/19=2.63% (95% CI: 0.0, 23.22)
Cumulative Incidence $_{IGRA-}$ = 2/133=1.50% (95% CI: 0.07, 5.66)	Cumulative Incidence $_{TST-}$ = 5/150=3.33% (95% CI: 1.22, 7.77)
Cumulative Incidence Ratio $_{IGRA}$ = 7.67 (95% CI: 1.34, 43.67)	Cumulative Incidence Ratio $_{TST}$ = 0.79 (95% CI: 0.04, 13.89)
Incidence density rate $_{IGRA+}$ = 5.43 per 100 p-y (95% CI: 1.12, 15.88)	Incidence density rate $_{TST+}$= 0 per 100 p-y (95% CI: 0.00, 8.41)
Incidence density rate $_{IGRA-}$ = 0.80 per 100 p-y (95% CI: 0.10, 2.88)	Incidence density rate $_{TST-}$ = 1.79 per 100 p-y (95% CI: 0.58, 4.18)
Incidence density rate ratio $_{IGRA}$ = 6.78 per 100 p-y (95% CI: NR)	Incidence density rate ratio $_{TST}$=0.00 per 100 p-y (95% CI: NR)
Other reported measure $_{IGRA}$ = incidence density rate difference: 4.7 per 100 person-years (95% CI: 1.10, 8.30)	Other reported measure $_{TST}$ = incidence density rate difference: -1.79 per 100 person-years (95% CI: NR)

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = 9.71 (95% CI: 1.71, 55.15)
Ratio of incidence density rate ratios= NA
Other reported measure= NR

Association between test results and incidence of active TB (if applicable)

IGRA [QFT-GIT]				**TST (≥10mm)**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	3	23	26	TST +	0	12	12
IGRA -	2	131	133	TST -	5	152	157
indeterminate	0	10	10	indeterminate	0	0	0
Total	5	154	159	Total	5	164	169

Test performance parameters	
IGRA	**TST**
Sensitivity = 3/5= 60.00% (95% CI: 23.07, 88.24)	Sensitivity = 0/5=0.0% (95% CI: 0.0, 43.45)
Specificity =131/154= 85.06% (95% CI: 78.59, 89.84)	Specificity = 152/164= 92.68% (95% CI: 87.65, 95.77)
PPV= 3/26=11.54% (95% CI: 4.00, 28.98)	PPV= 0/12= 0.0% (95% CI: 0.0, 24.25)
NPV= 131/133=98.5% (95% CI: 94.68, 99.59)	NPV=152/157=96.82% (95% CI: 92.76, 98.63)
Cumulative Incidence $_{IGRA+}$ = 3/26=11.54% (95% CI: 3.17, 29.80)	Cumulative Incidence $_{TST+}$ = 0/12=4.16% (95% CI: 0.0, 33.00)
Cumulative Incidence $_{IGRA-}$ = 2/133=1.50% (95% CI: 0.07, 5.66)	Cumulative Incidence $_{TST-}$ = 5/157=3.18% (95% CI: 1.16, 7.43)
Cumulative Incidence Ratio $_{IGRA}$ = 7.67 (95% CI: 1.34, 43.67)	Cumulative Incidence Ratio $_{TST}$ = 1.31 (95% CI: 0.07, 22.55)
Incidence density rate $_{IGRA+}$ = 5.43 per 100 p-y (95% CI: 1.12, 15.88)	Incidence density rate $_{TST+}$= 0.0% (95% CI: 0.0, 14.93)

Incidence density rate $_{IGRA-}$ = 0.80 per 100 p-y (95% CI: 0.10, 2.88)	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$= NA
Other reported measure $_{IGRA}$ = incidence density rate difference: 4.7 per 100 person-years (95% CI: 1.10, 8.30)	Other reported measure $_{TST}$ == incidence density rate difference: -3.18 per 100 person-years (95% CI: NR)

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = 5.85 (95% CI: 1.05, 32.70)
Ratio of incidence density rate ratios= NA
Other reported measure=NR

Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA
NPV= NA	NPV= NA
DOR (for T^+ calculated)= NA	DOR (for T^+ calculated)= NA
OR (crude; for T^+ reported)= NA	OR (crude; for T^+ reported)= NA
OR (regression-based; reported)= NA List of covariates: NA	OR (regression-based; reported)= NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated)= NA
Ratio of OR (crude; for T^+ reported)= NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure= NA

Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T+ reported) = NA
OR (regression-based; reported) $_{IGRA}$ = NA List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +≥5mm	TST -	Total

IGRA +	6	20	26
IGRA -	12	121	133
indeterminate	1	9	10
Total	18	141	159
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥5mm			
Parameters			
Kappa = 0.16 (95% CI: 0.01, 0.31)			
% concordance = 127/159 = 79.87% (95% CI: 72.97, 85.37)			
% discordance = 32/159 = 20.13% (95% CI: 14.63, 27.03)			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Conclusions			
Authors:			
Positive QFT predicts the incidence of active TB, whereas positive TST does not			
Reviewers:			
QFT performed better than TST at 5 or 10mm in predicting LTBI; sensitivity of QFT was better than that for TST at both thresholds; between test agreement was poor			
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation			

Name of first reviewer: Tara Gurung
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Moon 2013[115]
Country: Korea
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Asan Medical Center
Number of centres: One
Total length of follow up (if applicable): Median 0.8 years (IQR: 0.1–2.6)
Funding (government/private/manufacturer/other - specify)**:** Basic science research program through the National Research Foundation (NRF) funded by the Ministry of Education, Science and Technology (MEST) (grant 2010-0005898

Aim of the study

To compare the QFT-GIT with the TST in HCT candidates for detecting LTBI

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Hematopoietic stem cell transplant (HCT) candidates

Participants

Recruitment dates: Between April 2009 and July 2011
Total N of recruited patients: NR
Inclusion criteria: All adult patients admitted for HCT
Exclusion criteria: NR
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 244
Total N of patients with valid results for both IGRA and TST: 210
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Test results, concordance between the TST and QFT-GIT results, development of tuberculosis
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 47 (35-55)
Women (n [%]): 107 [44]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 201 [82]
History of anti-TB treatment (n [%]): 10 [4]
Total incidence of active TB (n [%]): 2 [0.80]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): Acute myelogenous leukemia (72 [30]), acute lymphoblastic leukemia (28 [11]), chronic myelogenous leukemia (4 [2]), aplastic anemia (17 [7]), myelodysplastic syndrome (19 [8]), non-hodgkin's lymphoma (58 [24]), hodgkin's lymphoma (3 [1]), multiple myeloma (38 [16]), plasmacytoma (2 [1]), others (3 [1])
Co-morbidity (n [%]): Diabetes mellitus (25 [10]), hypertension (38 [16]), chronic kidney disease (21 [9]), ESRD with dialysis (1 [0.4]), hepatitis (16 [7]), HIV infection (0 [0.0]), non-hematologic malignancy (9 [4])
Type of during-study treatment (n [%]): Cyclosporine (71 [29]), cyclosporine-MTX (65 [27]), cyclosporine-corticosteroid (8 [3]), corticosteroid therapy (111 [46])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (specify): QFT-	244	40	170	34	210

GIT					
TST: ≥5mm	244	39	205	0	244
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST: 210

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NA
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT (Cellestis Limited, carnegie, Australia	We used the criteria for positive, negative, and indeterminate outcomes recommended by the manufacturer	Blood samples were collected before performing the TST to avoid a possible boosting effect of the TST on theQFT-GIT test. The lab technicians did not know the results of TST
TST (≥ 5mm)	The TST was carried out using the Mantoux technique, injecting a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm	≥ 5mm induration 48-72h after injection	NR

Association between test results and incidence of active TB (if applicable)

IGRA (QFT-GIT)				**TST≥5mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	1	39	40	TST +	0	39	39
IGRA -	1	169	170	TST -	2	203	205
Indeterminate	0	34	34 (excluded)	Indeterminate	0	0	0
Total	2	208	210	Total	2	242	244

Test performance parameters

IGRA	**TST**
Sensitivity = 1/2 = 50.00%, 95% CI (9.45, 90.55)	Sensitivity = 0/2 = 0.00%, 95% CI (0.00, 65.76)
Specificity = 169/208 = 81.25%, 95% CI (75.4, 85.97)	Specificity = 203/242 = 83.88% (95% CI: 78.73, 87.98)
PPV = 1/40 = 2.50%, 95% CI (0.44, 12.88)	PPV = 0/39 = 0.00% (95% CI: 0.0, 8.96)
NPV = 169/170 = 99.41%, 95% CI (96.74, 99.9)	NPV = 203/205 = 99.02% (95% CI: 96.51, 99.73)
Cumulative Incidence $_{IGRA+}$ = 1/40 = 2.50% (0.44, 12.88)	Cumulative Incidence $_{TST+}$ = 0/39 = 2.56% (95% CI: 0.06, 13.5)
Cumulative Incidence $_{IGRA-}$ = 1/170 = 0.58%, 95% CI (0.00, 3.59)	Cumulative Incidence $_{TST-}$ = 2/205 = 0.97% (95% CI: 0.03, 3.71)
Cumulative Incidence Ratio $_{IGRA}$ = 4.25, 95% CI	Cumulative Incidence Ratio $_{TST}$ = 2.63% (95%

(0.27, 66.49)	CI: 0.04, 51.4)
Incidence density rate $_{IGRA+}$ = 2.80 per 100 person-years, 95% CI (0.07, 15.81)	Incidence density rate $_{TST+}$ = 0 per 100 person-years, 95% CI (0.00, 8.00)
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence = 1.62% (95% CI: 0.16, 16.18)
Ratio of incidence density rate ratios = 1.62% (95% CI: 0.16, 16.18)
Other reported measure (risk difference between QFT $^{+}$ and TST $^{+}$) = 2.80 [95% CI: -2.39, 8.00]; NS

Association between test results and levels of TB exposure (if applicable)

IGRA				TST			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^{+} calculated) = NA	DOR (for T^{+} calculated) = NA
OR (crude; for T^{+} reported) = NA	OR (crude; for T^{+} reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^{+} calculated) = NA
Ratio of OR (crude; for T^{+} reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample (≥5 mm induration)

	TST +	TST -	Total
IGRA +	9	31	40
IGRA -	24	146	170
Indeterminate	6	28	34 (excluded)
Total	33	177	210

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): total (indeterminate excluded)
TST + threshold: ≥ 5mm induration

Parameters

Kappa = 0.09, 95% CI (-0.04, - 0.22) indeterminate excluded Kappa similar if indeterminate considered as QFT-negative
% concordance = 155/210 = 73.81%, 95% CI (67.47, 79.29)
% discordance = 55/210 = 26.19%, 95% CI (20.71, 32.53)

Stratification (≥10 mm induration**)**

	TST +	TST -	Total
IGRA +	8	32	40

IGRA -	13	157	170
Indeterminate	4	30	34 (excluded)
Total	21	189	210
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total (indeterminate excluded)			
TST + threshold: ≥ 10mm induration			
Parameters			
Kappa = 0.15, 95% CI (0.02, 0.27) indeterminate excluded Kappa similar if indeterminate considered as QFT-negative			
% concordance = 165/210 = = 78.57%, 95% CI (72.53, 83.58)			
% discordance = 45/210 = 21.43%, 95% CI (16.42, 27.47)			
Stratification (Patients with BCG scars)			
	TST + ≥ 5mm	TST -	Total
IGRA +	9	23	32
IGRA -	22	122	144
Indeterminate	0	0	0
Total	31	145	176
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Patients with BCG scars			
TST + threshold: ≥5 mm induration			
Parameters			
Kappa = 0.13, 95% CI (-0.02, 0.27) Kappa similar if threshold ≥10 mm			
% concordance = 131/176 = 74.43%, 95% CI (67.51, 80.31)			
% discordance = 45/176 = 25.57%, 95% CI (19.69, 32.49)			
Stratification (Patients without BCG scars or history of BCG vaccination)			
	TST≥ 5mm +	TST -	Total
IGRA +	0	8	8
IGRA -	2	24	26
Indeterminate	0	0	0
Total	2	32	34
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): Patients without BCG scars or history of BCG vaccination			
TST + threshold: ≥ 5mm induration			
Parameters			
Kappa = -0.10, 95% CI (-0.35, 0.14) Kappa similar if threshold ≥10 mm			
% concordance = 70.59%, 95% CI (53.83, 83.17)			
% discordance = 29.41%, 95% CI (16.83, 46.17)			
Other outcomes			
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**		**Health related quality of life mean score (SD) (specify)**
IGRA:	NR		NR
TST:	NR		NR
Test 3 (specify):	NA		NA
Conclusions			
Authors:			
The authors demonstrated that the frequencies of positive outcomes in the two TB screening tests were similar, but the overall agreement between the TST and the QFT-GIT test was poor, regardless of BCG vaccination.			

Reviewers:
The overall agreement between the TST and the QFT-GIT test was poor, regardless of BCG vaccination and TST threshold; tests were similar in detecting LTBI through predicting incidence of active TB (risk difference NS)
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; ESRD = end stage renal disease; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Sherkat 2014[155]
Country: Iran
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify): Hospital-based
Number of centres: NR
Total length of follow up (if applicable): 21 months (FU included 9 months prophylactic treatment and 12 months post transplantation)
Funding (government/private/manufacturer/other - specify): Nil

Aim of the study

To compare IGRA (T-SPOT .TB) and TST test in detection of LTBI in kidney transplant candidates and evaluate the agreement between the two tests

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Immunocompromised (kidney transplant candidates – end stage renal disease)

Participants

Recruitment dates: March 2010 to February 2011
Total N of recruited patients: NR
Inclusion criteria: Candidates for receiving a kidney transplant
Exclusion criteria: Active pulmonary and extrapulmonary TB, history of prior TB or isoniazid prophylactic treatment, refusal to continue prophylactic treatment, symptoms of isoniazid-induced hepatitis or drug reaction
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 44
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: between test agreement, incidence of active TB
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 44 (15.5)
Women (n [%]): 15 [66]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): NR
BCG vaccination (n [%]): 12 [27.3]
History of anti-TB treatment (n [%]): None
Total incidence of active TB (n [%]): 1/44 [2.27]
Chest radiography (yes/no): NR
Clinical examination (yes/no): Yes
Morbidity (n [%]): End stage renal disease
Co-morbidity (n [%]): Dialysis (30 [68.2]), hypertension (10 [22.7]), diabetes (10 [22.7]), obstructive uropathy (6 [13.6]), polycystic kidney (6 [13.6]), other renal etiologies (17 [38.6]), others (3 [6.8])
Type of during-study treatment (n [%]): isoniazid prophylaxis (10 [22.7])

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT):	NR	6	38	NR	44
TST:≥10mm	NR	8	36	NR	44
Test 3 (specify)					

Total N of patients with valid results for both IGRA and TST: 44

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group – NA	
Non-exposed	

Exposed 1 **(specify)**:	NR
Exposed 2 **(specify)**:	NR
Exposed 3 **(specify)**:	NR
Exposed 4 **(specify)**:	NR

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA [TSPOT]	T-SPOT .TB assay (Oxford Immunotec, Oxford, UK) was performed according to the manufacturers' recommendation and defined as positive, negative or indeterminate based on manufacturers' recommended criteria. Briefly, before the TST, 8 ml peripheral venous blood was collected and processed within 4 h. The peripheral blood mononuclear cells) were isolated by standard ficoll-hypaque density-gradient centrifugation. The PBMCs were counted and adjusted to a cell number of 2.5 × 10 PBMCs/1 ml. Four wells of the 96-well Microtitre plates (nil control, positive control, panel A and panel B), precoated with monoclonal antibody to gamma IFN, were seeded with 100 µl of 2.5 × 10 PBMCs/well. Two wells contained different peptide antigens (ESAT-6 [panel A] and CFP-10 [panel B]), the nil control well contained the cell in medium alone, and the positive control well contained the cell that was stimulated with phytohemagglutinin. After the appropriate incubation time (16-20 h) at in a humidified incubator at 37°C and 5% CO, the plates were washed with phosphate-buffered saline (PBS) four times. An appropriate volume of conjugate working solution was prepared (1:200 dilution in PBS) for the secondary incubation (60 min at 2-8°C) after which the wells was washed again (×4), as suggested above. Results are presented as the number of spot-forming cells and the reaction was observed visually		
TST≥10mm	TST was performed using the 5 IU	If induration size was	

	purified protein derivative (PPD) (Pasteur Institute, Tehran, Iran) injection into the volar aspect of the forearm intradermally by trained personnel. A positive test was defined by the size of induration (not the erythema) induced by PPD 48-72 h after the injection	≥10 mm, test was considered positive as recommended by local guidelines (Ministry of Health and Medical Education)	

Association between test results and incidence of active TB (if applicable)

IGRA [TSPOT]				TST≥10mm			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	1	5	6	TST +	1	7	8
IGRA -	0	38	38	TST -	0	36	36
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	1	43	44	Total	1	43	44

Test performance parameters

IGRA	TST
Sensitivity =1/1= 100% (95% CI: 20.65, 100)	Sensitivity = 1/1=100% (95% CI: 20.65, 100)
Specificity = 38/43=88.37% (95% CI: 75.52, 94.93)	Specificity = 36/43=83.72% (95% CI: 70.03, 91.88)
PPV= 1/6=16.67% (95% CI: 3.00, 56.35)	PPV= 1/8=12.5% (95% CI: 2.24, 47.09)
NPV= 38/38=100% (95% CI: 90.82, 100)	NPV= 36/36=100% (95% CI: 90.36, 100)
Cumulative Incidence $_{IGRA+}$ = 1/6=16.67% (95% CI: 3.00, 56.35)	Cumulative Incidence $_{TST+}$ = 1/8=12.5% (95% CI: 0.11, 47.09)
Cumulative Incidence $_{IGRA-}$ = 0/38=1.31 (95% CI: 0.00, 12.86)	Cumulative Incidence $_{TST-}$ = 0/36=1.39 (95% CI: 0.00, 13.49)
Cumulative Incidence Ratio $_{IGRA}$ =12.67 (95% CI: 0.47, 337.8)	Cumulative Incidence Ratio $_{TST}$ =9.00 (95% CI: 0.33, 245.7)
Incidence density rate $_{IGRA+}$ =NR	Incidence density rate $_{TST+}$= NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$= NA
Other reported measure $_{IGRA}$ =NR	Other reported measure $_{TST}$ =NR

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios=1.41 (95% CI: 0.13, 15.20)
Ratio of incidence density rate ratios=NA
Other reported measure= NA

Association between test results and levels of TB exposure (if applicable)

IGRA (specify)				TST (specify)			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
indeterminate	NA	NA	NA	indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV= NA	PPV= NA
NPV= NA	NPV= NA
DOR (for T^+ calculated)= NA	DOR (for T^+ calculated)= NA

OR (crude; for T^+ reported)= NA	OR (crude; for T^+ reported)= NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				TST (≥10mm)			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	2	4	6	TST +	2	6	8
IGRA -	10	28	38	TST -	10	26	36
indeterminate	NR	NR	NR	indeterminate	NR	NR	NR
Total	12	32	44	Total	12	32	44

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$= 1.40 (95% CI: 0.22, 8.85)	DOR (for T+ calculated)$_{TST}$ = 0.86 (95% CI: 0.14, 5.03)
OR (crude; for T^+ reported)= NR (p=0.658)	OR (crude; for T+ reported) = NR (p=1.00)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +≥10mm	TST -	Total
IGRA [TSPOT] +	4	2	6
IGRA [TSPOT] -	4	34	38
indeterminate	NR	NR	NR
Total	8	36	44

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Total
TST + threshold: ≥10mm

Parameters

Kappa = 0.49 (95% CI: 0.20, 0.78)
% concordance = 38/44=86.36% (95% CI: 73.29, 93.6)
% discordance = 6/44=13.64% (95% CI: 6.40, 26.71)

Stratification (specify group 1):

	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NA
TST + threshold: NA

Parameters

Kappa = NA
% concordance = NA
% discordance = NA

Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NA	NA	NA
IGRA -	NA	NA	NA
indeterminate	NA	NA	NA
Total	NA	NA	NA
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NA			
TST + threshold: NA			
Parameters			
Kappa = NA			
% concordance = NA			
% discordance = NA			
Conclusions			
Authors:			
In kidney transplant candidates both TST and T-SPOT .TB test were comparable for the diagnosis of LTBI with reasonable agreement between the tests. However, further studies are needed to determine the ability of T-SPOT .TB test to detect LTBI and to evaluate the need for prophylaxis in these patients			
Reviewers:			
There was no evidence indicating the superiority of IGRA over TST or vise versa in detecting LTBI; the between test agreement was good; BCG status did not influence TST differentially from TSPOT			
Abbreviations: DOR=diagnostic odds ratio; 95% CI= 95 percent confidence intervals; TB=tuberculosis; BCG=Bacillus Calmette–Guérin; PPV= positive predictive value; NPV=negative predictive value; FPR=false positive rate; FNR=false negative rate; SD=standard deviation			

Recently arrived

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Lucas 2010[145]
Country: Australia
Study design: Retrospective cohort/cross sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community based
Number of centres: NR
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** Oxford Immunotech.

Aim of the study

Comparative study of IGRAs and TST for the diagnosis of LTBI in 524 recently resettled refugee children

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Recently arrived people

Participants

Recruitment dates: January 2007 and March 2008
Total N of recruited patients: 524
Inclusion criteria: Children aged from 5 months to 16 years from refugee families attending the Migrant Health Unit
Exclusion criteria: NR
Total N of excluded patients: Incomplete TSPOT (n = 57) and TST (n = 37)
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 239 (three tests)
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: Association of test positivity with exposure, agreement
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 7.5 (2.8-11.9)
Women (n [%]): 260 [49.6]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): African (411 [78.4]) and Asian (113 [21.56])
BCG vaccination (n [%]): 361 [69.0]
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NR
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): Malaria (486 [92.7]), hepatitis B (356 [68.0]), hepatitis C (492 [94.0]), schistosomiasis (431 [82.2])
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (TSPOT):	420 completed tests	38	374	8	412
IGRA (QFT-GIT):	460 completed tests	45	345	70	390
TST:	304 completed tests	54	250	0	304

Total N of patients with valid results for both IGRA and TST: 239

Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group – Household TB contact	
Non-exposed	none
Exposed 1 **(specify):**	definite/suspected
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests			
	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (TSPOT)	In keeping with the manufacturer's instructions, 4 ml of blood were drawn for the T-SPOT.TB assay, except for children <2 years when 2-3 ml were drawn depending on ease of venepuncture	Inconclusive assays were defined by an inability to complete the test due to inadequate peripheral blood mononuclear cell (PBMC) yield after PBMC separation, high background, machine failure or red blood cell contamination. Indeterminate assays were defined as a low mitogen-positive control response or a high response to the negative control	NA
IGRA (QFT-GIT)	A 3 ml aliquot of blood was drawn from all study children and the assay was performed according to the manufacturers' protocols	Indeterminate assays were defined as a high IFNg response to the negative control or a low IFNg response to mitogen stimulation in the absence of a positive antigen response	NA
TST≥10mm	TST was performed with purified protein derivative (PPD) by administration of 5 tuberculin units following the Mantoux method. The transverse diameter of skin induration was measured at 48-72 h	NR	NA

Association between test results and incidence of active TB (if applicable)							
IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA

Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = NA	
Ratio of incidence density rate ratios = NA	
Other reported measure = NA	

Association between test results and levels of TB exposure (if applicable)

IGRA (TSPOT)				**TST (≥10 mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	8	Indeterminate	NR	NR	0
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = 2.50 (95% CI: 0.90, 6.50)	OR (crude; for T^+ reported) = 4.00 (95% CI: 1.70, 9.50)
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = 0.63 (95% CI: 0.32, 1.22)	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10 mm)**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	70	Indeterminate	NR	NR	0
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = 2.40 (95% CI: 1.00, 5.80)	OR (crude; for T^+ reported) = 4.00 (95% CI: 1.70, 9.50)
OR (regression-based; reported) = NR	OR (regression-based; reported) = NR

List of covariates: NA	List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 0.60 (95%CI: 0.32, 1.12)
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (TSPOT)				**TST (≥10 mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	70	Indeterminate	NR	NR	70
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = 1.80 (95% CI: 0.80, 4.00)	OR (crude; for T+ reported) = 1.70 (95% CI: 0.80, 3.50)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA (QFT-GIT)				**TST (≥10 mm)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	70	Indeterminate	NR	NR	70
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	**TST**
DOR (for T^+ calculated)$_{IGRA}$ = NA	DOR (for T+ calculated)$_{TST}$ = NA
OR (crude; for T^+ reported) = 1.70 (95% CI: 0.80, 3.60)	OR (crude; for T+ reported) = 1.70 (95% CI: 0.80, 3.50)
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NA	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST + ≥10mm	TST -	Total
IGRA (TSPOT) +	NR	NR	NR
IGRA (TSPOT) -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Total
TST + threshold: ≥10mm

Parameters

Kappa = 0.45 (95% CI: 0.38, 0.53)
% concordance = NR

% discordance = NR			
Between-test agreement, concordance, and discordance (if applicable) This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition			
Total sample			
	TST + ≥10mm	TST -	Total
IGRA (QFT-GIT) +	NR	NR	NR
IGRA (QFT-GIT) -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): total			
TST + threshold: ≥10mm			
Parameters			
Kappa = 0.46 (95% CI: 0.39, 0.53)			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2):			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
The two IGRAs showed similar positivity rates across all age groups. Both IGRAs gave an unacceptably high proportion of inconclusive results. Failed tests were the primary cause of inconclusive T-SPOT.TB assays whereas indeterminate results were the primary cause of inconclusive QFT-GIT assays. It is

reasonable to screen using either IGRA with follow-up by the alternative if the test fails. In general, the QFT-GIT is the preferred option for non-African populations but the T-SPOT.TB is recommended when there are epidemiological and/or clinical high risk factors for TB infection. However, both IGRAs have methodological and performance characteristics that limit their usefulness in refugee children, highlighting the need for continued development of screening strategies
Reviewers:
Three tests performed similarly
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Orlando 2010[146]
Country: Italy
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community-based (outpatient ward)
Number of centres: NR
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** The Provincia di Milano, Assessorato alle Politiche Sociali

Aim of the study

To compare the efficiency and efficacy of TST and QFT-IT for the detection of LTBI in recent immigrants from highly endemic countries by intention-to-treat (strategy efficiency) and per-protocol (test efficacy) analyses; this was achieved through the assessment of LTBI prevalence using the one-step TST and QFT-IT, analysis of test results' association, determinants of drop-out and influence of variables related to increased risk of TB exposure on the TST or QFT-IT strategy

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Recently arrived people

Participants

Recruitment dates: July 2005 and July 2007
Total N of recruited patients: NR
Inclusion criteria: NR
Exclusion criteria: Active TB
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 1130
Total N of patients with valid results for both IGRA and TST: 899
Methods of active TB diagnosis (if applicable): Clinical evaluation and chest X-rays were performed by experienced pneumologists
Outcomes (study-based) list: Agreement, association of test positivity with exposure
Characteristics of participants (total study sample)
Mean (range or SD) age (years): Median 35.3 years (IQR: 27.7–44.5)
Women (n [%]): 630 [55.7]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Latin America (562 [49.73]), Eastern Europe (308 [27.26]), Africa (181 [16.02%]), Asia (79 [6.99])
BCG vaccination (n [%]): 72 [6.37], Unknown (46 [4.07])
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): Yes
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): Treatment for LTBI was offered to 57 of the 79 eligible patients according to standard guidelines

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	1130	337	778	15 (undetermined)	1115
TST (≥10mm):	1129	407 (≥10mm)	492	230 (dropouts)	899

Test 3 (specify):	NA	NA	NA	NA	NA
Total N of patients with valid results for both IGRA and TST: 899					
Levels/groups of exposure to TB in increasing order (if applicable):					
Definition of exposure group - Continent					
Non-exposed	Africa (reference group)				
Exposed 1 **(specify):**	Asia				
Exposed 2 **(specify):**	East Europe				
Exposed 3 **(specify):**	Latin America				
	Definition of exposure group – TB prevalence				
Non-exposed	<50 (reference group)				
Exposed 1 **(specify):**	50-200				
Exposed 2 **(specify):**	>200				
	Definition of exposure group – contact with TB patient				
Non-exposed	No (reference group)				
Exposed 1 **(specify):**	Yes				
Tests					
	Assay used, methodology, timing for test measurement, manufacturer		**Cut-off values/thresholds Definition of test+**		**Other information**
IGRA	QuantiFERON-TB Gold In-Tube (QFT-IT) test (Cellestis Limited, Victoria, Australia): 1 ml of blood was drawn directly into QFT-IT blood collection tubes coated with saline (Nil-control), peptides of ESAT-6, CFP-10 and TB7.7(p4) proteins (MTB specific antigens—TB-antigen) and phytohaemaglutinin (PHA) (Mitogen-control) After overnight incubation at 37◦C, blood collection tubes were centrifuged for 15 min at 2,000–3,000g and stored at -80◦C before testing. The concentration of IFN-c (IU/ml) was determined using an ELISA assay QFT-GIT Analysis Software Version 2.50 (Cellestis Limited, Victoria, Australia) was used to analyse raw data and calculate results		The results were defined positive if the INF-c value after stimulation with TB-antigen minus the value in the Nilcontrol was ≥0.35 UI/ml and ≥25% of Nil; negative if value of TB-antigen minus Nil was<0.35 UI/ml or if that difference was ≥0.35 UI/ml and <25% of Nil, with Mitogen minus Nil ≥0.5 UI/ml; indeterminate for TB antigen minus Nil<0.35 UI/ml or ≥0.35 UI/ml and <25% of Nil, with Mitogen minus Nil<0.5 UI/ml, or every time Nil was >0.8 UI/ml		NA
TST	For TST, 0.1 mL (5U) of tuberculin purified protein derivative (Biocine test PPD		A TST ≥ 10 mm of induration was considered positive in persons recently		NA

	Liofilo, Novartis Vaccines and Diagnostics) was injected intradermally into the forearm. Participants were asked to come back for the evaluation of the delayed type hypersensitivity reaction (mean of the induration transverse diameters) 72 h later	arrived from highly endemic areas	

Association between test results and incidence of active TB (if applicable)

IGRA				TST			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters

IGRA	TST
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA
Other reported measure $_{IGRA}$ = NA	Other reported measure $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)

Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				TST (≥10mm)			
	Continent		Total		Continent		Total
	Asia	Africa			Asia	Africa	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	79	181	260	Total	79	181	260

Test performance parameters

IGRA (QFT-GIT)	TST (≥10mm)
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) =
Asia vs. Africa OR (crude; for T^+ reported) = 1.61 (95% CI: 0.90, 2.88)	**Asia vs. Africa** OR (crude; for T^+ reported) = 0.91 (95% CI: 0.50, 1.64)

Asia vs. Africa OR (regression-based; reported) = 1.07 (95% CI: 0.52, 2.23) List of covariates: NR	**Asia vs. Africa** OR (regression-based; reported) = 0.72 (95% CI: 0.34, 1.53) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 1.77 (95% CI: 1.16, 2.70)
Ratio of ORs (regression-based; reported) = 1.49 (95% CI: 0.87, 2.53)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	Continent		Total		Continent		Total
	East Europe	Africa			East Europe	Africa	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	308	181	489	Total	308	181	489

Test performance parameters

IGRA (QFT-GIT)	**TST (≥10mm)**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
East Europe vs. Africa OR (crude; for T^+ reported) = 1.46 (95% CI: 0.96, 2.23)	**East Europe vs. Africa** OR (crude; for T^+ reported) = 0.83 (95% CI: 0.55, 1.25)
East Europe vs. Africa OR (regression-based; reported) = 1.68 (95% CI: 0.91, 3.08) List of covariates: NR	**East Europe vs. Africa** OR (regression-based; reported) = 1.19 (95% CI: 0.66, 2.14) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 1.76 (95% CI: 1.30, 2.37)
Ratio of ORs (regression-based; reported) = 1.41 (95% CI: 0.92, 2.18)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	Continent		Total		Continent		Total
	Latin America	Africa			Latin America	Africa	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	562	181	743	Total	562	181	743

Test performance parameters

IGRA (QFT-GIT)	**TST (≥10mm)**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR

NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
Latin America vs. Africa OR (crude; for T^+ reported) = 1.46 (95% CI: 0.99, 2.16)	**Latin America vs. Africa** OR (crude; for T^+ reported) = 0.86 (95% CI: 0.59, 1.26)
Latin America vs. Africa OR (regression-based; reported) = 0.81 (95% CI: 0.46, 1.42) List of covariates: NR	**Latin America vs. Africa** OR (regression-based; reported) = 0.57 (95% CI: 0.33, 1.00) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 1.70 (95% CI: 1.29, 2.24)
Ratio of ORs (regression-based; reported) = 1.42 (95% CI: 0.95, 2.24)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	TB prevalence		Total		TB prevalence		Total
	50-200	**<50**			**50-200**	**<50**	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA (QFT-GIT)	**TST (≥10mm)**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
50-200 vs. <50 OR (crude; for T^+ reported) = 1.76 (95% CI: 1.10, 2.80)	**50-200 vs. <50** OR (crude; for T^+ reported) = 0.66 (95% CI: 0.44, 1.01)
50-200 vs. <50 OR (regression-based; reported) = 1.34 (95% CI: 0.72, 2.49) List of covariates: NR	**50-200 vs. <50** OR (regression-based; reported) = 0.70 (95% CI: 0.39, 1.25) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 2.67 (95% CI: 1.94, 3.67)
Ratio of ORs (regression-based; reported) = 1.91 (95% CI: 1.24, 2.95)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	TB prevalence		Total		TB prevalence		Total
	>200	**<50**			**>200**	**<50**	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA (QFT-GIT)	**TST (≥10mm)**

Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
>200 vs. <50 OR (crude; for T^+ reported) = 2.31 (95% CI: 1.48, 3.61)	**>200 vs. <50** OR (crude; for T^+ reported) = 0.99 (95% CI: 0.66, 1.48)
>200 vs. <50 OR (regression-based; reported) = 2.72 (95% CI: 1.70, 5.02) List of covariates: NR	**>200 vs. <50** OR (regression-based; reported) = 1.45 (95% CI: 0.80, 2.62) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 2.33 (95% CI: 1.72, 3.17)
Ratio of ORs (regression-based; reported) = 1.88 (95% CI: 1.25, 2.83)
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA (QFT-GIT)				**TST (≥10mm)**			
	Contact with TB case		Total		Contact with TB case		Total
	Yes	**No**			**Yes**	**No**	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA (QFT-GIT)	**TST (≥10mm)**
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
Contact vs. No contact OR (crude; for T^+ reported) = 2.54 (95% CI: 1.82, 3.54)	**Contact vs. No contact** OR (crude; for T^+ reported) = 1.87 (95% CI: 1.30, 2.69)
Contact vs. No contact OR (regression-based; reported) = 2.11 (95% CI: 1.47, 3.03) List of covariates: NR	**Contact vs. No contact** OR (regression-based; reported) = 1.87 (95% CI: 1.24, 2.80) List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)

Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = 1.36 (95% CI: 1.06, 1.75)
Ratio of ORs (regression-based; reported) = 1.13 (95% CI: 0.85, 1.49)
Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR

Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR
Test performance parameters							
IGRA				**TST**			
DOR (for T^+ calculated)$_{IGRA}$ = NR				DOR (for T+ calculated)$_{TST}$ = NR			
OR (crude; for T^+ reported) = NR				OR (crude; for T+ reported) = NR			
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR				OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR			
Other reported measure = NR				Other reported measure = NR			
Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**							
Total sample							
	TST +			TST -			Total
IGRA +	NR			NR			NR
IGRA -	NR			NR			NR
Indeterminate	NR			NR			NR
Total	NR			NR			887
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): Total							
TST + threshold: ≥ 10mm							
Parameters							
Kappa = 0.38 (95% CI: NR)							
% concordance = 625/887 = 70.46% (95% CI: 67.32, 73.43)							
% discordance = 262/887 = 29.53% (95% CI: NR)							
Stratification (BCG vaccinated)							
	TST +			TST -			Total
IGRA +	NR			NR			NR
IGRA -	NR			NR			NR
Indeterminate	NR			NR			NR
Total	NR			NR			56
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG vaccinated							
TST + threshold: ≥10mm							
Parameters							
Kappa = 0.35 (95% CI: NR)							
% concordance = 37/56 = 66.07% (95% CI: 52.09, 77.84)							
% discordance = 19/56 = 33.92% (95% CI: NR)							
Stratification (BCG non-vaccinated)							
	TST +			TST -			Total
IGRA +	NR			NR			NR
IGRA -	NR			NR			NR
Indeterminate	NR			NR			NR
Total	NR			NR			789
Description							
Sample definition (e.g., total, if stratified by BCG or condition – specify): BCG non-vaccinated							
TST + threshold: ≥ 10mm							
Parameters							
Kappa = 0.40 (95% CI: NR)							
% concordance = 563/789 = 71.36% (95% CI: 68.04, 74.46)							
% discordance = 226/789 = 28.64% (95% CI: NR)							
Other outcomes							
Test and cut-off (if applicable)			**Adverse events n/N (%) (specify)**			**Health related quality of life mean score (SD)**	

		(specify)
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
Continent of origin, class of TB prevalence in the country of origin and contacts with TB patients were found to be significantly associated with the probability of TST and QFT-IT positive result; The drawback of the TST screening strategy in recent immigrants from highly endemic countries is due to low sensitivity/specificity of the test and to high drop-out rate with an overall significant lowering in strategy efficacy/efficiency. Disagreement is due to differences in sensitivity/specificity and in rate of drop-out which is higher for the TST		
Reviewers:		
Kappa was influenced by BCG status which was higher in non-vaccinated people; QFT performed better than TST in relation to contact with TB and TB prevalence; TST was better than QFT in relation to continent		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Saracino 2009[147]
Country: Italy
Study design: Retrospective cohort/cross-sectional study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community-based
Number of centres: NR
Total length of follow up (if applicable): NA
Funding (government/private/manufacturer/other - specify)**:** NR

Aim of the study

To evaluate the agreement between QFT-GIT and TST for latent TB screening in a population of recent immigrants to Italy from high-incidence countries

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Recently arrived people

Participants

Recruitment dates: September 2004 and December 2005
Total N of recruited patients: NR
Inclusion criteria: Recent (less than two months) immigrants to Italy
Exclusion criteria: Active TB, HIV
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: 452
Total N of patients with valid results for both IGRA and TST: 279
Methods of active TB diagnosis (if applicable): NA
Outcomes (study-based) list: Agreement, associations of test positivity and risk factors (born in a country of TB burden, region of origin)
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 27.1 (6.2)
Women (n [%]): 11 [4]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): African (135 [48.4]), Eastern Mediterranean (131 [46.95]), European (7 [2.5]), South-East Asian (6 [2.2])
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): NA
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): NR
Co-morbidity (n [%]): NR
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	452	107	172	173 (169 dropouts and 4 HIV/active TB)	279
TST (≥10mm):	452	72	207	173 (169 dropouts and 4	279

				HIV/active TB)	

Total N of patients with valid results for both IGRA and TST: 279	
Levels/groups of exposure to TB in increasing order (if applicable):	
Definition of exposure group	
Non-exposed	NR
Exposed 1 **(specify):**	30-100
Exposed 2 **(specify):**	101-200
Exposed 3 **(specify):**	201-300
Exposed 4 **(specify):**	>301
Definition of exposure group – Region of origin	
Non-exposed	NR
Exposed 1 **(specify):**	African
Exposed 2 **(specify):**	Eastern Mediterranean
Exposed 3 **(specify):**	European
Exposed 4 **(specify):**	South-East Asian

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	QFT-GIT (Cellestis, Carnegie, Australia) was performed, according to the manufacturer's instructions, by collecting 1mL of whole heparinized blood in two tubes, one containing only heparin as negative control, and the other containing three MT specific antigens: ESAT-6, CFP-10 and TB 7.7 (p4). Tubes were kept at room temperature for a maximum of 16 hours and then incubated at 37°C for 16-24 hours; the tubes were then centrifuged, and the plasma removed and harvested to perform the ELISA. The IFN-γ value for TB-specific antigens was corrected by subtracting the value obtained for the respective negative controls	the test was considered positive if the IFN-γ level was above the cut-off test value (≥0.35 IU/mL)	NA
TST (≥10mm)	TST was administered by injecting 0.1 mL of the standard test dose (5 tuberculin unit, TU) of PPD (BiocineTest-PPD®; Chiron S.r.l., Sovicille, Siena, Italy) according to the Mantoux method	Skin induration was evaluated after 72 hours and considered positive if ≥10 mm. Cut-off points of 5 mm and 15 mm, respectively, were also used for comparison	NA

Association between test results and incidence of active TB (if applicable)

IGRA				**TST**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA

Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
Cumulative Incidence $_{IGRA+}$ = NA	Cumulative Incidence $_{TST+}$ = NA
Cumulative Incidence $_{IGRA-}$ = NA	Cumulative Incidence $_{TST-}$ = NA
Cumulative Incidence Ratio $_{IGRA}$ = NA	Cumulative Incidence Ratio $_{TST}$ = NA
Incidence density rate $_{IGRA+}$ = NA	Incidence density rate $_{TST+}$ = NA
Incidence density rate $_{IGRA-}$ = NA	Incidence density rate $_{TST-}$ = NA
Incidence density rate ratio $_{IGRA}$ = NA	Incidence density rate ratio $_{TST}$ = NA

Comparison between tests (IGRA vs. TST)
Ratio of cumulative incidence ratios = NA
Ratio of incidence density rate ratios = NA
Other reported measure = NA

Association between test results and levels of TB exposure (if applicable)

IGRA						TST					
	Exposure level Region of origin				Total		Exposure level Region of origin				Total
	South-East Asia	Europe	Eastern Mediterranean	Africa			South-East Asia	Europe	Eastern Mediterranean	Africa	
IGRA+	NR	NR	NR	NR	107	TST+	NR	NR	NR	NR	72
IGRA-	NR	NR	NR	NR	172	TST -	NR	NR	NR	NR	207
Indeterminate	NR	NR	NR	NR	173 (excluded)	Indeterminate	NR	NR	NR	NR	173 (excluded)
Total	6	7	131	135	279	Total	6	7	131	135	279

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T+ reported) = Africa: OR = 1.00, 95% CI: 0.60, 1.70 Eastern Mediterranean: OR = 1.00, 95% CI: 0.60, 1.70 Europe: OR = 1.20, 95% CI: 0.20, 7.30 South-East Asia: OR = 0.30, 95% CI: 0.01,	OR (crude; for T+ reported) = Africa: OR = 1.10, 95% CI: 0.60, 1.90 Eastern Mediterranean: OR = 0.80, 95% CI: 0.50, 1.40 Europe: OR = 4.00, 95% CI: 0.70, 27.80 South-East Asia: OR = 0.60, 9% CI: 0.10, 5.20

2.90	
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = 0.91 (95% CI: 0.61, 1.35) [Africa vs. reference group]	
Ratio of ORs (regression-based; reported) = NA	
Other reported measure = NA	

Association between test results and levels of TB exposure (if applicable)											
IGRA (QFT-GIT)						**TST (≥10mm)**					
	Exposure level Born in a country with a TB burden (# cases per 100,000)				Total		Exposure level Born in a country with a TB burden (# cases per 100,000)				Total
	>301	201-300	101-200	30-100			>301	201-300	101-200	30-100	72
IGRA +	NR	NR	NR	NR	107	TST +	NR	NR	NR	NR	207
IGRA -	NR	NR	NR	NR	172	TST -	NR	NR	NR	NR	173 (excluded)
Indeterminate	NR	NR	NR	NR	173 (excluded)	Indeterminate	NR	NR	NR	NR	279
Total	54	197	15	12	279	Total	54	197	15	12	72

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
30-100: OR (crude; for T+ reported) = 1.20, 95% CI: 0.30, 4.30 101-200: OR (crude; for T+ reported) = 0.80, 95% CI: 0.20, 2.60 201-300: OR (crude; for T+ reported) = 1.00, 95% CI: 0.60, 1.80 >301: OR (crude; for T+ reported) = 1.00, 95% CI: 0.50, 2.00	30-100: OR (crude; for T+ reported) = 3.00, 95% CI: 0.80, 11.8 101-200: OR (crude; for T+ reported) = 1.00, 95% CI: 0.20, 3.70 201-300: OR (crude; for T+ reported) = 0.80, 95% CI: 0.40, 1.40 >301: OR (crude; for T+ reported) = 1.00, 95% CI: 0.50, 2.10
OR (regression-based; reported) = NR List of covariates: NA	OR (regression-based; reported) = NR List of covariates: NA
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = NA	
Ratio of OR (crude; for T^+ reported) = 1.00 (95% CI: 0.60, 1.66) [>301 vs. reference group]	
Ratio of ORs (regression-based; reported) = NA	

Other reported measure = NA

Association between test results and BCG status (if applicable)

IGRA (specify)				**TST (specify)**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	49	58	107
IGRA -	23	149	172
Indeterminate	NR	NR	173 (excluded)
Total	72	207	279

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): Total

TST + threshold: ≥10mm

Parameters

Kappa = 0.35 (95% CI: 0.23, 0.46)

% concordance = 198/279 = 70.97% (95% CI: 65.39, 75.98)

% discordance = 81/279 = 29.03% (95% CI: 24.02, 34.61)

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR

Parameters

Kappa = NR

% concordance = NR

% discordance = NR

Stratification (specify group 2)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description

Sample definition (e.g., total, if stratified by BCG or condition – specify): NR		
TST + threshold: NR		
Parameters		
Kappa = NR		
% concordance = NR		
% discordance = NR		
Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR
Conclusions		
Authors:		
The findings indicate that QFT-GIT could be useful for screening recent immigrants with a high rate of unavailable TST results. The overall agreement between QFT-GIT and TST was 70.9%, with a k statistics of 0.35. No single demographic characteristic including sex, age, region of origin and TB burden in the country of origin, was associated with TST and/or QFT-GIT positivity		
Reviewers:		
None of the risk factors was associated with test positivity of either IGRA or TST		
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation		

Name of first reviewer: AlexanderTsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Harstad 2010[143]
Country: Norway
Study design: Prospective cohort study
Study setting (e.g., outbreak investigation, community-based - specify)**:** Community - based
Number of centres: NR
Total length of follow up (if applicable): 23-32 months
Funding (government/private/manufacturer/other - specify)**:** Norwegian Health Association; The Regional Health Authorities

Aim of the study

To compare PPV and NPV between QuantiFERON®-TB Gold (QFT-G) and the TST in asylum seekers in Norway

Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)

Recently arrived people

Participants

Recruitment dates: September 2005 to June 2006
Total N of recruited patients: NR
Inclusion criteria: Asylum seekers aged ≥18 years
Exclusion criteria: Active TB
Total N of excluded patients: NR
Total N of patients tested with both IGRA and TST: NR
Total N of patients with valid results for both IGRA and TST: 823
Methods of active TB diagnosis (if applicable): NR
Outcomes (study-based) list: PPV and NPV
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 18–34 yrs (n = 587), 35–49 yrs (n = 201), and ≥ 50 yrs (n = 35)
Women (n [%]): 206 [25.0]
Race/ethnicity (n [%]): NR
Geographic origin (n[%]): Europe (103[12.5]), Africa (347[42.0]), Asia (346[42.0]), other (27[3.3])
BCG vaccination (n [%]): NR
History of anti-TB treatment (n [%]): NR
Total incidence of active TB (n [%]): 9/823 [1.1]
Chest radiography (yes/no): Yes
Clinical examination (yes/no): NR
Morbidity (n [%]): NA
Co-morbidity (n [%]): NA
Type of during-study treatment (n [%]): NR

Number of patients tested

	Total N (tested)	Total N (test+)	Total N (test-)	Total N (indeterminate)	Total N (test results available)
IGRA (QFT-GIT):	NR	246	577	NR	823
TST:	NR	426 (≥ 6mm) 128 (≥15mm)	395 (<6mm) 693 (<15mm)	NR	821
Test 3 (specify):	NA	NA	NA	NA	NA

Total N of patients with valid results for both IGRA and TST:

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NA

Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	Cut-off values/thresholds Definition of test+	Other information
IGRA	QuantiFERON-TB Gold In-Tube, Cellestis Ltd, Carnegie, VIC, Australia)	NR	NA
TST	TSTs (purified protein derivative RT 23, 2 tuberculin units [TU] from Statens Serum Institute, Copenhagen, Denmark)	≥ 6mm ≥15mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA (QFT-GIT)				TST ≥ 6mm			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	8	230	238	TST +(≥ 6mm)	8	407	415
IGRA -	1	576	577	TST – (<6mm)	1	394	395
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	9	806	815	Total	9	801	810

Test performance parameters

IGRA	TST
Sensitivity = 8/9 = 88.89% (95% CI: 56.5, 98.01)	Sensitivity = 8/9 = 88.89% (95% CI: 56.5, 98.01)
Specificity = 576/806 = 71.46% (95% CI: 68.25, 74.47)	Specificity = 394/801 = 49.19% (95% CI: 45.74, 52.65)
PPV = 8/238 = 3.36% (95% CI: 1.71, 6.49)	PPV = 8/415 = 1.92% (95% CI: 0.98, 3.75)
NPV = 576/577 = 99.83% (95% CI: 99.02, 99.97)	NPV = 394/395 = 99.75% (95% CI: 98.58, 99.96)
Cumulative Incidence $_{IGRA+}$ = 8/238 = 3.36% (95% CI: 1.71, 6.49)	Cumulative Incidence $_{TST+}$ = 8/415 = 1.92% (95% CI: 0.98, 3.75)
Cumulative Incidence $_{IGRA-}$ = 1/577 = 0.17% (95% CI: 0.00, 1.08)	Cumulative Incidence $_{TST-}$ = 1/395 = 0.25% (95% CI: 0.00, 1.57)
Cumulative Incidence Ratio $_{IGRA}$ = 19.39 (95% CI: 2.43, 154.2)	Cumulative Incidence Ratio $_{TST}$ = 7.61 (95% CI: 0.95, 60.59)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR

Comparison between tests (IGRA vs. TST⩾6mm)

Ratio of cumulative incidence ratios = 2.55(95% CI: 0.57, 11.40)
Ratio of incidence density rate ratios = NR
Other reported measure = NR

Association between test results and incidence of active TB (if applicable)

TST (≥ 15mm)

	Incidence of active TB		Total
	Yes	No	
TST + (≥	3	118	121

15mm)			
TST -(< 15mm)	6	686	692
Indeterminate	NR	NR	NR
Total	9	804	813

Test performance parameters (TST≥ 15mm)
Sensitivity = 3/9 = 33.33% (95% CI: 12.06, 64.58)
Specificity = 686/804 = 85.32% (95% CI: 82.71, 87.60)
PPV = 3/121 = 2.48% (95% CI: 0.84, 7.03)
NPV = 686/692 = 99.13% (95% CI: 98.12, 99.6)
Cumulative Incidence $_{IGRA+}$ 3/121 = 2.48% (95% CI: 0.84, 7.03)
Cumulative Incidence $_{IGRA-}$ = 6/692 = 0.86% (95% CI: 0.35, 1.92)
Cumulative Incidence Ratio $_{IGRA}$ = 2.86 (95% CI: 0.725, 11.28)
Incidence density rate $_{IGRA+}$ = NR
Incidence density rate $_{IGRA-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR
Comparison between tests (IGRA vs. TST⩾15mm)
Ratio of cumulative incidence ratios = 0.38(95% CI: 0.11, 1.34)
Ratio of incidence density rate ratios = NR
Other reported measure = NR
Association between test results and levels of TB exposure (if applicable)

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NA	NA	NA	TST +	NA	NA	NA
IGRA -	NA	NA	NA	TST -	NA	NA	NA
Indeterminate	NA	NA	NA	Indeterminate	NA	NA	NA
Total	NA	NA	NA	Total	NA	NA	NA

Test performance parameters	
IGRA	**TST**
Sensitivity = NA	Sensitivity = NA
Specificity = NA	Specificity = NA
PPV = NA	PPV = NA
NPV = NA	NPV = NA
DOR (for T^+ calculated) = NA	DOR (for T^+ calculated) = NA
OR (crude; for T^+ reported) = NA	OR (crude; for T^+ reported) = NA
OR (regression-based; reported) = NA List of covariates: NA	OR (regression-based; reported) = NA List of covariates: NA
Other reported measure = NA	Other reported measure = NA

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NA
Ratio of OR (crude; for T^+ reported) = NA
Ratio of ORs (regression-based; reported) = NA
Other reported measure = NA
Association between test results and BCG status (if applicable)

IGRA				**TST**			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters	
IGRA	**TST**

DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable) **This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition**			
Total sample			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 1)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
Neither PPV nor NPV differed significantly from the corresponding values for TST
Reviewers:
Small sample; differences in follow up between test positives and negatives may have biased the results; some cases may have been prevalent (not incident)
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details
First author surname year of publication: Kik 2010[144] (companion**:** Kik 2009) **Country:** The Netherlands **Study design:** Prospective cohort study **Study setting** (e.g., outbreak investigation, community-based - specify)**:** Community-based **Number of centres:** Multicenter (n = 15) **Total length of follow up (if applicable):** 24 mo **Funding** (government/private/manufacturer/other - specify)**:** Unrestricted grants from the Netherlands Organization for Health Research and Development (ZonMw; the Hague, the Netherlands)
Aim of the study
To assess the positive/negative predictive values (PPV/NPV), sensitivity, and specificity for TB disease of QFT-GIT, T-SPOT.TB1 and TST in immigrant individuals in the Netherlands who were recently exposed to infectious pulmonary TB patients
Subgroup of interest (i.e., children, recently arrived people, immunocompromised people)
Recently arrived people
Participants
Recruitment dates: April 2005 to July 2007 **Total N of recruited patients:** 433 **Inclusion criteria:** Close contacts (aged ≥16 yrs and born in a TB endemic country) of sputum smear-positive pulmonary TB patients who tested positive on TST (≥5mm) **Exclusion criteria:** Contacts with known conditions associated with an increased risk of progression to disease (including diabetes and HIV infection) and individuals who were given preventive treatment **Total N of excluded patients:** 94 (TST<5mm) **Total N of patients tested with both IGRA and TST:** 339 **Total N of patients with valid results for both IGRA and TST:** 327 **Methods of active TB diagnosis (if applicable):** Contacts diagnosed with TB ≥ 3 months after the diagnosis of the index patient were considered to be incident cases, whereas TB cases diagnosed < 3 months after the diagnosis of the index patient were considered to be co-prevalent and were excluded from the analysis. The diagnosis of TB disease was based on chest radiography, symptoms, smear and/or culture results **Outcomes (study-based) list:** PPV/NPV, sensitivity, and specificity for the incidence of TB disease for QFT-GIT, T-SPOT.TB1 and TST **Characteristics of participants (total study sample)** Mean (range or SD) age (years): n = 53 [15.6%] (range: 16–24), n = 80 [23.6%] (range: 25–34), n = 115 [33.9%] (range: 35–44), and n = 91 [26.8%] (range: ≥45) Women (n [%]): 147 [43.4] Race/ethnicity (n [%]): NR Geographic origin (n[%]): Europe/North America (27 [8.0]), South America (27 [8.0]), Asia (123 [36.3]), Other Africa (98 [28.9]), Sub-Saharan Africa (59 [17.4]), Unknown (5 [1.5]) BCG vaccination (n [%]): 274 [80.8] History of anti-TB treatment (n [%]): None Total incidence of active TB (n [%]): 9/339 [2.65] Chest radiography (yes/no): Yes Clinical examination (yes/no): Yes Morbidity (n [%]): NR Co-morbidity (n [%]): NR Type of during-study treatment (n [%]): None
Number of patients tested

	Total N (tested)	**Total N**	**Total N (test-)**	**Total N (indeterminate)**	**Total N (test results**

		(test+)			available)
IGRA (QFT-GIT)	339	178	149	12	327
IGRA (T-SPOT.TB)	339	181	118	40	299
TST (≥10mm)	339	288	51	0	339
TST (≥15mm)	322	184	138	0	322

Total N of patients with valid results for both IGRA and TST: TST (n = 339), QFT-GIT (n = 327), and T-SPOT.TB (n = 299)

Levels/groups of exposure to TB in increasing order (if applicable):

Definition of exposure group	
Non-exposed	NA
Exposed 1 **(specify):**	NA
Exposed 2 **(specify):**	NA
Exposed 3 **(specify):**	NA
Exposed 4 **(specify):**	NA

Tests

	Assay used, methodology, timing for test measurement, manufacturer	**Cut-off values/thresholds Definition of test+**	**Other information**
IGRA (QFT-GIT)	Performed according to the instructions of the manufacturers and tested in a single laboratory (Leiden University Medical Center, Leiden, the Netherlands)	Two-tube format positive test was defined as ≥ 0.35 IU/mL-[1]	NA
IGRA (T-SPOT.TB)	Performed according to the instructions of the manufacturers and tested in a single laboratory (Leiden University Medical Center, Leiden, the Netherlands)	Interpretation of results was according to the latest criteria defined by the manufacturer	NA
TST	two tuberculin units, purified protein derivative RT23 in Tween-80; Statens Serum Institute, Copenhagen, Denmark) and read after 48–72 h	≥ 10mm ≥ 15mm	NA

Association between test results and incidence of active TB (if applicable)

IGRA(QFT-GIT)				**TST≥10mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	5	173	178	TST +	9	279	288
IGRA -	3	146	149	TST -	0	51	51
Indeterminate	1	11	12	Indeterminate	0	0	0
Total	9	330	339	Total	9	330	339

Test performance parameters

IGRA (excluding indeterminate)	**TST**
Sensitivity = 5/8 = 62.50% (95% CI: 30.57, 86.32)	Sensitivity = 9/9 = 100.00% (95% CI: 70.08, 100.00)
Specificity = 146/319 = 45.77% (95% CI: 40.38, 51.25)	Specificity = 51/330 = 15.45% (95% CI: 11.95, 19.75)
PPV = 5/178 = 2.80% (95% CI: 1.20, 6.40)	PPV = 9/288 = 3.12% (95% CI: 1.65, 5.83)
NPV = 146/149 = 98.0% (95% CI: 94.20, 99.31)	NPV = 51/51 = 100.00% (95% CI: 93.00, 100.00)
Cumulative Incidence $_{IGRA+}$ = 5/178 = 2.80%	Cumulative Incidence $_{TST+}$ = 9/288 = 3.12%

(95% CI: 1.20, 6.40)	(95% CI: 1.65, 5.83)
Cumulative Incidence $_{IGRA-}$ = 3/149 = 2.00% (95% CI: 0.42, 6.02)	Cumulative Incidence $_{TST-}$ = 0/51 = 1.96 (95% CI:0.21, 10.4)
Cumulative Incidence Ratio $_{IGRA}$ = 1.39 (95% CI: 0.34, 5.74)	Cumulative Incidence Ratio $_{TST}$ = 1.59 (95% CI: 0.21, 71.2)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Other reported measure $_{IGRA}$ = NR	Other reported measure $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = 0.87 (95% CI: 0.17, 4.56)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and incidence of active TB (if applicable)	

IGRA (T-SPOT.TB)				**TST≥15mm**			
	Incidence of active TB		Total		Incidence of active TB		Total
	Yes	No			Yes	No	
IGRA +	6	175	181	TST +	7	177	184
IGRA -	2	116	118	TST -	1	137	138
Indeterminate	1	39	40	Indeterminate	0	0	0
Total	9	330	339	Total	8	314	322

Test performance parameters	
IGRA (excluding indeterminate)	**TST**
Sensitivity = 6/8 = 75.00% (95% CI: 40.93, 92.85)	Sensitivity = 7/8 = 87.5% (95% CI: 52.91, 97.76)
Specificity = 116/291 = 39.86% (95% CI: 34.4, 45.58)	Specificity = 137/314 = 43.63% (95% CI: 38.25, 49.16)
PPV = 6/181 = 3.31% (95% CI: 1.52, 7.04)	PPV = 7/184 = 3.80% (95% CI: 1.85, 7.64)
NPV = 98.31% (95% CI: 94.03, 99.53)	NPV = 137/138 = 99.28% (95% CI: 96.01, 99.87)
Cumulative Incidence $_{IGRA+}$ = 6/181 = 3.31% (95% CI: 1.52, 7.04)	Cumulative Incidence $_{TST+}$ = 7/184 = 3.80% (95% CI: 1.85, 7.64)
Cumulative Incidence $_{IGRA-}$ = 2/118 = 1.69% (95% CI: 0.08, 6.35)	Cumulative Incidence $_{TST-}$ = 1/138 = 0.72% (95% CI:0.00, 4.39)
Cumulative Incidence Ratio $_{IGRA}$ = 1.95 (95% CI: 0.40, 9.52)	Cumulative Incidence Ratio $_{TST}$ = 5.25 (95% CI: 0.65, 42.17)
Incidence density rate $_{IGRA+}$ = NR	Incidence density rate $_{TST+}$ = NR
Incidence density rate $_{IGRA-}$ = NR	Incidence density rate $_{TST-}$ = NR
Incidence density rate ratio $_{IGRA}$ = NR	Incidence density rate ratio $_{TST}$ = NR
Comparison between tests (IGRA vs. TST)	
Ratio of cumulative incidence ratios = 0.37(95% CI: 0.10, 1.41)	
Ratio of incidence density rate ratios = NR	
Other reported measure = NR	
Association between test results and levels of TB exposure (if applicable)	

IGRA				**TST**			
	Exposure level		Total		Exposure level		Total
	High/Yes	Low/No			High/Yes	Low/No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
Sensitivity = NR	Sensitivity = NR
Specificity = NR	Specificity = NR
PPV = NR	PPV = NR
NPV = NR	NPV = NR
DOR (for T^+ calculated) = NR	DOR (for T^+ calculated) = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T^+ reported) = NR
OR (regression-based; reported) = NR List of covariates: NR	OR (regression-based; reported) = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Comparison between tests (IGRA vs. TST)
Ratio of DORs (for T^+ calculated) = NR
Ratio of OR (crude; for T^+ reported) = NR
Ratio of ORs (regression-based; reported) = NR
Other reported measure = NR

Association between test results and BCG status (if applicable)

IGRA				TST			
	BCG status		Total		BCG status		Total
	Yes	No			Yes	No	
IGRA +	NR	NR	NR	TST +	NR	NR	NR
IGRA -	NR	NR	NR	TST -	NR	NR	NR
Indeterminate	NR	NR	NR	Indeterminate	NR	NR	NR
Total	NR	NR	NR	Total	NR	NR	NR

Test performance parameters

IGRA	TST
DOR (for T^+ calculated)$_{IGRA}$ = NR	DOR (for T+ calculated)$_{TST}$ = NR
OR (crude; for T^+ reported) = NR	OR (crude; for T+ reported) = NR
OR (regression-based; reported) $_{IGRA}$ = NR List of covariates: NR	OR (regression-based; reported) $_{TST}$ = NR List of covariates: NR
Other reported measure = NR	Other reported measure = NR

Between-test agreement, concordance, and discordance (if applicable)
This table may be stratified by TST cut-off value, BCG vaccination status, and/or condition

Total sample

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR
TST + threshold: NR

Parameters
Kappa = NR
% concordance = NR
% discordance = NR

Stratification (specify group 1)

	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR

Description
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR

TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			
Stratification (specify group 2)			
	TST +	TST -	Total
IGRA +	NR	NR	NR
IGRA -	NR	NR	NR
Indeterminate	NR	NR	NR
Total	NR	NR	NR
Description			
Sample definition (e.g., total, if stratified by BCG or condition – specify): NR			
TST + threshold: NR			
Parameters			
Kappa = NR			
% concordance = NR			
% discordance = NR			

Other outcomes		
Test and cut-off (if applicable)	**Adverse events n/N (%) (specify)**	**Health related quality of life mean score (SD) (specify)**
IGRA:	NR	NR
TST:	NR	NR
Test 3 (specify):	NR	NR

Conclusions
Authors:
PPVs of QFT-GIT and T-SPOT.TB for subsequent development of TB disease during the first 2 yrs after a contact investigation were comparable to that of the TST, irrespective of the TST cut off (10 or 15 mm)
Reviewers:
The three tests demonstrated similar performance in predicting active TB incidence (PPV and sensitivity); TST (≥15mm) and QFT-GIT demonstrated better specificity compared to TST (≥15mm) and TSPOT.TB
Abbreviations: DOR = diagnostic odds ratio; 95% CI = 95 percent confidence intervals; TB = tuberculosis; BCG = Bacillus Calmette–Guérin; PPV = positive predictive value; NPV = negative predictive value; FPR = false positive rate; FNR = false negative rate; SD = standard deviation

Appendix 10 Included studies and incidence of tuberculosis[228]

TABLE 58 Included studies and incidence of TB

Study ID, country	Category[a]	Estimated rate per 100,000 population
Studies in children and adolescents: incidence studies		
Diel 2011,[102] Germany	Low incidence	5.6
Mahomed 2011,[103] South Africa	High incidence	1003
Metin Timur 2014,[150] Turkey	Intermediate incidence	22
Noorbakhsh 2011,[104] Iran	Intermediate incidence	21
Song 2014,[152] South Korea	High incidence	409
Studies in children and adolescents: exposure studies		
Adetifa 2010,[105] Gambia	High incidence	284
Cruz 2011,[106] USA	Low incidence	3.6
Kasambira 2011,[107] South Africa	High incidence	1003
Laniado-Laborın 2014,[148] Mexico	Intermediate incidence	23
Mahomed 2011,[108] South Africa	High incidence	1003
Pavic 2011,[109] Croatia	Low incidence	14
Perez-Porcuna 2014,[151] Brazil	High incidence	46
Rutherford 2012,[110,111] Indonesia	High incidence	185
Talbot 2012,[112] USA	Low incidence	3.6
Tieu 2014,[154] Thailand	High incidence	119
Tsolia 2010,[113] Greece	Low incidence	4.5
Studies in immunocompromised people: incidence studies		
Anibarro 2012,[117] Spain	Low incidence	14
Chang 2011,[119] South Korea	High incidence	409
Elzi 2011,[114] Switzerland	Low incidence	6
Kim 2011,[116] South Korea	High incidence	409
Lee 2009,[118] Taiwan	High incidence	73
Lee 2014,[149] South Korea	High incidence	409
Moon 2013,[115] South Korea	High incidence	409
Sherkat 2014,[155] Iran	Intermediate incidence	21

continued

TABLE 58 Included studies and incidence of TB (*continued*)

Study ID, country	Category[a]	Estimated rate per 100,000 population
Studies in immunocompromised people: exposure studies		
Ahmadinejad 2013,[120] Iran	Intermediate incidence	21
Al Jahdali 2013,[121] Saudi Arabia	Low incidence	15
Ates 2009,[122] Turkey	Intermediate incidence	22
Casas 2011,[123] Spain	Low incidence	14
Casas 2011,[124] Spain	Low incidence	14
Chkhartishvili 2013,[125] Georgia	High incidence	116
Chung 2010,[126] South Korea	High incidence	409
Costantino 2013,[127] France	Low incidence	8.2
Hadaya 2013,[128] Switzerland	Low incidence	6
Hsia 2012,[129] USA	Low incidence	3.6
Kim 2010,[130] South Korea	High incidence	409
Kim 2013,[131] South Korea	High incidence	409
Kim 2013,[132] South Korea	High incidence	409
Kleinert 2012,[133] Germany	Low incidence	5.6
Laffitte 2009,[134] Switzerland	Low incidence	6
Maritsi 2011,[135] UK	Low incidence	15
Mutsvangwa 2010,[136] Zimbabwe	High incidence	562
Papay 2011,[137] Austria	Low incidence	7.9
Ramos 2013,[138] Spain	Low incidence	14
Seyhan 2010,[139] Turkey	Intermediate incidence	22
Shen 2012,[140] China	High incidence	83
Souza 2014,[153] Brazil	High incidence	46
Takeda 2011,[141] Japan	Low incidence	19
Vassilopoulos 2011,[142] Greece	Low incidence	4.5
Studies in people recently arrived from high burden TB countries: incidence studies		
Harstad 2010,[143] Norway	Low incidence	7.5
Kik 2010,[144] the Netherlands	Low incidence	6.3
Studies in people recently arrived from high burden TB countries: exposure studies		
Lucas 2010,[145] Australia	Low incidence	6.5
Orlando 2010,[146] Italy	Low incidence	6.7
Saracino 2009,[147] Italy	Low incidence	6.7

ID, identification.

a 'Low incidence' defined as countries with an incidence of TB of < 20 cases per 100,000 population; 'intermediate incidence' defined as countries with an incidence of TB of ≥ 20 but < 40 cases per 100,000; 'high incidence' defined as countries with an incidence of TB of ≥ 40 cases per 100,000.[229,230]

Appendix 11 Data extraction tables for included cost-effectiveness studies

Date:
Name of first reviewer:
Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Baseline characteristics	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Target population and subgroups	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	
Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Analytical methods	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Discussion	
Study findings	

Limitations	
Generalizability	
Other	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

Date: 18th August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumour necrosis factor-α antagonist therapy
First author	Kowada
Co-authors	None
Source of publication Journal yy;vol(issue):pp	Molecular diagnosis and therapy 2010;14(16):367-373
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Immunocompromised (Rheumatoid arthritis patients prior to tumour necrosis factor-α (TNF- α) therapy
Intervention(s)	QuantiFERON gold-in-tube (QFT-GIT)
Comparator(s)	Tuberculin skin test (TST)
Outcome(s)	Cost per quality-adjusted life-year (cost per QALY)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Not reported
Study perspective	Societal perspective
Time horizon	Lifetime horizon with one-year time cycle lengths
Discount rate	3% per annum
Measurement of effectiveness	Quality-adjusted life-years
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Screening test for QFT-GIT and TST, costs for treatment of LTBI/TB and adverse events
Currency, price date and conversion	US dollars, costs were adjusted to 2009 Japanese Yen and converted to US dollars in 2009, 1 US$ = 93 Japanese Yen
Model type	Decision tree model with Markov nodes (No LTBI, LTBI, TB and death)
Assumptions	1) The sensitivities for QFT-GIT and TST in people with rheumatoid arthritis are assumed to be lower than the sensitivities for an immunocompetent population.
Analytical methods	The author conducted one-way and two-way sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, probabilistic sensitivity analysis (PSA) was undertaken to determine the uncertainty in the key model input parameters
Results	
Study parameters	Sensitivity and specificity for QFT and TST. Other parameters included probability of successful treatment, probability of recurrence of active TB

	after TB adherence to rate of treatment
Incremental costs and outcomes	In the base-case analysis, QFT was less costly and more effective than TST, US$1040 vs. US$1820 and 23.0350 vs. 22.9815 QALYs, respectively
Characterising uncertainty	The results from the PSA showed that at society's willingness-to-pay per QALY, the probability of QFT testing strategy has a 100% probability of being cost-effective compared to the TST strategy
Discussion	
Study findings	The results showed/demonstrated that QFT was less costly and more effective than TST strategy
Limitations	1) The sensitivities for QFT-GIT and TST in people with rheumatoid arthritis are assumed to be lower than the sensitivities for an immunocompetent population 2) There was a lack of information to populate the model on the natural history of TB regarding QFT-GIT conversion and reversion rate 3) A paucity of information exists on the incidence of LTBI and active TB in people with rheumatoid arthritis treated with TNF-α antagonists and this may have an impact on the results
Generalizability	The model presented here may be useful to determine the cost-effectiveness of QFT-GIT compared with TST for the diagnosis of LTBI in patients with rheumatoid arthritis prior to TNF-α treatment. The results presented here suggested that QFT is the dominant strategy compared to TST alone, but some of the key inputs are questionable, for example the utility value of 0.9 for nonfatal TB in people with rheumatoid arthritis. This utility value appears to be high for people who have rheumatoid arthritis. The model may be useful, but these results should be interpreted with caution
Other	
Source of funding	No source of funding
Conflicts of interest	No conflicts of interest
Comments	In table 1, Kowada presented the utility value of non-fatal TB, but have not presented other utility values for other health states Additionally, the starting age of the hypothetical cohort is 40 years, but the author included information on the mortality due to people ages 20-29 years and 30-39 years The author conducted probabilistic sensitivity analysis (PSA) on the outcome measure of cost per QALY. However, the distributions placed around the key model inputs have not been reported
Authors conclusion	
The author concluded that the QFT testing strategy is more effective and less costly than TST testing strategy for diagnosing LTBI in people with rheumatoid arthritis prior to treatment with TNF-α antagonists for both BCG vaccinated and unvaccinated groups	
Reviewer's conclusion	
The author used an appropriate modelling technique to demonstrate the cost-effectiveness of QFT compared to TST in people with rheumatoid arthritis. Various key health states which relate to LTBI/TB have been included in the model structure, but there is some uncertainty in key model input parameters. The authors have attempted to address this uncertainty by using sensitivity analysis and PSA, but have not presented information on the distribution used around these model parameters. Hence, we believe that these results should be interpreted with caution	

Date: 15 August 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of interferon-gamma release assay for school-based tuberculosis screening
First author	Kowada
Co-authors	None
Source of publication Journal yy;vol(issue):pp	Molecular diagnosis and therapy 2012;16(3):181-190
Language	English Language
Publication type	Journal article
Baseline characteristics	
Population	Children/adolescents: Immunocompetent children/adolescents aged 16-19 years old; Students divided into BCG-vaccinated individuals and non BCG-vaccinated individuals
Intervention(s)	QFT-GIT, chest x-ray
Comparator(s)	TST
Outcome(s)	Cost per quality-adjusted life-years
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Not reported
Study perspective	Societal perspective
Time horizon	Life time horizon (up to 80 years old), one-year cycle length
Discount rate	3% discount rate per annum
Measurement of effectiveness	Quality-adjusted life-years (QALYs)
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Cost of TST and QFT screening and cost of treatment and adverse events
Currency, price date and conversion	2009 Japanese yen, converted to US$, using the OECD purchasing power parity rate in 2009
Model type	Markov model (Healthy, LTBI, TB and dead)
Assumptions	The author assumed a high prevalence of LTBI in the Japanese population
Analytical methods	One-way and two-way sensitivity analyses were performed on key model input parameters Probabilistic sensitivity analyses was undertaken to address the uncertainty around key model input parameters and was based on the outcome measure of cost per quality-adjusted life-year
Results	
Study parameters	Sensitivity and specificity for QFT, TST and chest x-ray. Other parameters included probability of successful treatment, probability of recurrence of active TB after TB adherence to rate of treatment
Incremental costs and outcomes	In the 16-year old sub-group QFT was less costly and more effective than

	TST, US$628 vs. US$944 and 29.6984 vs. 29.6977 QALYs, respectively
Characterising uncertainty	Results from the sensitivity analyses showed that the results were robust to changes made to model input parameters. From the PSA, the author suggested that there was a 100% probability that QFT was cost-effective compared to TFT at all society's willingness-to-pay levels
Discussion	
Study findings	Base-case results showed that in the 16-year old sub-group the QFT test was cheaper and produced a moderate benefit in terms of QALYs
Limitations	1) The author assumed that the prevalence of LTBI was high in this Japanese population, this estimate was based on the TST positivity rates 2) The Markov model did not include health states for people who received treatment for LTBI 3) The distress for LTBI testing was not measured in this study.
Generalizability	The author suggested that the results may be applicable to other countries where school-based TB testing is being conducted
Other	
Source of funding	No sources of funding
Conflicts of interest	No conflicts of interest
Comments	The author mentioned that in 2008 over 95% of the population had received BCG vaccination at least once. Specificity of TST were stratified by BCG-vaccinated and non-BCG vaccinated people, however, this was not done for QFT or chest x-ray
Authors conclusion	
The author demonstrated that the use of QFT provided greater benefits than screening with TST or chest x-ray in terms of lower costs and identifying more cases of LTBI in this population	
Reviewer's conclusion	
The author used an appropriate modelling technique to demonstrate the cost-effectiveness of QFT compared to TST. There were some limitations in the model which the author alluded to, for example, not including health states where people have received treatment for LTBI/TB. The author did not state the study setting within which the analysis would be undertaken, hence compromising the generalizability of these results. Additionally, we assumed the perspective of the study was the societal perspective because the author suggested that indirect costs relating to loss of productivity would be included, these costs were not reported in this paper. We did not think it would have been necessary to include indirect costs due to loss of productivity because these children/adolescents are assumed to be full-time students	

Date: 18th August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of interferon-ɣ release assay for tuberculosis screening of hemodialysis patients
First author	Kowada
Co-authors	None
Source of publication Journal yy;vol(issue):pp	Nephrology Dialysis Transplantation 2013;28:682-688
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Immunocompromised (haemodialysis patients 40 years of age); sub-groups for people who were BCG-vaccinated
Intervention(s)	QFT-GIT,
Comparator(s)	Tuberculin skin test (TST), chest x-ray (CXR)
Outcome(s)	Cost per quality-adjusted life-year (Cost per QALY)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Not reported
Study perspective	Societal perspective
Time horizon	Lifetime horizon
Discount rate	3% per annum for costs and benefits
Measurement of effectiveness	QALY
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Direct (inpatient/outpatient) and indirect (loss of productivity) costs, screening costs for QFT, TST and CXR. Other costs included treatment for active TB, costs of smear and culture examinations of sputum and treatment of adverse events
Currency, price date and conversion	US$, 2012, costs adjusted to 2012 Japanese Yen, then converted to US dollars, using the OECD purchasing power parity rate in 2009
Model type	Markov model (maintenance dialysis with no disorder, maintenance dialysis with LTBI, maintenance dialysis with TB and death)
Assumptions	1) Kowada assumed that the risk of TB-related mortality in ESRD patients will increase with age 2) Key model input parameters (probability of developing TB from LTBI, adherence rate of standard treatment, the probability of treatment-induced hepatitis, the efficacy if the standard treatment, and the recurrence of active TB after treatment) were assumed/derived 3) Further assumptions were on the sensitivity and specificity of QFT, TST and CXR
Analytical methods	The author conducted one-way and two-way sensitivity analyses by changing key model input parameters to determine the impact on the

	deterministic results. Additionally, probabilistic sensitivity analysis (PSA) was undertaken to determine the uncertainty in the key model input parameters
Results	
Study parameters	Sensitivity and specificity for QFT, TST and chest x-ray. Other parameters included probability of successful treatment, probability of recurrence of active TB after TB adherence to rate of treatment
Incremental costs and outcomes	In the base-case analysis, QFT was less costly and more effective than TST, US$7690 vs. US$9340 and 4.1926 vs. 4.1854 QALYs, respectively
Characterising uncertainty	One-way sensitivity analysis The cost effectiveness of the QFT compared with the TST was sensitive to the BCG vaccination rate. TST strategy was more cost-effective than QFT strategy at the willingness-to-pay level of US$50,000 per QALY gained when the BCG vaccination rate was o.18 or lower Probabilistic sensitivity analysis The cost-effectiveness acceptability curve of 40-year-old patients by Monte Carlo simulations for 10,000 trials demonstrated that the QFT was the most cost-effective, with a value of 100% at all willingness-to-pay level compared with TST and CXR strategies
Discussion	
Study findings	Base-case results showed that the QFT test was cheaper and produced a moderate benefit in terms of QALYs. The QFT testing strategy was dominant compared to TST testing strategy
Limitations	1) No gold standard to diagnose LTBI in the end stage renal disease (ESRD) population 2) Paucity of information on the sensitivity and specificity of QFT-GIT and TST in people with ESRD 3) The parameters included in the model may be changeable in more precise investigations of TB dynamics
Generalizability	The model presented here may be useful to determine the cost-effectiveness of QFT-GIT compared with TST/CXR for the diagnosis of LTBI, but given the limitations highlighted on the key model input parameters, results should be interpreted here with caution
Other	
Source of funding	Not reported
Conflicts of interest	None declared
Comments	Author has not provided an illustrative structure of the Markov nodes used in the model. The author mentioned that in the TST testing strategy, BCG – vaccinated people with an induration of ≥5mm and unvaccinated people would have undergone a CXR. However, this has not been illustrated in the model. The author conducted PSA around the outcome measure cost per QALY. However, the distributions used around key model input parameters were not stated in this paper. Additionally, the cost-effectiveness acceptability curve was not provided in this paper
Authors conclusion	
The results demonstrated that that QFT screening strategy produced greater benefits in terms of QALYs and lower costs compared to TST/CXR for people who have ESRD	
Reviewer's conclusion	
The author used an appropriate modelling technique to demonstrate the cost-effectiveness of QFT compared to TST/CXR in people with ESRD. The author did not state the study setting within which the analysis would be undertaken, hence compromising the generalizability of these results. Additionally, we assumed the perspective	

of the study was the societal perspective because the author suggested that indirect costs relating to loss of productivity would be included, these costs were not reported in this paper

Date: 21st August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of interferon-gamma release assay for TB screening of HIVE positive pregnant women in low TB incidence countries
First author	Kowada
Co-authors	None
Source of publication Journal yy;vol(issue):pp	Journal of infection 2014;68:32-42
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Immunosuppression (HIV positive pregnant women). Immunosuppressed (20-year old HIV positive pregnant women) four sub-groups were analysed: non-BCG vaccinated cohort during pregnancy, BCG-vaccinated cohort during pregnancy, non-BCG vaccinated cohort postpartum period and BCG vaccinated cohort in postpartum period
Intervention(s)	Five strategies 1) TST alone, 2) QFT alone, 3) T-SPOT.TB, 4) TST followed by QFT and 5) TST followed by T-SPOT.TB
Comparator(s)	See above five compared strategies
Outcome(s)	Cost per QALY
Study design	Cost-effectiveness analysis
Setting and location	Hypothetical cohort followed until age 50 years in three most common screening situations; close contacts, immigrants from high burden countries and occasional screening in low TB incidence countries
Methods	
Study perspective	Health service perspective
Comparators	TST alone
Time horizon	30-year time horizon with yearly cycles
Discount rate	3% per annum for costs and benefits
Measurement of effectiveness	QALY
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Screening test for TST, QFT, T-SPOT.TB, chest x-ray, costs for treatment of LTBI/TB and adverse events (Hepatitis).
Currency, price date and conversion	US$, 2012, 1US$ = ¥ 103.9 (OECD purchasing power parity rate in 2012)
Model type	Markov model (Non-LTBI and non-TB, LTBI, non MDR-TB, MDR-TB and Dead)
Assumptions	Not clearly stated
Analytical methods	The author conducted one-way sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, probabilistic sensitivity analysis (PSA) was undertaken to

	determine the uncertainty in the key model input parameters
Results	
Study parameters	Probability of having LTBI among HIV positive pregnant women, incidence of TB among HIV positive pregnant, increased mortality among HIV positive pregnant women, probability of successful treatment, adherence rate of treatment, sensitivity and specificity for TST, QFT, T-SPOT.TB and chest x-ray
Incremental costs and outcomes	The results from the base-case analysis showed that T-SPOT.TB was least costly and more effective with an incremental cost of US$ 596 and incremental QALYs of 0.00705 compared with TST in HIV positive pregnant women (non-BCG vaccinated) in close contacts
Characterising uncertainty	Results from the one-way sensitivity analysis showed that the cost-effectiveness was sensitive to the sensitivity of T-SPOT.TB, the sensitivity of QFT, specificity of T-SPOT.TB and the specificity of QFT in close contacts during pregnancy and other changes in key model input parameters The results from the PSA showed that at society's willingness-to-pay per QALY, there was a 100% probability that TST followed by QFT strategy is likely to be cost-effective compared to other testing strategies
Discussion	
Study findings	The results showed that the T-SPOT.TB is less costly and was more effective compared to other strategies
Limitations	There were some assumptions which the author acknowledged:- 1) The probability estimates used in the model were obtained from different countries 2) Estimates on sensitivity and specificity of IGRAs and TST were values based on meta-analysis of published literature and assumptions made. The author further suggested that there is little evidence to suggest the impact of pregnancy on the sensitivity/specificity of IGRAs and TST to diagnose LTBI. 3) The cost of the side effect by MDR-TB therapy was not calculated in the model 4) The use of chemoprophylaxis for pregnant women is still a controversial issue 5) A paucity of information on the incidence of TB in pregnant women and the prevalence of LTBI in HIV positive pregnant women
Generalizability	Given the assumptions and the limitations, the model presented may be generalizable in a population with women who are pregnant and have HIV
Other	
Source of funding	Author reported no source of funding
Conflicts of interest	Author reported no conflict of interest
Comments	None
Authors conclusion	
Kowada concluded that the use of IGRA to screen for TB in HIV positive pregnant women is cost-effective in countries with low incidence of TB	
Reviewer's conclusion	
The model presented here is very useful to inform on the cost-effectiveness of IGRAs compared with TST for the diagnosis of TB in this patient group. The author has used an appropriate modelling structure to show LTBI progression	

Date: 18th August 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of latent tuberculosis screening before steroid therapy for idiopathic nephrotic syndrome in children
First author	Laskin
Co-authors	J Goebel, JR Starke, DP Schauer
Source of publication Journal yy;vol(issue):pp	American journal of kidney diseases 2013;61(1):22-32
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Immunosuppressed (Idiopathic nephrotic syndrome in children): children up to five years old with idiopathic syndrome
Intervention(s)	Interferon-gamma release assays (second model)
Comparator(s)	Tuberculin skin test
Outcome(s)	Marginal cost per quality-adjusted life-years (cost per QALY)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Not reported
Study perspective	Societal perspective
Time horizon	Life-time horizon with a three-month cycle length
Discount rate	3% per annum on costs and benefits
Measurement of effectiveness	Quality- adjusted life-years
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Screening tests, nephrotic onset, nephrotic relapse and treatment of LTBI/TB
Currency, price date and conversion	US$, 2010 prices
Model type	Decision tree structure to model the short term events followed by a Markov modelling structure (Well, LTBI, TB, nephrotic relapse and dead) for the longer-term events
Assumptions	1) Children in the model are assumed to be adherent to the medication 2) Initial risk of reactivation decreases by 10% per decade 3) Children can only develop active TB on one occasion throughout their lifetime 4) After presentation with LTBI, children were not allowed to be screened again for LTBI 5) In the model, children did not develop multidrug-resistant disease 6) Authors assumed that people surviving acute infection have decreased lung function, hence, lower utility values
Analytical methods	These authors conducted one-way and two-way sensitivity analyses by changing key model input parameters to determine the impact on the deterministic results. Additionally, probabilistic sensitivity analysis (PSA) was undertaken to determine the uncertainty in the key model input

	parameters
Results	
Study parameters	Screening test characteristics, prevalence, nephrotic onset, nephrotic relapse, mortality and treatment of LTBI/TB
Incremental costs and outcomes	In the base-case analysis, universal IGRA was less costly and more effective than universal TST, US$2300 vs. US$2480 and 29.3355 vs. 29.3347 QALYs, respectively. However the 'no screening' strategy dominated the other strategies (universal IGRA, universal TST) being less costly and more effective
Characterising uncertainty	The base-case results were robust when indirect medical costs were excluded from the analysis In the secondary model, targeted screening with a questionnaire followed by IGRA was cost-effective compared with no screening at a prevalence >4.9%
Discussion	
Study findings	These authors demonstrated that universal IGRA was less costly and produced moderately more QALYs compared to universal TST
Limitations	1) Lack of gold standard for the diagnosis of LTBI in this patient population 2) The authors acknowledged that indeterminate results and the need for venepuncture. They suggested that indeterminate results which can lead to false-negative results in children may have an impact on the overall results
Generalizability	The model presented here may be useful to determine the cost-effectiveness of IGRAs compared with TST for the diagnosis of LTBI in children with idiopathic nephrotic syndrome. The results presented here suggested that the 'no screen' strategy was the dominant strategy compared to universal IGRA and universal TST alone. However, these results should be interpreted with caution because the discounted and undiscounted costs were similar in the base case results
Other	
Source of funding	No source of funding to conduct study has been stated
Conflicts of interest	No conflicts of interest declared
Comments	A discount rate of 3% per annum was applied both to the costs and benefits. These authors presented results both on the undiscounted and discounted costs and benefits. From these results presented, the undiscounted and discounted costs are identical. These authors have not distinguished between the IGRAs being used in the model. They justified this by suggesting that the use of IGRAs in this population has not yet been approved
Authors conclusion	
Based on the results, these authors demonstrated that at a LTBI prevalence of 1.1%, both universal testing and targeted TST testing are not cost-effective prior to commencing treatment for five-year olds who are newly diagnosed with idiopathic nephrotic syndrome	
Reviewer's conclusion	
The model used here may be useful, and adds to the existing literature to demonstrate the various screening strategies for the diagnosis of LTBI in a population at risk of immunosuppression. The model includes key health states to show the disease progression of LTBI. Given the limitations outlined by the authors, these results showed that the no screening strategy dominated other strategies compared in the model. However, these results should be interpreted with caution because the undiscounted and discounted costs are similar	

Date: 19th August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Priorities for screening and treatment of latent tuberculosis infection in the United States
First author	Linas
Co-authors	AY Wong, KA Freedberg and CR Horsburgh
Source of publication Journal yy;vol(issue):pp	American journal respiratory and critical care medicine 2011;184:590-601
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Various risk groups (immunocompromised and recently arrived immigrants)
Intervention(s)	Interferon-gamma release assays (IGRAs), Tuberculin skin test (TST)
Comparator(s)	No screening
Outcome(s)	Number needed to screen to prevent one case of active TB, life expectancy, quality-adjusted life expectancy
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Setting not reported
Study perspective	Health service
Time horizon	Lifetime horizon
Discount rate	3% per annum for costs and benefits
Measurement of effectiveness	Health-related quality of life
Measurement and valuation of preference based outcomes	Euroqol five dimensions (EQ-5D) and Medical Outcomes Study (SF-36)
Resource use and costs	Costs for screening LTBI with TST, IGRA, costs of treatment of LTBI and active TB, costs of treatment of adverse events
Currency, price date and conversion	US$, 2011
Model type	Markov model (health states included, LTBI with Isoniazid (INH), LTBI no INH, INH related hepatitis, < 6 months INH, 6-8 months INH, 9 months INH, Active TB, post active TB and death)
Assumptions	1) People who did not return for TST reading were not eligible for INH therapy 2) Approximately 10% of TST-positive persons lose their skin test reactivity over a decade of follow-up. People here are believed to have self-cured. These authors assumed that a 10% reduction in the rate of reactivation each year 3) The health-related quality of life for people cured for active TB was assumed to be the same for healthy people 4) High-risk groups for screening were already identified and managed by existing resources, and did not require programmatic costs associated with expanded screening interventions
Analytical methods	Authors conducted one- and two-way sensitivity analysis by varying all

	model input parameters to explore the uncertainty in these parameter estimates
Results	
Study parameters	Estimates of the prevalence of true LTBI in each risk-group, sensitivity and specificity for IGRA and TST, probability of people with TST +ve who start INH treatment, probability of INH-related hepatitis and utility values for various health states
Incremental costs and outcomes	People who had end-stage renal disease (ESRD), the reported ICER for TST screen compared to no screen was $824, 500 and $1, 168, 300 for the IGRA strategy compared with no screen In the base-case analysis, for people who are HIV-infected, TST screen was marginally more costly and more effective than the no screen option with an ICER of $12, 800. In this same sub-group, IGRA was marginally more costly and more effective than the no screen option with an ICER of $23, 800 For people who were on immunosuppressive medication, the reported ICER for TST screen compared to no screen was $129, 000 and $227, 900 for the IGRA screen compared with no screen For people who were recent immigrant adults, TST screening strategy dominated the no screen strategy. Whilst IGRA was marginally more costly and more effective than the no screen strategy with an ICER of $35, 200
Characterising uncertainty	Various sensitivity analyses were conducted. Results from the sensitivity analysis showed that increasing the reactivation TB rate in people who are immunosuppressive reduced the ICER to below $100, 000 per QALY. Additionally, increasing the proportion of people with INH-induced hepatitis did not have an impact on the results. The base-case results were sensitive to changes in the health-related quality of life of people treated for active TB. The authors applied a 10% decrement on utility instead of assuming people returned to full health. The results demonstrated that screening with IGRA or TST the ICER was less than $100, 000 per QALY
Discussion	
Study findings	Based on the results reported by these authors, people who are taking immunosuppressive medications, TST screen was not likely to be cost-effectives to the no screening strategy. Similar results were reported for people with ESRD
Limitations	There were some limitations to which the authors acknowledged 1) There are no prospective observational data in the united stated to inform on the rate of reactivation TB. The availability of INH prophylaxis for patients with identified LTBI renders natural history cohorts unethical 2) There is no gold standard available to confirm the diagnosis of LTBI 3) The model included direct medical costs, but not indirect costs, such as loss of productivity time and transportation costs
Generalizability	Authors may have used information relevant to setting and location that the study was conducted. However, they have not reported the setting the analysis was undertaken. Hence, compromising the generalizability of the results
Other	
Source of funding	Supported by the National Institute of Allergy and Infectious Diseases (K01AI073193, K24AI062476, R37AI42006)
Conflicts of interest	No conflicts of interest declared

Comments	The model presented here adds to the existing literature on the cost-effectiveness of IGRA compared to TST for the diagnosis of LTBI in various high-risk populations. The model incorporates key health states for the treatment pathway for people being screened and treated for LTBI. Table 3 presents the base-case results, these authors have presented information on the number needed to screen to prevent a case of active TB, discounted lifetime costs per person, undiscounted per person life expectancy, discounted per person quality-adjusted life expectancy (in months) and cost per QALY. From this table of results, we question the authors' values to estimate the ICER given the values presented in this table
Authors conclusion	
These authors concluded that the use of IGRA in screening people who are close contacts, infected with HIV, and foreign-born is likely to be cost-effective when compared to TST	
Reviewer's conclusion	
The model seems useful and adds to the existing literature on the diagnosis of LTBI. However, these authors have not suggested which IGRA is being used in the model. In terms of diagnosing LTBI, the sensitivity and/or specificity may differ between these populations	

Date: 28th August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Clinical diagnosis and management of tuberculosis, and measures for its prevention and control: cost-effectiveness analysis of interferon gamma release assay (IGRA) testing for latent tuberculosis
First author	CG117
Co-authors	Not applicable
Source of publication Journal yy;vol(issue):pp	Clinical guideline
Language	English language
Publication type	Clinical guideline
Baseline characteristics	
Population	Recently arrived adults from high endemic countries with active TB
Intervention(s)	IGRA, tuberculin (TST) followed by IGRA for people with +ve TST results, no testing
Comparator(s)	TST
Outcome(s)	Cost per quality adjusted life-year (cost per QALY)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	UK
Study perspective	National Health Service (NHS) and Personal Social Service (PSS) perspective
Time horizon	15-year time horizon
Discount rate	3.5% per annum on costs and benefits
Measurement of effectiveness	QALY
Measurement and valuation of preference based outcomes	Not reported
Resource use and costs	Cost of assessment of active TB, cost of tests (IGRA and TST), cost of treatment (LTBI and active TB)
Currency, price date and conversion	UK £ sterling, 2008/2009 prices
Model type	Decision tree structure
Assumptions	1) Authors used a decision tree model structure which does not take into account the dynamic transmission of tuberculosis. Assumed that each primary case of active TB is associated with a fixed number of secondary cases 2) People who did not have a TST test result were assumed to have the same prevalence of LTBI and of active disease as those who do 3) An average time delay of 0.5 years before people with LTBI who go on to develop active TB 4) For people without current LTBI or active TB who develop TB later in life, authors assumed this will occur after an average time delay of 0.5 years 5) The number of secondary cases is assumed to be reduced when the index case is detected through contact tracing

	6) Side-effects as a result of treatment were ignored 7) People who started treatment for LTBI/TB were assumed to have adhere to treatment
Analytical methods	One-way and two-way sensitivity analyses were performed on key model input parameters (costs of the IGRA, return rate of the TST results, secondary cases, test accuracies, varying the prevalence of LTBI and varying the transformation from LTBI to active TB)
Results	
Study parameters	Prevalence of LTBI in population, proportion of infected people with active TB. Proportion of TST results read, sensitivity and specificity (IGRA and TST), cost of assessment of active TB, cost of tests, cost of treatment
Incremental costs and outcomes	TST/IGRA compared with the no testing strategy was more costly and produced more QALYs, £316 vs. £403 and 9.08686 vs. 9.99015, respectively. IGRA compared with no testing strategy was more costly, and produced more QALYs. Both strategies were likely to be cost-effective with incremental cost-effectiveness ratios (ICERs) below the £30, 000 per QALY threshold
Characterising uncertainty	There was no impact on the results when the return rate for TST test results where changed. The increase in the number of secondary cases had a positive effect on the cost-effectiveness results. Results from varying the accuracy of the tests showed that at high levels of specificity of an IGRA test the results showed to be cost-effective at £20, 000 per QALY. For the TST test alone, when the specificity was increased to 80% or above, the results showed to be cost-effective. Conversely, the specificity of the combined strategy needed to be low to achieve £20, 000 per QALY
Discussion	
Study findings	The results showed that TST +ve followed by IGRA and IGRA testing strategies were associated with ICERs below £30, 000 per QALY compared with no testing strategy. The results from the sensitivity analyses showed that varying the cost of an IGRA (£50 to £60) changes the direction of the cost-effectiveness results
Limitations	The model used here is subject to limitations, but these were not acknowledged by the authors
Generalizability	The model structure used here may be helpful to show the cost-effectiveness between testing strategies for LTBI in this population. The authors have stated assumptions made in the model but have not fully accounted for uncertainty in the analyses, hence compromising the generalizability of the model
Other	
Source of funding	NICE
Conflicts of interest	Not reported
Comments	The model here adds to the existing literature on the use of IGRA and TST for the diagnosis of LTBI in the recently arrived immigrants from high prevalence of TB countries. The model structure used here, along with some of the assumptions are subject to limitations which were not highlighted by the authors
Authors conclusion	
These authors concluded that IGRA and the TST followed by IGRA testing strategies are likely to be cost-effective	
Reviewer's conclusion	

Given the assumptions and the limitations of the model, these results demonstrated that TST +ve followed by IGRA and IGRA testing strategies are likely to be cost-effective in a population with people from high endemic TB countries. The decision tree structure may be subject to some limitations, for example, introducing too much static for people developing active TB

Date: 15th August 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting
First author	A Mandalakas
Co-authors	A Hesseling, R Gie, H Schaaf, B Marais
Source of publication Journal yy;vol(issue):pp	Thorax 2012;68(3):247-255
Language	English Language
Publication type	Journal article
Inclusion criteria/study eligibility/PICOS	
Population	Children
Intervention(s)	QFT and T-SPOT.TB
Comparator(s)	TST
Outcome(s)	Cost per life year saved (LYS)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	High-burden TB setting
Study perspective	Provider and societal perspectives
Comparators	TST alone, IGRA alone, +ve TST followed by IGRA and –ve TST followed by IGRA
Time horizon	15 year time horizon
Discount rate	3% discount rate per annum
Measurement of effectiveness	Life years saved
Measurement and valuation of preference based outcomes	Not applicable
Resource use and costs	Tests for infection, chest radiography, culture, HIV testing, in/outpatient visits, laboratory tests, treatment for LTBI and TB
Currency, price date and conversion	US dollars, 2009 prices, conversion not stated
Model type	Decision tree structure with Markov nodes (no infection, re-infection, LTBI, PTB, disseminated TB, death and death from other causes)
Assumptions	When used as a confirmatory test following an accurate tuberculin skin test (TST), the interferon γ release assay (IGRA) is 100% accurate (sensitive and specific) Test properties do not vary by age The duration of protection offered by a 6-month course of IPT is limited to the initial exposure and for the duration of treatment only Following Mycobacterium tuberculosis infection and completion of IPT, children remain M tuberculosis infected Following the initial exposure, children cannot progress from the M tuberculosis infection state to active disease states unless they are re-infected Children with a history of household TB exposure have the same subsequent annual risk of infection as calculated by formal surveys in the setting

	Children can only progress to the TB death state from the pulmonary or disseminated TB states. The disseminated disease state includes TB meningitis and other forms of non-pulmonary TB Children have the same risk of disease progression following each subsequent TB exposure Isoniazid-related adverse events are negligible/rare in children
Results	
Study parameters	Sensitivity and specificity for TST, IGRA, TST +ve followed by IGRA, TST –ve followed by IGRA. Transition probabilities between health states
Incremental costs and outcomes	In the 0-2 cohort, the no testing strategy dominated other strategies, it was least costly and most effective In the 0-3 cohort, the TST –ve followed by IGRA was the most cost-effective with a reported ICER of approximately US$233 000 per LYS
Characterising uncertainty	One-way sensitivity analysis In the 0-2 cohort, TST –ve followed by IGRA strategy was the most effective strategy when reducing the sensitivity of TST In the 3-5 cohort, the no testing strategy dominated the TST –ve followed by IGRA when increasing the estimates of sensitivity of TST Increasing the rates of LTBI, the IGRA after negative TST became more effective that the no testing strategy in both age cohorts
Discussion	
Study findings	In the 0-2 cohort, the no testing strategy dominated other strategies. In the 3-5 cohort, the TST –ve strategy followed by IGRA was the most cost-effective
Limitations	Test performance estimates were derived from studies that examined the test accuracy for the identification of TB disease. These authors assumed that IPT usage was similar across strategies
Generalizability	Unclear
Other	
Source of funding	Thrasher Research Fund
Conflicts of interest	No conflicts of interest
Comments	Authors have not conducted probabilistic sensitivity analysis
Authors conclusion	
Screening for TB infection and provision of IPT in young children < 5 years is highly cost-effective	
Reviewer's conclusion	
These authors used an appropriate modelling technique to estimate the cost-effectiveness of various strategies for the prevention of TB. The model was subject to some limitations, for which the authors acknowledge and the impact these would have made to the results. Authors have conducted one-way sensitivity analysis, but have not undertaken probabilistic sensitivity analysis to show the joint parameter uncertainty and its impact on the base-case results	

Date: 20th August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Community-based evaluation of immigrant tuberculosis screening using interferon-gamma release assays and tuberculin skin testing: observational study and economic analysis
First author	M Pareek 2013
Co-authors	M Bond, J Shorey, S Seneviratne et al.
Source of publication Journal yy;vol(issue):pp	Thorax 201;68:230-239
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Recently arrived immigrants to the UK: Recently arrived immigrants to the UK (arrival within the last five years, aged ≥ 16 years (with symptoms of TB) or from a country with a TB incidence of ≥ 40/100 000 (asymptomatic)
Intervention(s)	T-SPOT.TB alone, QFT-GIT alone, TST plus confirmatory T-SPOT.TB (if TST positive), and TST plus confirmatory QFT-GIT (if TST positive)
Comparator(s)	No screen
Outcome(s)	Cost per case of active TB avoided
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Primary care setting and UK
Study perspective	National health service (NHS) perspective
Time horizon	20-year time horizon
Discount rate	3.5% per annum for costs and benefits
Measurement of effectiveness	Cases of active TB
Measurement and valuation of preference based outcomes	Not applicable
Resource use and costs	Costs for screening LTBI with TST, IGRA, costs of treatment of LTBI and active TB, costs of treatment of adverse events
Currency, price date and conversion	UK £ sterling, 2010
Model type	Decision tree model
Assumptions	A number of assumptions were made for which the authors acknowledged:- 1) Immigrants are screened for LTBI once at the start of the time horizon 2) Tuberculin skin test positivity is classified as per UK guidelines (≥6mm in BCG unvaccinated and ≥15mm in BCG vaccinated 3) All IGRA results are determinate and no repeat testing is required 4) The proportion of immigrants with HIV is reflective of the HIV prevalence in their country of origin 5) A proportion of immigrants with LTBI are infected by a resistant strain of Mycobacterium tuberculosis 6) A proportion of active tuberculosis cases are drug-resistant 7) Amongst those individuals identified with LTBI and treated with

	chemoprophylaxis, a three month course of rifampicin and isoniazid is considered to have equivalent efficacy to six months of isoniazid 8) Individuals who commence chemoprophylaxis and subsequently develop drug-induced liver injury which does not resolve are assumed to only complete 4 weeks of therapy which affords no reduction in the risk of progressing from LTBI to active TB 9) No individuals who develop drug induced liver injury die due to this adverse effect 10) Equal proportions of HIV negative and positive immigrants develop drug-induced liver injury from chemoprophylaxis 11) Chemoprophylaxis will have no efficacy in those immigrants who have a resistant strain causing their LTBI 12) An individual with LTBI who has completed successful chemoprophylaxis is assumed to have cleared the infection with Mycobacterium tuberculosis and will not experience any further outcomes during the time course of the model (such as reinfection) 13) An individual who does not have LTBI on arrival in the UK does not become infected during the time-period considered by the model 14) Drug sensitive and drug resistant strains are assumed to be equally transmissible (in other words drug resistance does not result in any fitness cost) 15) There is no HIV acquisition within the cohort during the time horizon of the model 16) Data on the test performance of the IGRA was based on the most recent meta-analysis obtained from meta-analyses where sensitivity was calculated using culture-confirmed active TB as the reference standard whilst specificity was calculated from BCG-vaccinated individuals at low risk of infection 17) Point estimates for test sensitivity were assumed to be different for HIV positive individuals 18) All individuals diagnosed with drug-sensitive active tuberculosis are assumed to accept treatment for active TB and to complete the 6 month course of drugs 19) All individuals diagnosed with drug-resistant active tuberculosis are assumed to accept treatment for active TB and to complete the course of drugs
Analytical methods	Authors conducted one-way sensitivity analyses on key model input parameters to explore the impact on the results of the cost-effectiveness
Results	
Study parameters	HIV prevalence, drug-resistant tuberculosis, sensitivity and specificity of various screening tests, prevalence of LTBI and progression rate from LTBI to active tuberculosis disease
Incremental costs and outcomes	Base-case results of the cost-effectiveness showed that the screening strategy no port-of-entry chest x-ray and screening with one-step QFT-GIT was cost-effective with an ICER of 21,570 per case of TB avoided and the no port-of-entry chest x-ray and screening with one-step QFT-GIT was cost-effective, with an ICER of £31,870 per case of active TB avoided. These strategies were cost-effective in immigrants whose country of origin had an incidence of TB of 250/100,000 and 150/100,000, respectively
Characterising uncertainty	Results from the sensitivity analyses showed that varying some key model input parameters affected the ICER for each of the strategies, but the order of the cost-effectiveness results remained the same. The authors found that varying the diagnostic specificity of the different screening tests. Reducing the specificity of the screening strategies resulted in high ICERs. Additionally, changing the proportion of immigrants who commenced, and

	adhered ti treated also had an impact of the results, making them less cost-effective. Furthermore, the estimates for ICERs were sensitive to changes in the costs of screening tests
Discussion	
Study findings	Using the decision analytical model, these authors demonstrated that screening of recently arrived immigrants from countries of origin with moderate (not defined) TB incidence is likely to be cost-effective by the use of one-step IGRA testing for LTBI
Limitations	There were some limitations to which the authors have acknowledged while undertaking this study. They highlighted that the sample size was relatively small and not all of the immigrants received the three tests. Additionally, other areas in the UK may have a greater number of immigrants compared to the areas that have been included in the study. Finally, in line with the UK guidelines, the HIV status of immigrants was not tested
Generalizability	The model structure used here may be helpful to show the cost-effectiveness between testing strategies for LTBI in this population. The authors have stated assumptions made in the model, and have used information relevant to the setting in which the analyses were undertaken
Other	
Source of funding	This study was conducted at St. Mary's Hospital, Imperial College Healthcare NHS Trust which is supported by the NIHR Biomedical Research Centre funding scheme. Westminster Primary Care Trust provided funding for this project
Conflicts of interest	AL is inventor for patents underpinning T-cell-based diagnosis. The ESAT-6/CFP-10 ELISpot was commercialised by an Oxford University spin-out company (Oxford Immunotec, Abingdon, UK) in which Oxford University and Professor Lalvani have a minority share of equity. All other authors have no conflict of interest
Comments	Drug induced liver injury as a result of treatment for active TB/LTBI. The authors suggested that this may be a rare occurrence in this population. However, they have not included other adverse events such as hepatitis C Authors have not conducted any probabilistic sensitivity analysis The illustrative modelling structure was presented in a supplementary web-appendix, but unfortunately, these figures were illegible
Authors conclusion	
The authors concluded that immigrant screening may be cost-effective in the UK by removing the mandatory chest x-ray on arrival of immigrants and to screen for LTBI with an IGRA. They suggested that this screening should be undertaken in recently arrived people from countries where the incidence is greater than 250, 150 or 40 cases per 100,000 of active TB	
Reviewer's conclusion	
These authors evaluated, with the aid of a decision analytical model, the cost-effectiveness of various screening strategies for LTBI. They have collected data to inform on the performance (sensitivity and specificity) of these test based on immigrants from three areas in the UK. The methods used to undertake these analyses seem to be robust, but due to the illegibility of the modelling structure, it was difficult to appraise the model	

Date: 22nd August, 2014
Name of first reviewer: Peter Auguste
Name of second reviewer: Alexander Tsertsvadze

Study details	
Study title	Cost-effectiveness of quantiferon testing before indication of biological therapy in inflammatory bowel disease
First author	A Swaminath
Co-authors	N Bhadelia and C Wang
Source of publication Journal yy;vol(issue):pp	Inflammatory bowel diseases 2013;19(11):2444-2449
Language	English language
Publication type	Journal article
Baseline characteristics	
Population	Immunosuppression (inflammatory bowel disease before anti-TNF-α): Hypothetical cohort of people with moderate to severe active Crohn's disease currently being treated with immunomodulators or prednisone
Intervention(s)	QuantiFERON- Gold (QFT-G)
Comparator(s)	Tuberculin skin test (TST)
Outcome(s)	Cost per false negative cases of LTBI avoided, cost per TB deaths avoided, cost per reactivation TB avoided (this can be derived from the information provided)
Study design	Cost-effectiveness analysis
Methods	
Setting and location	Not reported
Study perspective	Health care payer
Time horizon	One-year time horizon
Discount rate	Not applicable
Measurement of effectiveness	Reduction of reactivation of tuberculosis (TB), death from reactivation of TB, false positive test results
Measurement and valuation of preference based outcomes	Not applicable
Resource use and costs	Costs for screening LTBI with QFT-G, TST, costs of treatment of LTBI and , costs of treatment of adverse events, survival of reactivation and death from reactivation
Currency, price date and conversion	US$, price year unknown
Model type	Decision tree structure
Assumptions	1) If the model showed superiority of testing within the first year, benefits will increase over longer periods 2) An indeterminate test result would lead to a second test immediately 3) A second indeterminate result would lead to a consultation rather than treatment with anti-TNF-α 4) Some outcomes were not modelled because they were considered rare: secondary cases of TB from reactivation, reactivation TB despite successful treatment with INH, outcomes resulting from indeterminate tests or non-adherence with LTBI prophylaxis

	5) The authors suggested that multidrug resistance is rare in the USA, hence this was not modelled
Analytical methods	Authors conducted one-way sensitivity analysis by varying key model input parameters to explore the uncertainty in these parameter estimates. Two-way sensitivity analyses were also conducted and the results were presented in an online supplement of the paper
Results	
Study parameters	Estimates of the prevalence of true LTBI in the USA, sensitivity and specificity for QFT-G and TST, anergy TST in immunosuppressed people, reactivation TB with biological exposure, probability of death from reactivation, side-effect (hepatitis) of INH treatment, probability of surviving from hepatitis, costs (QFT-G, TST, LTBI treatment, survival of reactivation and death from reactivation)
Incremental costs and outcomes	In a cohort of 1000 immunosuppressed IBD people being screened for LTBI, the QFT-G strategy was cheaper than the TST strategy, $84, 850 compared with $156, 370, respectively. The use of QFT-G would avoid 30 false-negative cases, 4.92 TB reactivations and 1.4 deaths compared with TST
Characterising uncertainty	From the sensitivity analysis, the QFT-G strategy continued to dominate the TST strategy by varying key model input parameters. The authors suggested that the results would change at extreme values, but these variations are unlikely to be unrealistic in reality
Discussion	
Study findings	The base-case results showed that QFT-G dominated the TST strategy. QFT-G was least costly, and produced greater benefits
Limitations	1) The accuracy of the model structure to reflect what happens in reality is based on the model input parameters used. 2) There is no gold standard for the diagnosis of LTBI. 3) The costs used in the model are specific to the USA
Generalizability	The generalizability of these results may be compromised here because of the lack of reporting on the setting and location and not presenting the cost-year for which these costs represent
Other	
Source of funding	Dr. Wang is partially funded by NIH grant KM1 CA156709-01
Conflicts of interest	No conflicts of interest declared
Comments	The authors here have presented a model that illustrates the testing and treatment pathway that someone with IBD will undergo if being screened for LTBI. The model demonstrates that the QFT strategy is cheaper and offers greater benefits in this patient population. However, these authors have not suggested the year for which these costs represent, hence making these results less generalizable
Authors conclusion	
Based on the results of the cost-effectiveness analysis, they concluded that the QFT-G strategy dominated TST in this population, and suggested that QFT-G should be the choice of testing strategy for identifying LTBI in people who are immunosuppressed	
Reviewer's conclusion	
This model adds to the existing literature on the diagnosis of LTBI in an immunosuppressed population. The model is subject to some limitations to which the authors acknowledged. However, the generalizability of the model is somewhat compromised by no suggesting the study setting within which the analyses were conducted, and the cost year was not mentioned. Furthermore, these authors have not stated in this paper the index used to	

inflate the cost information that was obtained from published sources

Appendix 12 Critical appraisal of the economic evaluation using the Consolidated Health Economic Reporting Standards checklist

TABLE 59 Consolidated Health Economic Reporting Standards quality assessment checklist for economic evaluation studies

Assessment	Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
Title	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Introduction										
Background and objectives	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods										
Target population and subgroups	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	UNC	UNC	UNC	UNC	UNC	UNC	Y	Y	Y	Y
Study perspective	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discount rate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement and valuation of preference-based outcomes	N	N	N	N	N	Y	NA	N	Y	Y
Estimating resources and costs	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Currency, price date and conversion	Y	Y	Y	Y	Y	Y	Y	Y	Y	UNC
Choice of model	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assumptions	Y	Y	Y	UNC	Y	Y	Y	Y	Y	Y
Analytical methods	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Assessment	Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
Results										
Study parameters	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Incremental costs and outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Characterising uncertainty	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion										
Study findings	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalisability	Y	Y	UNC	Y	UNC	UNC	UNC	Y	Y	N
Other										
Source of funding	Y	Y	UNC	Y	Y	Y	Y	Y	Y	Y
Conflicts of interest	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

N, no; NA, not applicable; UNC, unclear; Y, yes.

Appendix 13 Critical appraisal of the economic models using an adapted Philips *et al.*[195] checklist

TABLE 60 Philips *et al.*'s quality assessment checklist for studies that include an economic model

	Criteria	Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
Structure											
1	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Is the primary decision maker specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Are the model inputs consistent with the stated perspective?	N	N	N	Y	Y	Y	Y	Y	Y	Y
6	Has the scope of the model been stated and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	UNC	Y
9	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Are the causal relationships described by the model structure justified appropriately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Are the structural assumptions transparent and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
13	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14	Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
15	Is there justification for the exclusion of feasible options?	NA	NA	NA	NA	NA	NA	NA	NA	NA	N

Criteria		Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18	Are the time horizon of the model and the duration of treatment described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	Y	Y	Y	NA	Y	NA	NA	NA
Data											
21	Are the data identification methods transparent and appropriate given the objectives of the model?	UNC	Y	UNC	Y	Y	Y	Y	Y	Y	Y
22	Where choices have been made between data sources are these justified appropriately?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC
23	Has particular attention been paid to identifying data for the important parameters of the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
24	Has the quality of the data been assessed appropriately?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC	UNC
25	Where expert opinion has been used are the methods described and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
27	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	Are transition probabilities calculated appropriately?	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA
29	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	N	N	N	N	N	N	N

continued

TABLE 60 Philips *et al.*'s quality assessment checklist for studies that include an economic model (*continued*)

Criteria		Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
30	If not, has the omission been justified?	N	N	N	N	N	N	N	N	N	N
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	NA	NA	NA	NA	NA	UNC	NA	NA	NA
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
36	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
37	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
38	Have discount rates been described and justified given the target decision maker?	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
39	Are the utilities incorporated into the model appropriate?	Y	Y	Y	Y	Y	Y	NA	Y	NA	NA
40	Is the source of utility weights referenced?	Y	Y	Y	Y	Y	Y	NA	Y	NA	NA
41	Are the methods of derivation for the utility weights justified?	UNC	UNC	UNC	UNC	UNC	Y	NA	UNC	NA	NA
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
44	Is the process of data incorporation transparent?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Criteria		Kowada 2010[196]	Kowada 2012[197]	Kowada 2013[198]	Kowada 2014[199]	Laskin 2013[200]	Linas 2011[201]	Mandalakas 2013[203]	CG117[10]	Pareek 2013[77]	Swaminath 2013[202]
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N	N	N	N	Y	NA	NA	NA	NA	NA
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	UNC	UNC	UNC	UNC	Y	NA	NA	NA	NA	NA
47	Have the four principal types of uncertainty been addressed?	N	N	N	N	N	N	N	N	N	N
48	If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	N	N	N	N
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	N	Y	NA	N	N	N	Y	N
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	N	N	N	N	N	N
51	Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	Y	Y	Y	Y	N	Y	N	Y	NA
52	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y	Y	Y	Y	UNC	Y	Y	Y
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	UNC	UNC	UNC	UNC	UNC	UNC	UNC	Y	UNC	UNC
55	Are any counterintuitive results from the model explained and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
56	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
57	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	NA	Y	N	Y	N	Y	N

N, no; NA, not applicable; UNC, unclear; Y, yes.

Appendix 14 List of studies excluded from the cost-effectiveness review with reasons for exclusion ($n = 15$)

TABLE 61 List of studies excluded from the cost-effectiveness review

Number	Author ID	Details	Reason(s) for exclusion
1	Burgos JL	Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *Int J Tuberc Lung Dis* 2009;**13**:962–8	No comparator
2	Deuffic-Burban	Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. *Int J Tuberc Lung Dis* 2010;**14**:471–81	Close contacts
3	Diel R	Enhanced cost–benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany. *Respir Med* 2009;**103**:1838–53	Cost analysis
4	Hardy AB	Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries. *Thorax* 2010;**65**:178–80	No economic model
5	Iqbal AZ	Cost-effectiveness of using QuantiFERON Gold (QFT-G) versus tuberculin skin test (TST) among US and foreign born populations at a public health department clinic with a low prevalence of tuberculosis. *Public Health Nurs* 2014;**31**:144–52	No economic model
6	Jit M	Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ* 2011;**343**:d5376	Active TB
7	Kawamura LM	IGRAs in public health practice: economic issues. *Int J Tuberc Lung Dis* 2010;**14**(Suppl. 1):60–3	Letter to editor
8	Langley I	Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. *Health Care Manag Sci* 2012;**15**:239–53	Active TB
9	Mancuso JD	Cost-effectiveness analysis of targeted and sequential screening strategies for latent tuberculosis. *Int J Tuberc Lung Dis* 2011;**15**:1223–30	Military recruits
10	Pareek M	Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011;**11**:435–44	No comparator
11	Pooran A	Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost-effectiveness analysis. *BMC Pulm Med* 2010;**10**:7	Close contacts
12	Shah M	QuantiFERON-TB Gold in-Tube implementation for latent tuberculosis diagnosis in a public health clinic: a cost-effectiveness analysis. *BMC Infect Dis* 2012;**12**:360	TST-positive referrals

continued

TABLE 61 List of studies excluded from the cost-effectiveness review (*continued*)

Number	Author ID	Details	Reason(s) for exclusion
13	Steffen RE	Cost-effectiveness of QuantiFERON-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. *PLOS ONE* 2013;**8**:e59546	Immunocompetent close contacts
14	van der Have M	Optimizing screening for tuberculosis and hepatitis B prior to starting tumor necrosis factor-alpha inhibitors in Crohn's disease. *Dig Dis Sci* 2014;**59**:554–63	Intervention not of interest
15	Verma G	Tuberculosis screening for long-term care: a cost-effectiveness analysis. *Int J Tuberc Lung Dis* 2013;**17**:1170–7	Compared screening strategies (no screening, LTBI screening and active TB screening)

ID, identification.

Appendix 15 Illustrative structures for the immunocompromised population, recent arrivals from countries with a high incidence of active tuberculosis and the general population

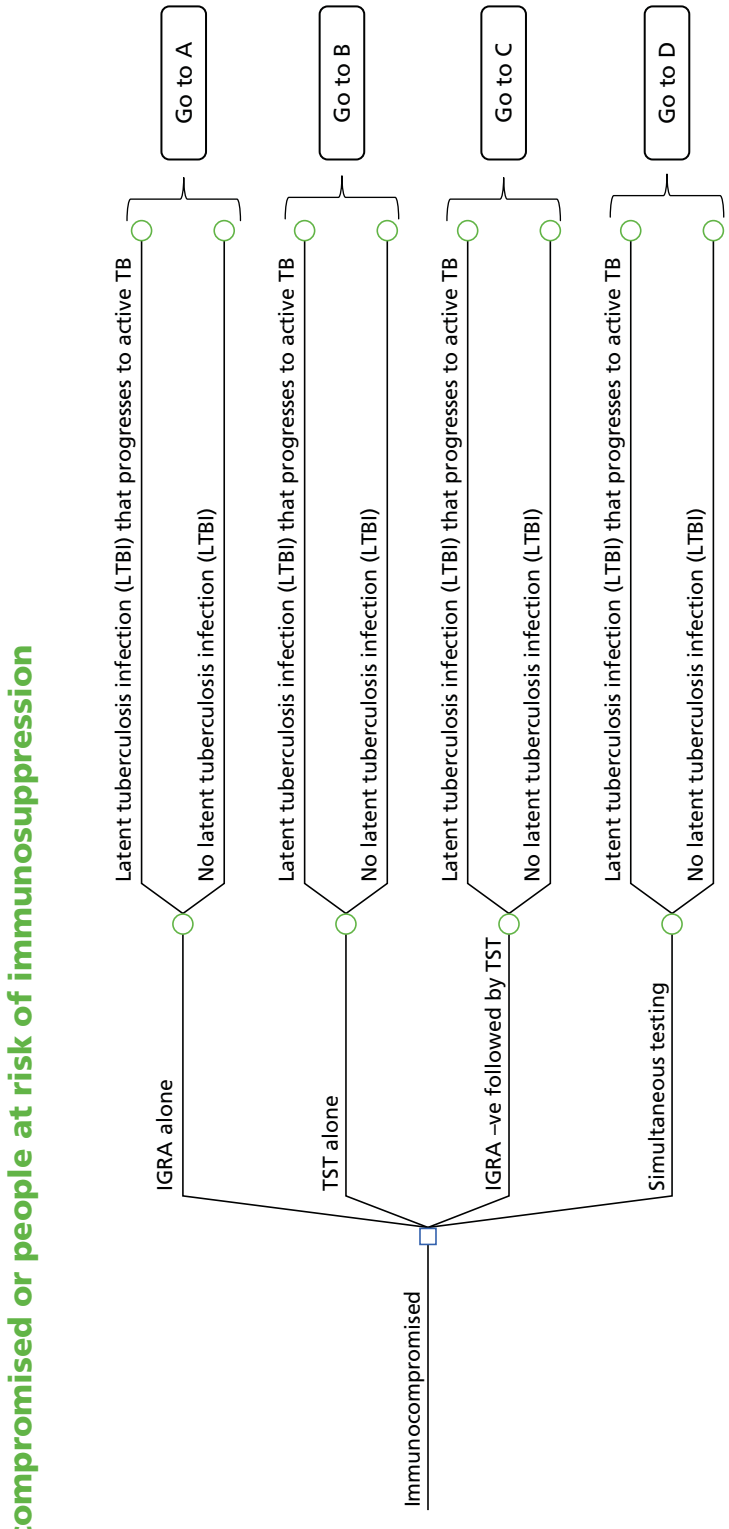

FIGURE 60 Decision tree pathway for the immunocompromised population. –ve, negative.

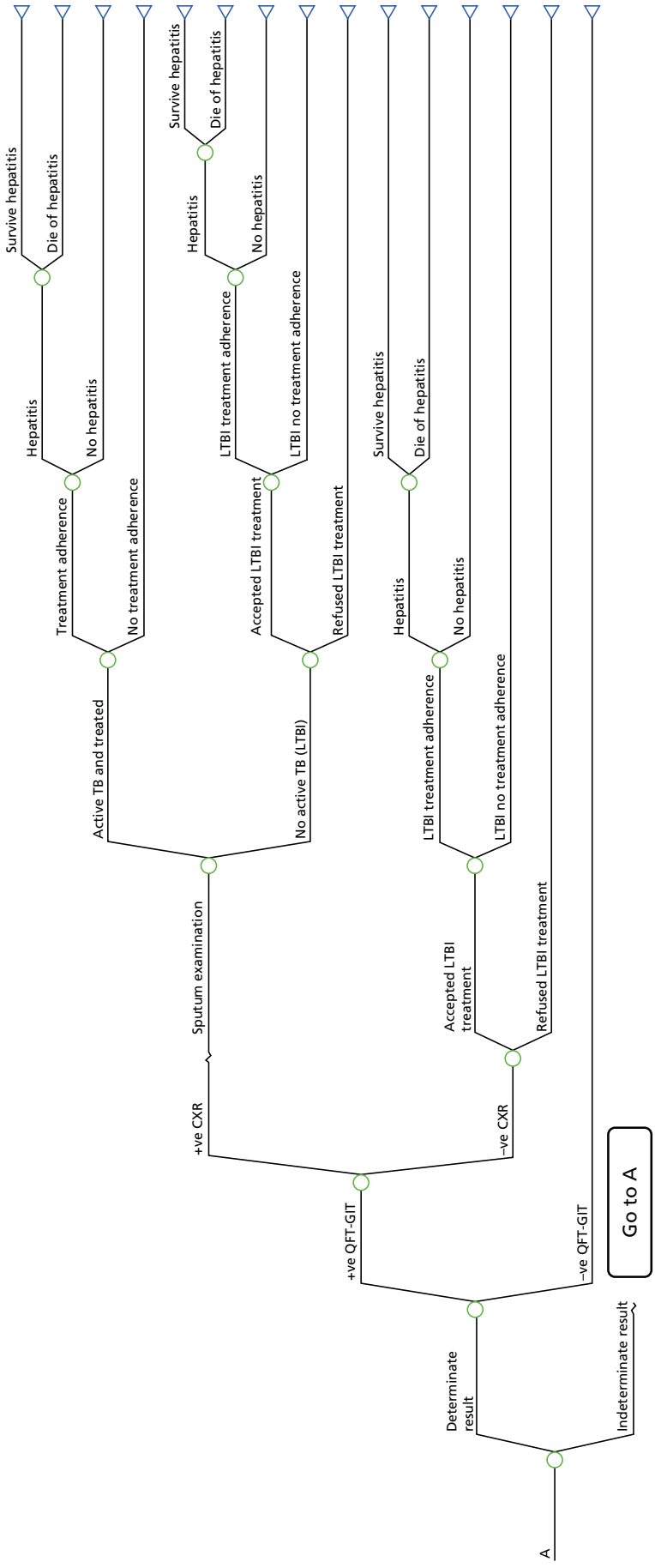

FIGURE 61 Pathway for the IGRA-alone diagnostic strategy in the immunocompromised population. –ve, negative; +ve, positive; CXR, chest radiography.

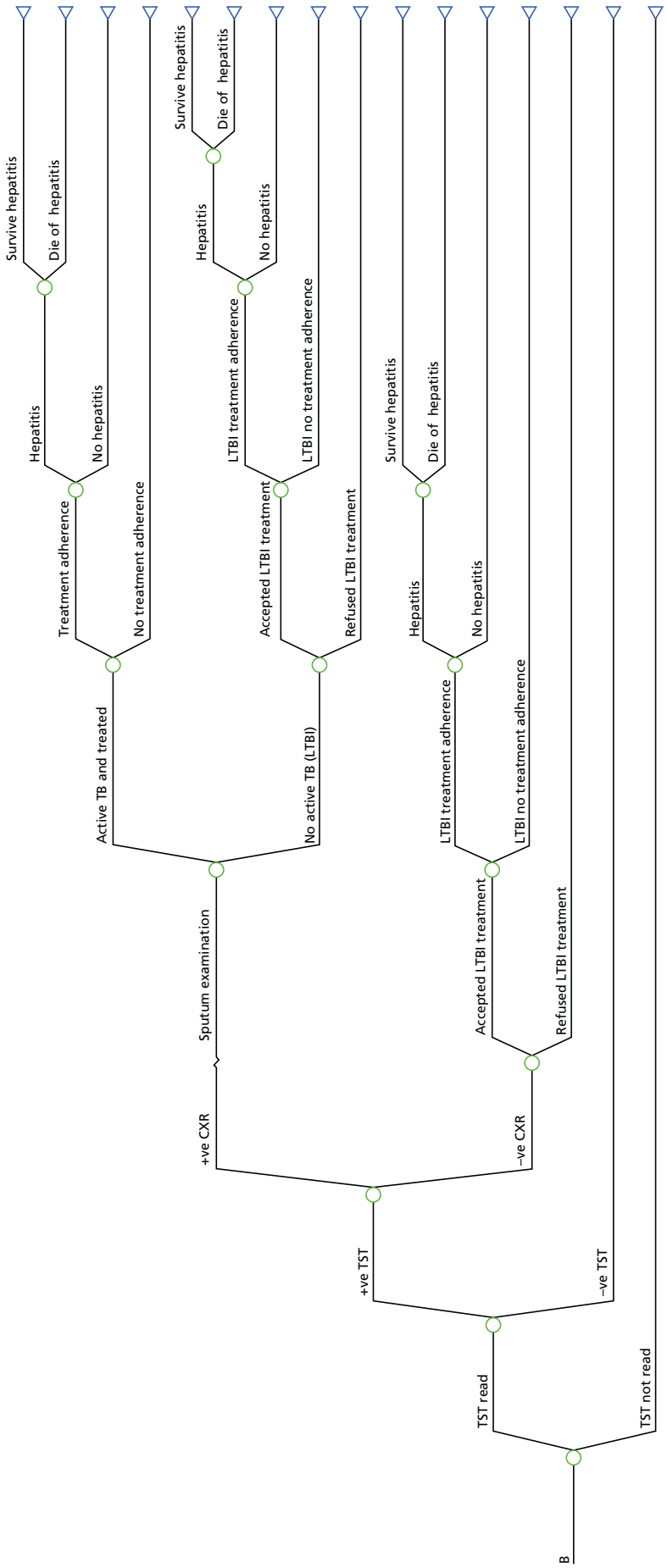

FIGURE 62 Pathway for the TST-alone diagnostic strategy in the immunocompromised population. –ve, negative; +ve, positive; CXR, chest radiography.

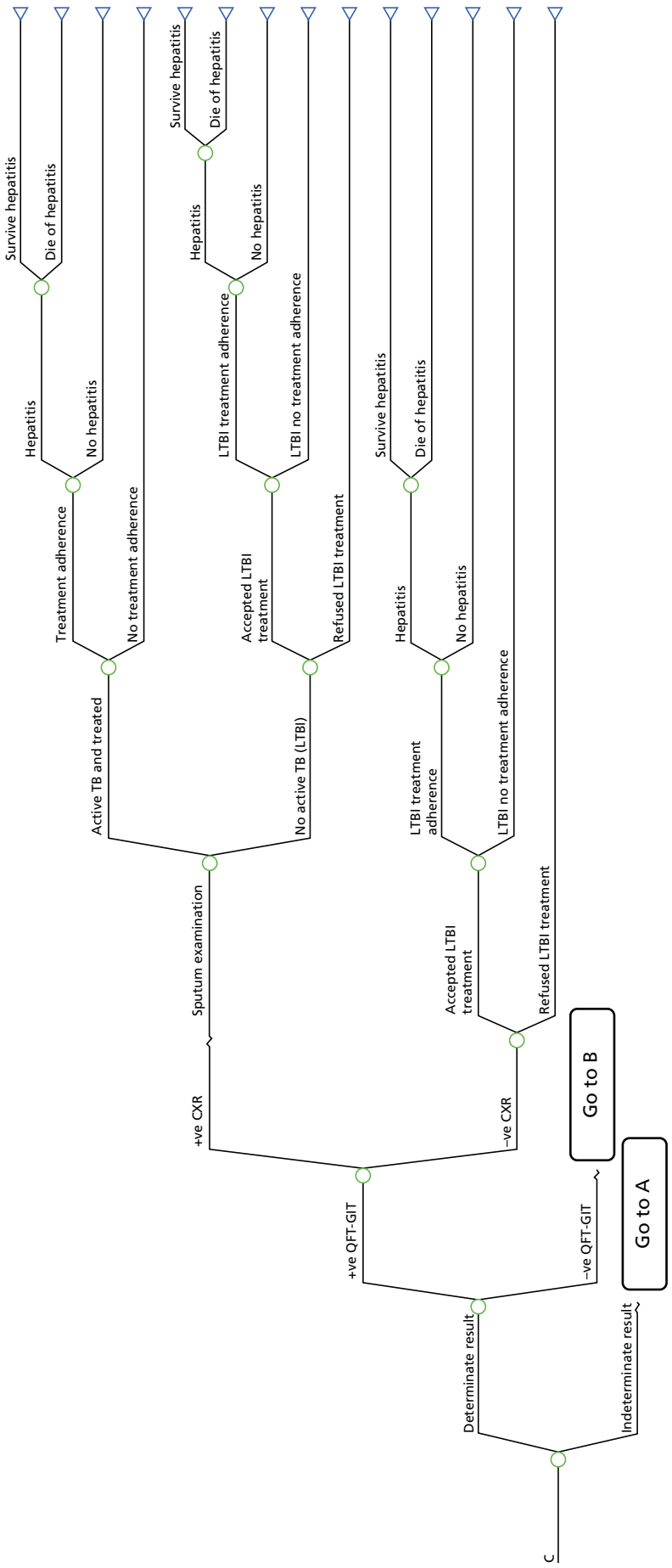

FIGURE 63 Pathway for the diagnostic strategy IGRA negative followed by TST in the immunocompromised population. –ve, negative; +ve, positive; CXR, chest radiography.

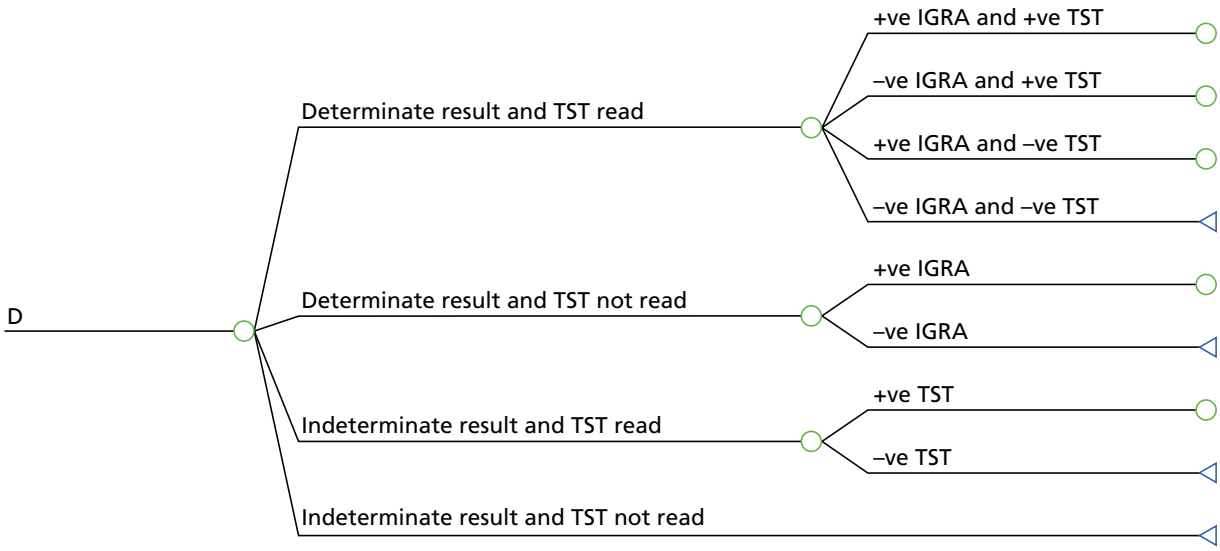

FIGURE 64 Pathway for the diagnostic strategy IGRA and TST in the immunocompromised population. –ve, negative; +ve, positive.

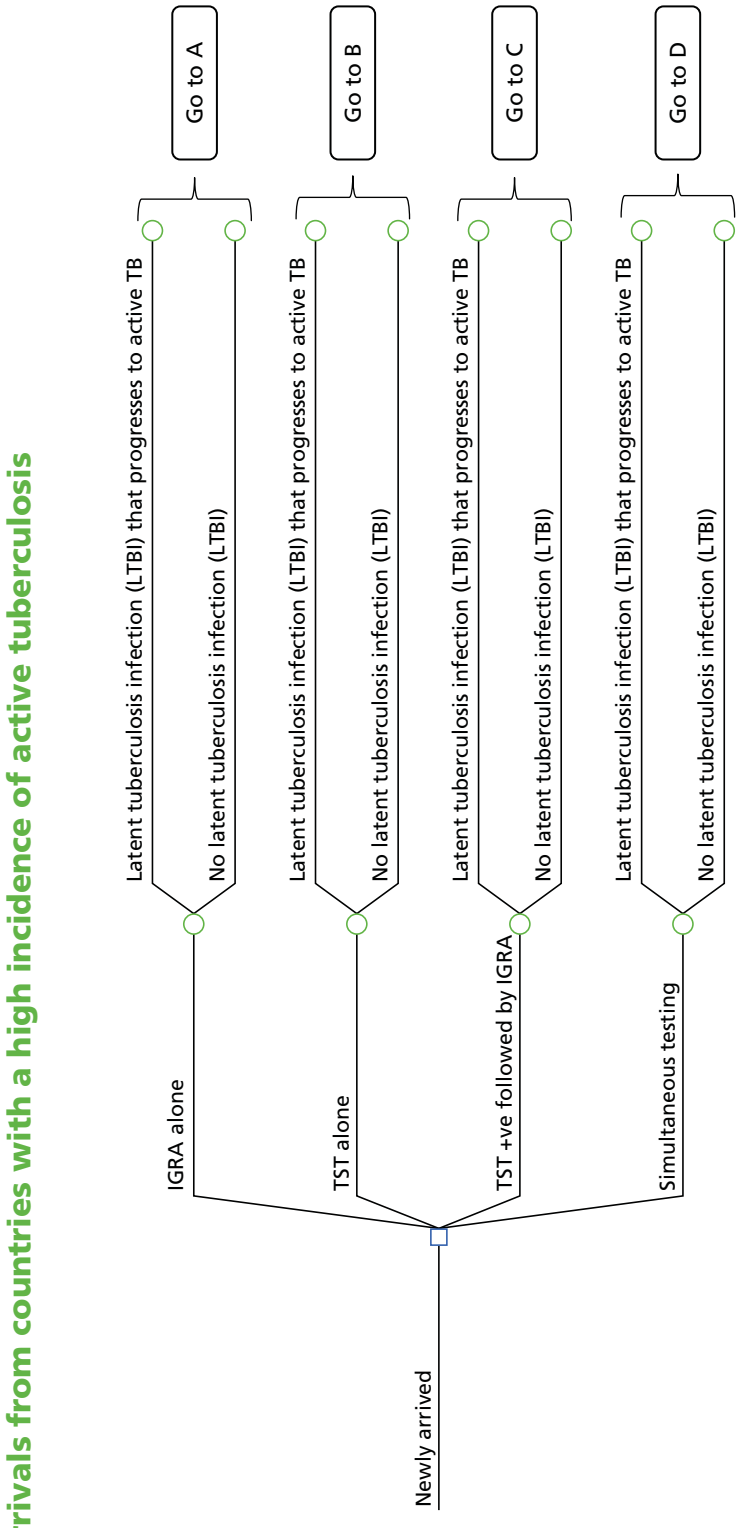

FIGURE 65 Decision tree structure for recent arrivals from countries with a high incidence of active TB. +ve, positive.

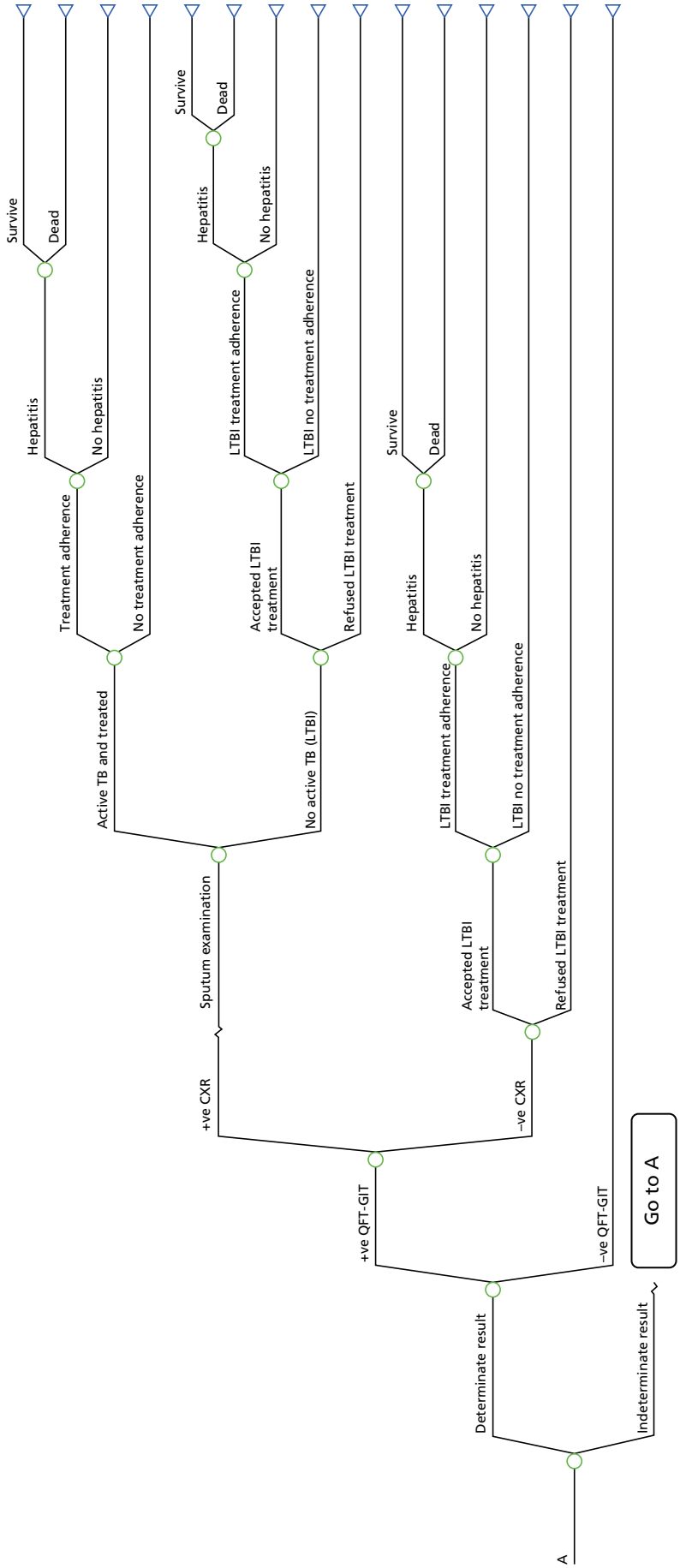

FIGURE 66 Pathway for the IGRA-alone diagnostic strategy in recently arrived population. –ve, negative; +ve, positive; CXR, chest radiography.

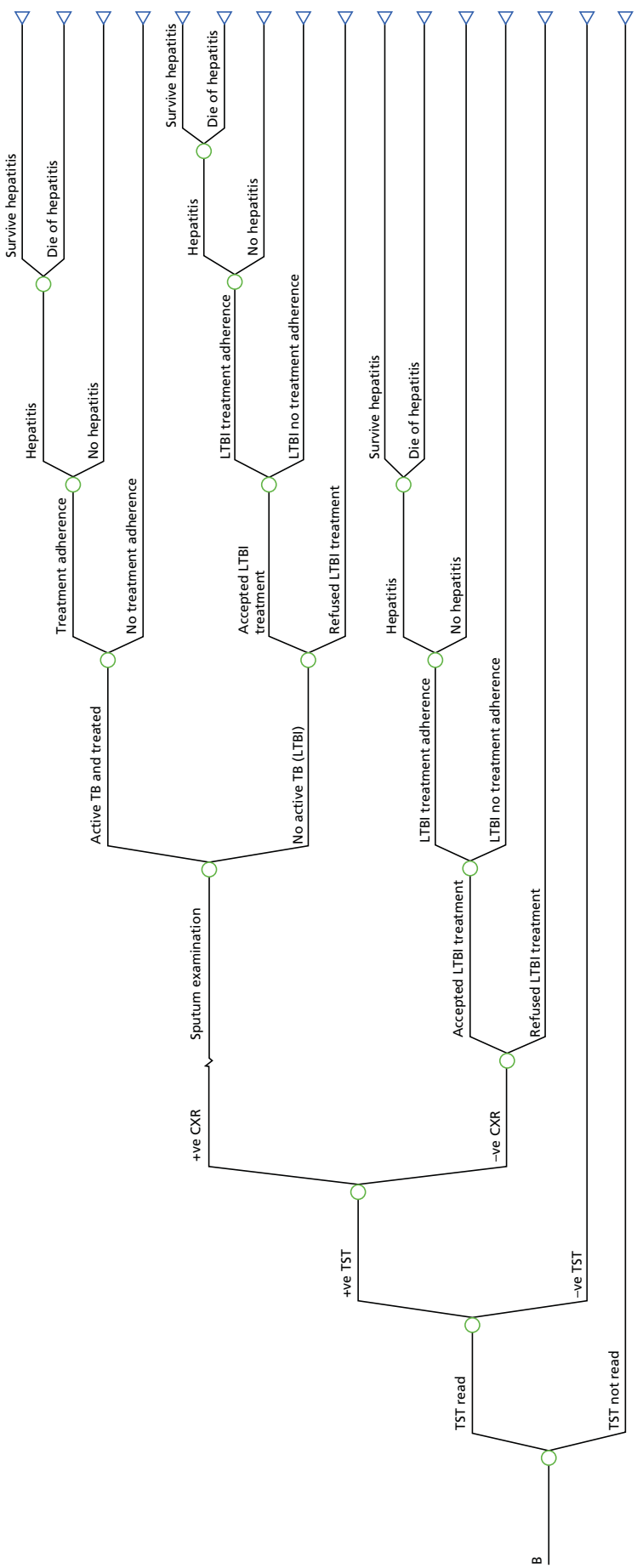

FIGURE 67 Pathway for the TST-alone diagnostic strategy in the recently arrived population. –ve, negative; +ve, positive; CXR, chest radiography.

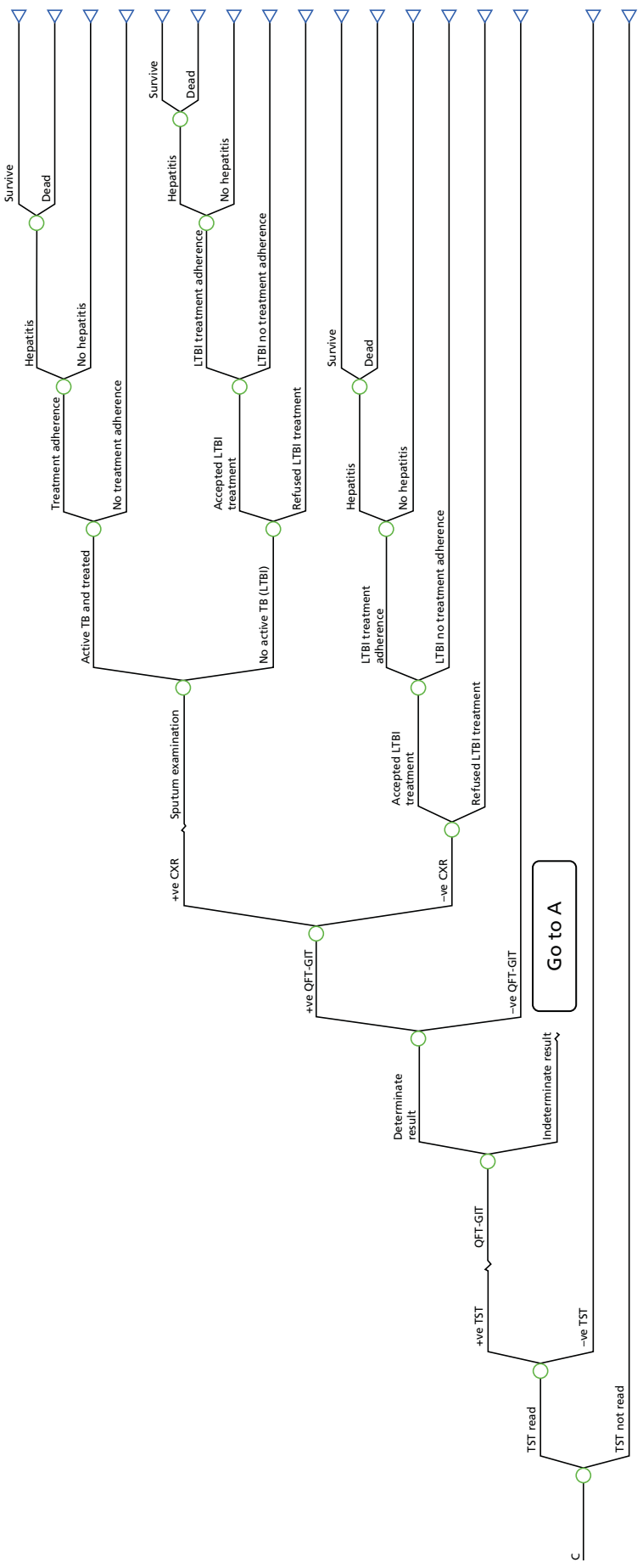

FIGURE 68 Pathway for the diagnostic strategy of TST positive followed by IGRA in the recently arrived population. –ve, negative; +ve, positive; CXR, chest radiography.

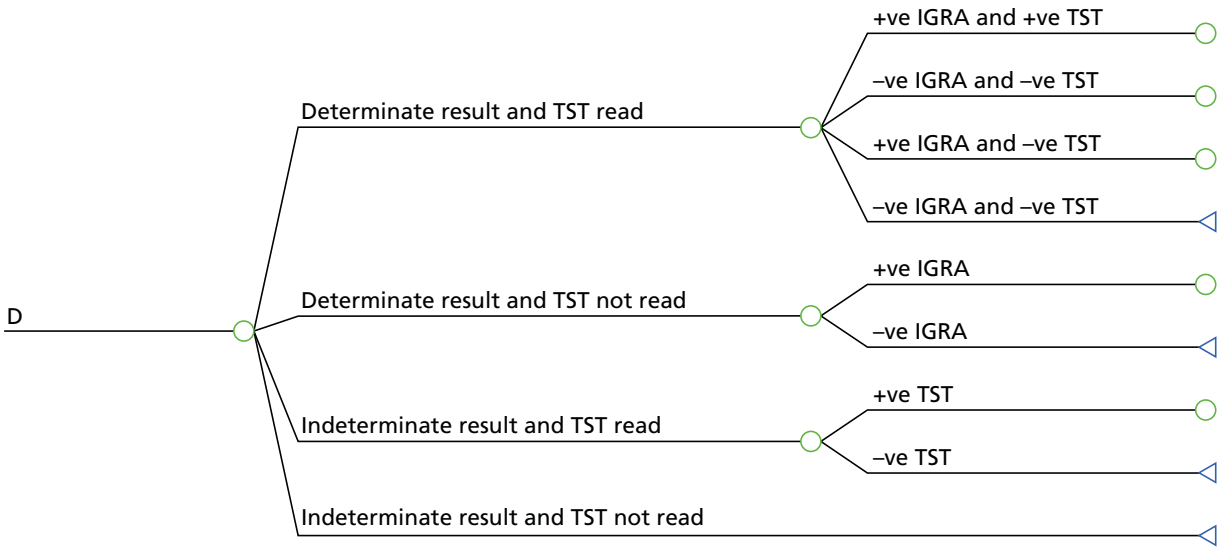

FIGURE 69 Pathway for the diagnostic strategy of IGRA and TST in the recently arrived population. –ve, negative; +ve, positive.

General population

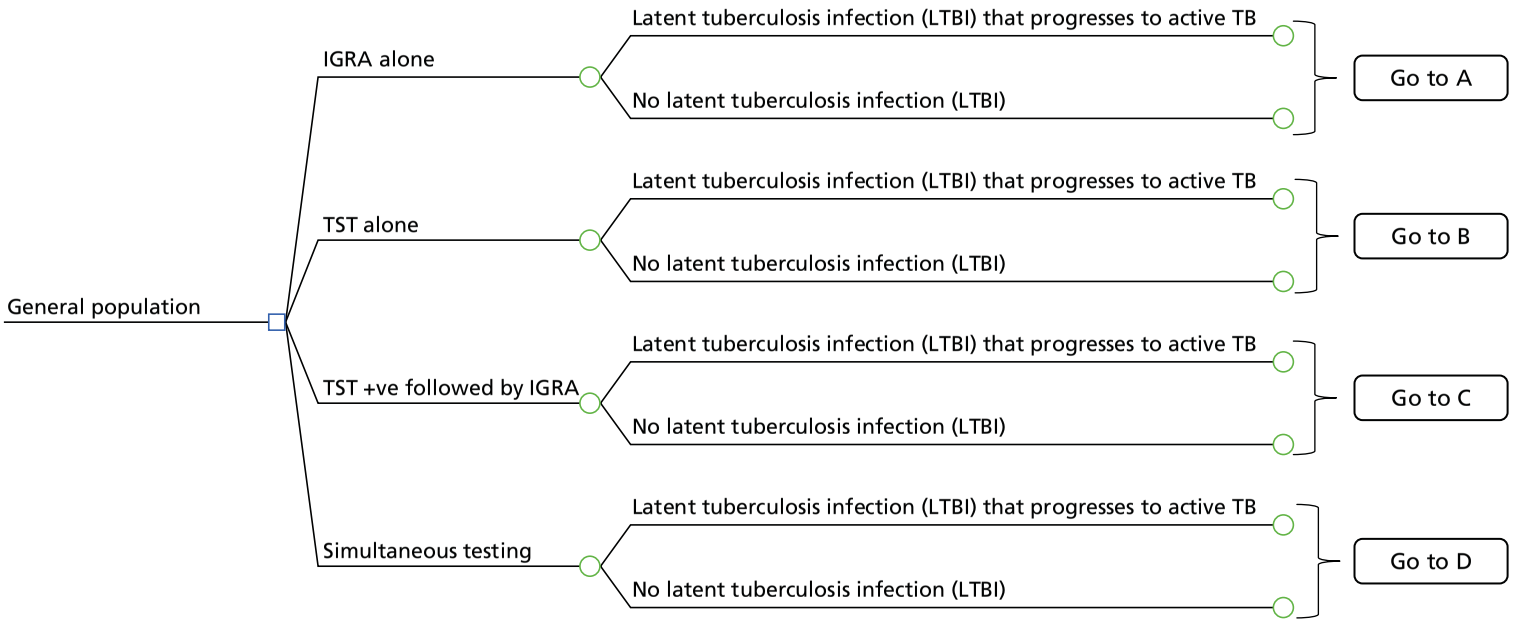

FIGURE 70 Decision tree structure for the general population. +ve, positive.

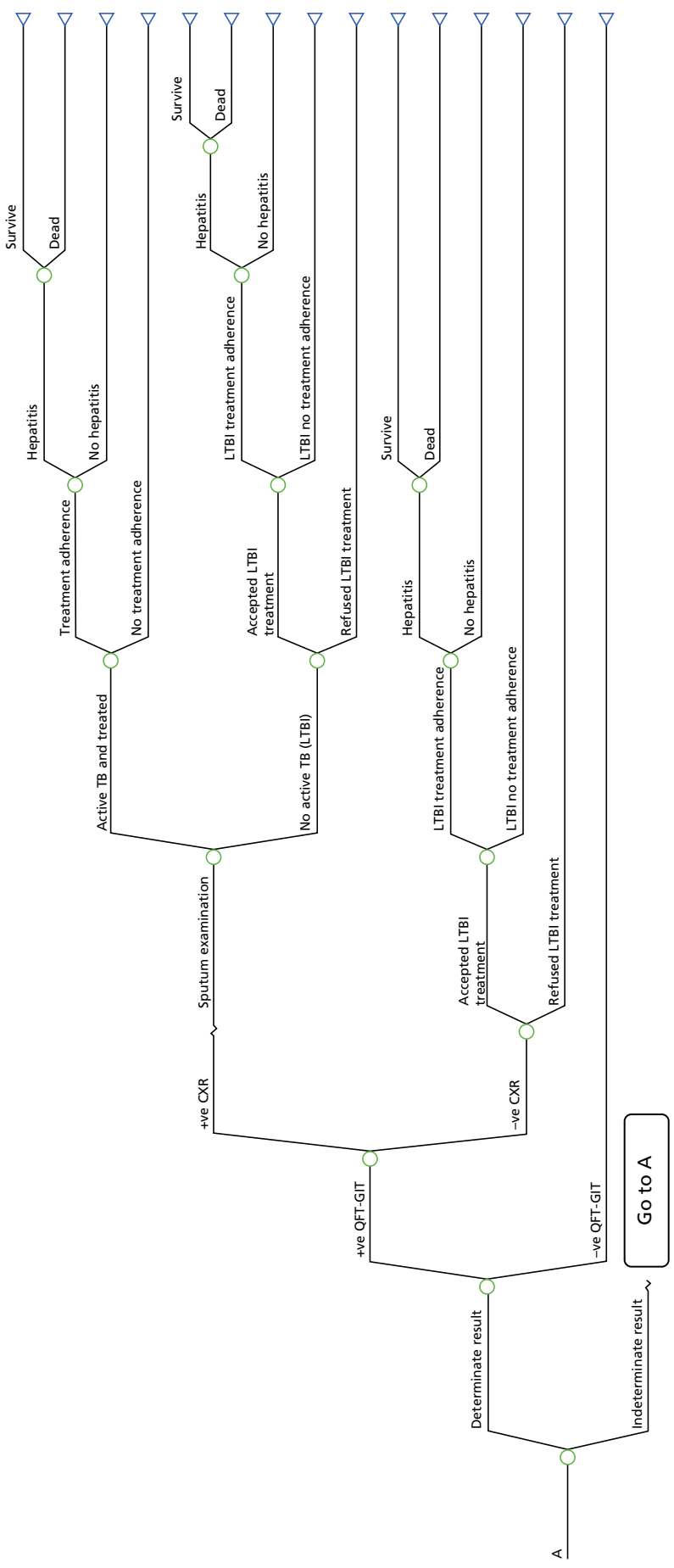

FIGURE 71 Pathway for the IGRA-alone diagnostic strategy in the general population. –ve, negative; +ve, positive; CXR, chest radiography.

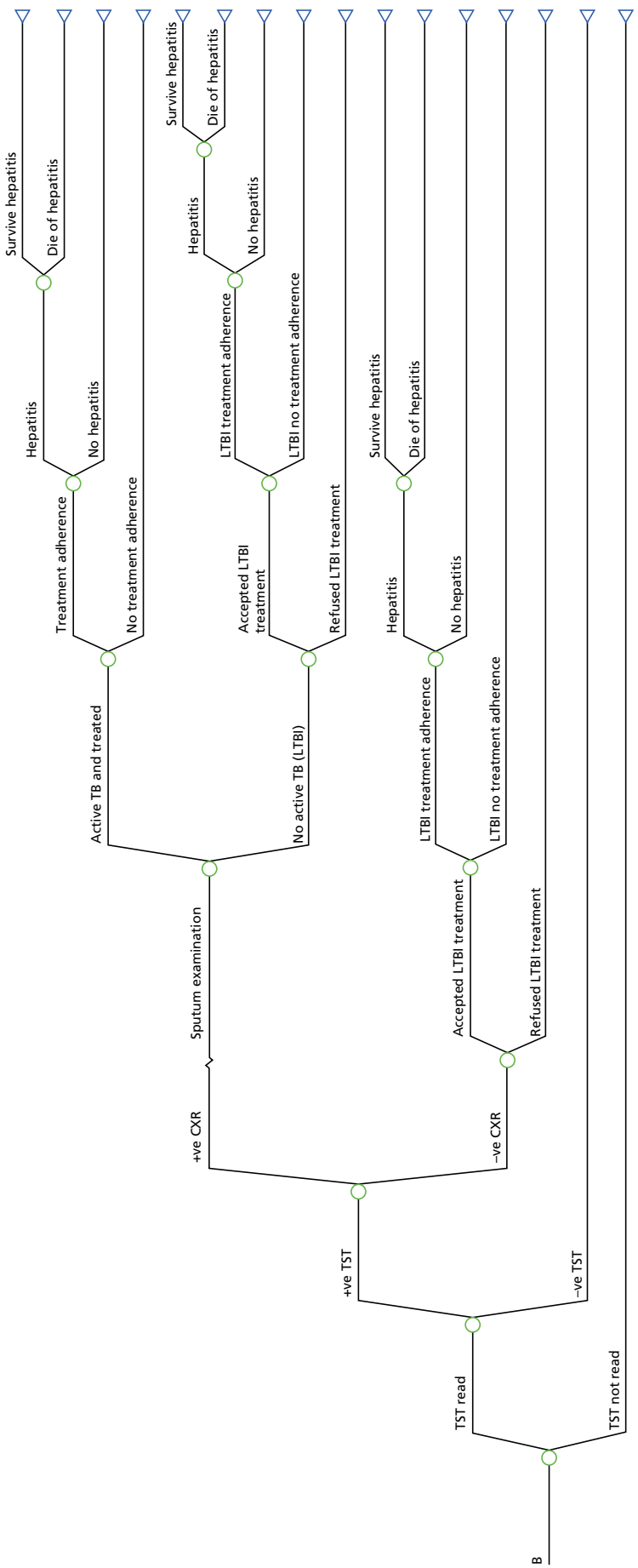

FIGURE 72 Pathway for the TST-alone diagnostic strategy in the general population. –ve, negative; +ve, positive; CXR, chest radiography.

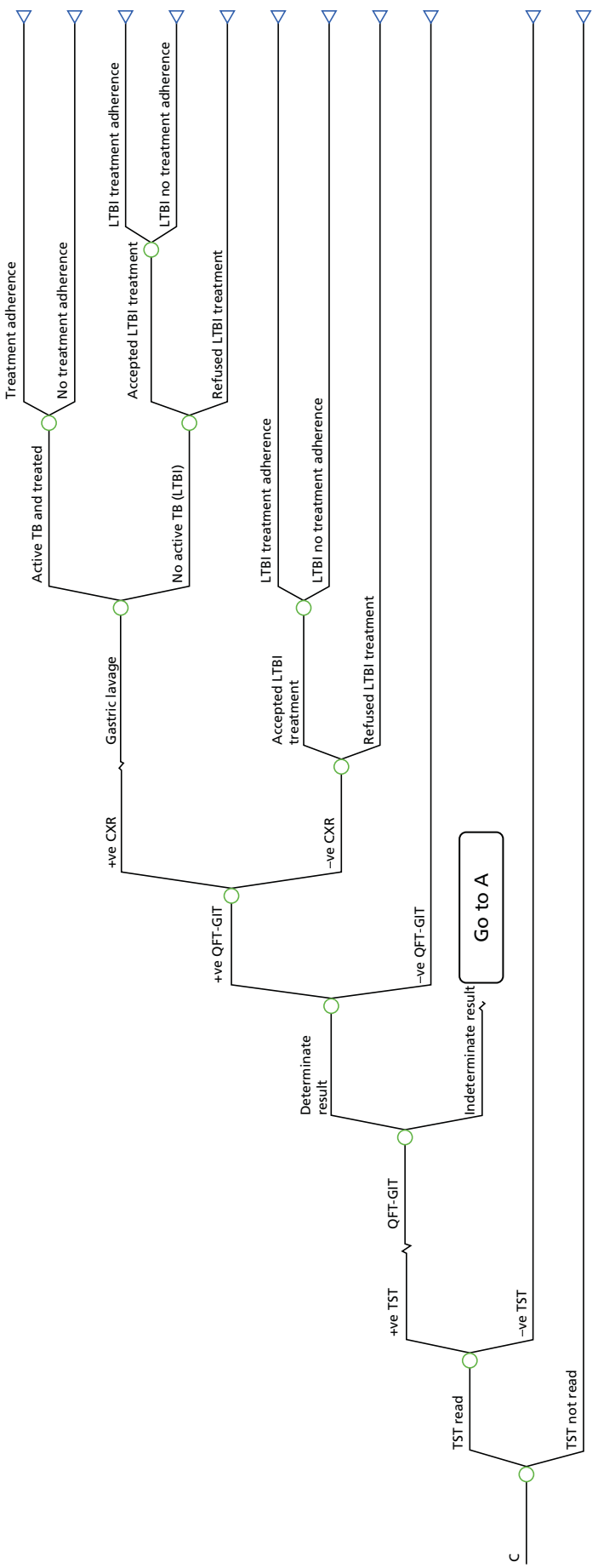

FIGURE 73 Pathway for the diagnostic strategy of TST positive followed by IGRA in the general population. –ve, negative; +ve, positive; CXR, chest radiography.

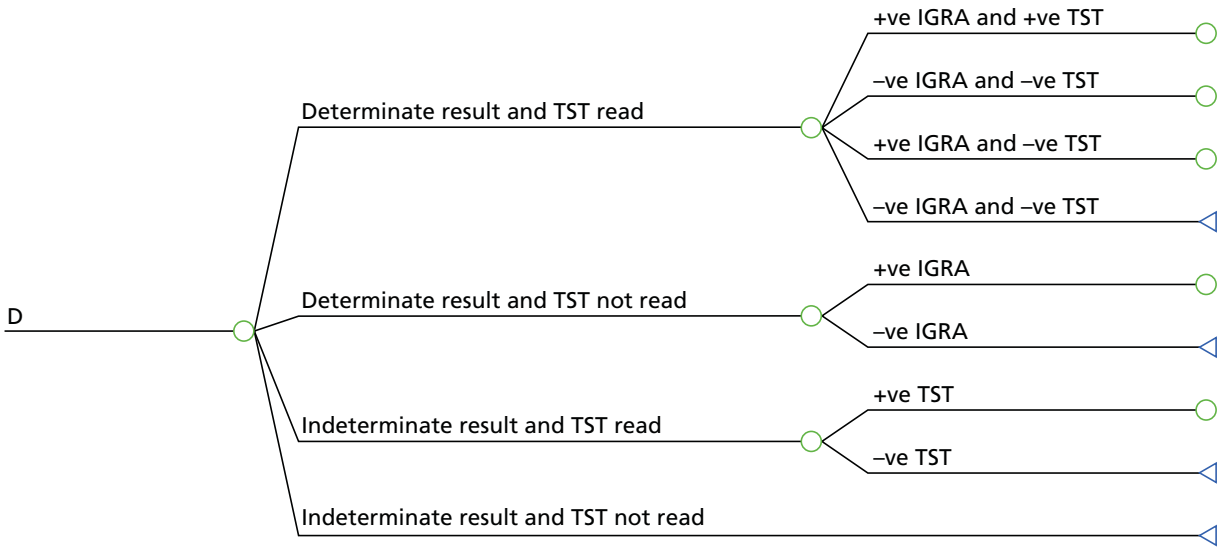

FIGURE 74 Pathway for the diagnostic strategy of IGRA and TST in the general population. –ve, negative; +ve, positive.

Appendix 16 Resources used to derive unit costs for the treatment of latent tuberculosis infection and tuberculosis and model input parameters

TABLE 62 Treatment for LTBI

Resource use	Quantity	Description	Unit costs (£, 2013)	Source
Investigations				
Full blood count	2	DAPS08 – Phlebotomy	4	Assumptions and consultation with clinical expert on the number of full blood counts, liver function tests and outpatient visits (NICE TB Guideline Development Group, 12 January 2015, personal communication); NHS reference costs 2012/13;[214] Curtis[217]
Liver function test	4	DAPS08 – Phlebotomy	4	
Outpatient visits	2 visits	Weighted average of all outpatient procedures	135	
Nurse contact (in clinic)[a,b]	3 visits	15 minutes	12.25	Assumption and consultation with clinical expert; Curtis[217]
Drug treatment				
Isoniazid	18 packs (28 × 100-mg tablets per pack)	6 months of isoniazid[c]	19.24	NHS electronic drug tariff[216]
Estimated cost per person for treatment of LTBI			677.07 (6H)	

a We assumed that a nurse specialist employed on the NHS scale Agenda for Change band 6 point 27 would require 15 minutes of contact time with a LTBI patient.
b People who refuse treatment are informed and advised. We assumed that a nurse specialist employed on the NHS scale Agenda for Change band 6 point 27 would require 15 minutes to inform and advise an individual.
c Based on a requirement of 300 mg daily for 6 months.

TABLE 63 Treatment for TB

Resource use	Quantity	Description	Unit costs (£, 2013)	Source
Investigations				
Chest radiography	3	DAPF – Direct access plain film	28	NHS reference costs 2012/13[214]
Sputum examination	6	DAPS07 – Microbiology	7	
Full blood count	2	DAPS08 – Phlebotomy	4	
Liver function test	8	DAPS08 – Phlebotomy	4	
Inpatient stay	7.28 days	DZ14E – Pulmonary, Pleural or Other Tuberculosis, with CC Score 0–1	492	Bothamley *et al.*[215]
Outpatient visits	8 visits	Weighted average of all outpatient procedures	135	
Drug treatment				
Ethambutol	6 packs	1200 mg daily for 2 months	256.44	BNF[231]
Pyrazinamide	8 packs	2 g daily for 2 months	250.80	BNF[231]
Rifinah® (300 mg/150 mg) (Sanofi) (isoniazid 150 mg, rifampicin 300 mg)	6 packs	Two tablets daily for 6 months	126.12	BNF[231]
Estimated cost for treatment of active TB per person			5461.12	

BNF, *British National Formulary*; CC, complication and comorbidity.

TABLE 64 Model input parameters required for the immunocompromised population

Variable	Base-case value	Range for SA	PSA distribution	Source
Probabilities				
Prevalence of LTBI	0.0222	0.0152–0.0306	[a]	Derived from the current clinical effectiveness study
Sensitivity TST (≥ 5 mm)	0.3242	0.1119–0.5848	[a]	
Specificity TST (< 5 mm)	0.7422	0.7288–0.7557	[a]	
Sensitivity TST (≥ 10 mm)	0.1682	0.0252–0.3899	[a]	
Specificity TST (< 10 mm)	0.8397	0.7899–0.8831	[a]	
Sensitivity QFT-GIT	0.5548	0.2473–0.8373	[a]	
Specificity QFT-GIT	0.8227	0.8052–0.8396	[a]	
Sensitivity T-SPOT.*TB*	0.6665	0.3517–0.9144	[a]	
Specificity T-SPOT.*TB*	0.6846	0.6346–0.7331	[a]	
Sensitivity of TST conditional on negative QFT-GIT (LTBI arm)	0.2775	0.0121–0.7989	Not varied	
Specificity of TST conditional on negative QFT-GIT (no LTBI arm)	0.4465	0.3909–0.4993	Not varied	
Sensitivity of TST conditional on positive QFT-GIT (LTBI arm)	0.4206	0.0023–0.3891	Not varied	
Specificity of TST conditional on positive QFT-GIT (no LTBI arm)	0.8058	0.00006–0.8058	Not varied	
Determinate QFT-GIT	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
Determinate T-SPOT.*TB*	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
TST read	0.9400	0.6–1.00	Beta(164,10.5)	Pareek *et al.*[77]
Initial active TB	0.00001	–	Not varied	Laskin *et al.*[200]
TB treatment adherence	1.0000	–	Not varied	Pareek *et al.*[77]
Accepting LTBI treatment	0.9400	0.50–1.00	Beta(141,9)	CG117[10]
Adherence to LTBI treatment	0.8000	0.50–0.90	Beta(41,10)	Kowada[198]
Isoniazid-induced hepatitis after TB treatment	0.0040	0.001–0.010	Beta(2.7,664)	Assumption
Isoniazid-induced hepatitis after LTBI treatment	0.0040	0.001–0.010	Beta(2.7,664)	Laskin *et al.*[200]
Death from isoniazid-induced hepatitis	0.00002	0.00001–0.0001	Beta(0.5,25125)	Pooran *et al.*[209]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	–	Log-normal (–1.065,0.842)	White and Jit[210]
Average number of secondary cases from one index case	0.2	0.1–0.3	Log-normal (–1.609,0.354)	Pareek *et al.*[6]
Average delay from infection to activation	2.88	–	Log-normal (1.058,0.333)	Okuonghae *et al.*[211]

continued

TABLE 64 Model input parameters required for the immunocompromised population (*continued*)

Variable	Base-case value	Range for SA	PSA distribution	Source
Annualised reactivation rate from resolved TB	0.013	0.004–0.025	Beta(7,513)	Oxlade *et al.*[212]
Case fatality rate for active TB (0–4 years)	0.0477	–	Beta(628,12543)	Crofts *et al.*[213]
Case fatality rate for active TB (5–14 years)	0.0034	–	Beta(1,290)	Crofts *et al.*[213]
Case fatality rate for active TB (15–44 years)	0.0018	–	Beta(1,564)	Crofts *et al.*[213]
Case fatality rate for active TB (45–64 years)	0.0476	–	Beta(125,2500)	Crofts *et al.*[213]
Case fatality rate for active TB (≥ 65 years)	0.1755	–	Beta(413,1940)	Crofts *et al.*[213]
Resource use and costs (£)				
TST	17.48		Not varied	Pooran *et al.*[209]
QFT-GIT	48.73		Not varied	Pooran *et al.*[209]
T-SPOT.*TB*	59.57		Not varied	Pooran *et al.*[209]
Chest radiography	35.00		Not varied	NHS reference costs 2012/13[214]
Sputum examination	7.00		Not varied	NHS reference costs 2012/13[214]
Adherence to active TB treatment	5461.12		Gamma (10.41,524.6)	Bothamley *et al.*[215]
Cost of non-adherence to active TB treatment	910.19		Not varied	Assumption
Adherence to LTBI treatment[b]	677.07		Uniform (511.69,842.45)	NHS electronic drug tariff[216]
Cost of non-adherence to LTBI treatment	112.85		Uniform (85.24,140.41)	Assumption
Treatment of isoniazid-induced hepatitis	389.51		Gamma (7.13,55.64)	Pareek *et al.*[77]
Utility decrements				
Active TB (while on treatment)	0.15[c]	Not reported	Gamma (11.2,0.0134)	Derived from Kowada[197]
Treatment for LTBI	0.0010	Not reported	Uniform(0,0.002)	
Other				
Discount rate per annum (costs and QALYs)	3.5%			

SA, sensitivity analysis.
a Calculated from posterior distributions generated by MCMC.
b Management of LTBI in children includes drug treatment alone.
c QALY decrement for people being treated for active TB.

TABLE 65 Model input parameters required for the recently arrived population

Variable	Base-case value	Range for SA	PSA distribution	Source
Probabilities				
Prevalence of LTBI	0.0237	0.0150–0.0345	[a]	Derived from the current clinical effectiveness study
Sensitivity TST (≥ 5 mm)	0.9356	0.7786–0.9977	[a]	
Specificity TST (< 5 mm)	0.5011	0.4790–0.5229	[a]	
Sensitivity TST (≥ 10 mm)	0.5915	0.3584–0.8172	[a]	
Specificity TST (< 10 mm)	0.7929	0.7780–0.8073	[a]	
Sensitivity T-SPOT.*TB*	0.7001	0.3978–0.9242	[a]	
Specificity T-SPOT.*TB*	0.3992	0.3439–0.4554	[a]	
Sensitivity of QFT-GIT conditional on negative TST (LTBI arm)	0.6009	0.3465–0.8514	[a]	
Specificity of QFT-GIT conditional on positive TST (no LTBI arm)	0.6102	0.5775–0.6421	[a]	
Sensitivity of QFT-GIT conditional on negative TST (LTBI arm)	0.4807	0.0225–0.9724	[a]	
Specificity of QFT-GIT conditional on negative TST (no LTBI arm)	0.9746	0.9555–0.9893	[a]	
Sensitivity of CXR for diagnosing active TB	0.7800	Not reported	Not varied	Kumar *et al.*[208]
Specificity of CXR for diagnosing active TB	0.5100	Not reported	Not varied	Kumar *et al.*[208]
Determinate QFT-GIT	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
Determinate T-SPOT.*TB*	0.97	–	Beta(873,27)	Derived from Laskin *et al.*[200]
TST read	0.9400	0.6–1.00	Beta(164,10.5)	Pareek *et al.*[77]
Initial active TB	0.00001	–	Not varied	Laskin *et al.*[200]
TB treatment adherence	1.0000	–	Not varied	Pareek *et al.*[77]
Accepting LTBI treatment	0.9400	0.50–1.00	Beta(141,9)	CG117[10]
Adherence to LTBI treatment	0.8000	0.50–0.90	Beta(41,10)	Kowada[198]
Isoniazid-induced hepatitis after TB treatment	0.0040	0.001–0.010	Beta(2.7,664)	Assumption
Isoniazid-induced hepatitis after LTBI treatment	0.0040	0.001–0.010	Beta(2.7,664)	Laskin *et al.*[200]
Death from isoniazid-induced hepatitis	0.00002	0.00001–0.0001	Beta(0.5,25125)	Pooran *et al.*[209]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	–	Log-normal (–1.065,0.842)	White and Jit[210]
Average number of secondary cases from one index case	0.2	0.1–0.3	Log-normal (–1.609,0.354)	Pareek *et al.*[6]

continued

TABLE 65 Model input parameters required for the recently arrived population (*continued*)

Variable	Base-case value	Range for SA	PSA distribution	Source
Average delay from infection to activation	2.88	–	Log-normal (1.058,0.333)	Okuonghae *et al.*[211]
Annualised reactivation rate from resolved TB	0.013	0.004–0.025	Beta(7,513)	Oxlade *et al.*[212]
Case fatality rate for active TB (0–4 years)	0.0477	–	Beta(628,12543)	Crofts *et al.*[213]
Case fatality rate for active TB (5–14 years)	0.0034	–	Beta(1,290)	Crofts *et al.*[213]
Case fatality rate for active TB (15–44 years)	0.0018	–	Beta(1,564)	Crofts *et al.*[213]
Case fatality rate for active TB (45–64 years)	0.0476	–	Beta(125,2500)	Crofts *et al.*[213]
Case fatality rate for active TB (≥ 65 years)	0.1755	–	Beta(413,1940)	Crofts *et al.*[213]
Resource use and costs				
TST	17.48	–	NA	Pooran *et al.*[209]
QFT-GIT	48.73	–	NA	Pooran *et al.*[209]
T-SPOT.*TB*	59.57	–	NA	Pooran *et al.*[209]
CXR	35.00	–	NA	NHS reference costs 2012/13[214]
Sputum examination	7.00	–	NA	NHS reference costs 2012/13[214]
Cost of adherence to active TB treatment	5461.12	–	Gamma (10.41,524.6)	Bothamley *et al.*[215]
Cost of non-adherence to active TB treatment	910.19	–	Not varied	Assumption
Adherence to LTBI treatment	677.07	–	Uniform (511.69,842.45)	NHS electronic drug tariff[216]
Cost of non-adherence to LTBI treatment	112.85	–	Gamma (85.24,140.41)	Assumption
Treatment of INH-induced hepatitis	389.51	–	Gamma (7.13,55.64)	Pareek *et al.*[77]
Utility decrements				
Active TB (while on treatment)	0.15[b]	Not reported	Gamma (11.2,0.0134)	Derived from Kowada[197]
Treatment for LTBI	0.001	Not reported	Uniform(0,0.002)	
Other				
Discount rate per annum (costs and QALYs)	3.5%			

CXR, chest radiography; NA, not applicable; SA, sensitivity analysis.
a Calculated from posterior distributions generated by MCMC.
b QALY decrement for people being treated for active TB.

Appendix 17 WinBUGS code

In this appendix we report on the WinBUGS code used in the evidence synthesis for the child population. The WinBUGS codes used for the immunocompromised and recently arrived populations are very similar but use different sample data. *Table 66* shows the variables and descriptions used in the models.

TABLE 66 Variables and descriptions used in the WinBUGS model

Variable name	Description
Prev	Prevalence
pposQFTG	Probability of a positive QFT-G result
sensQFTG	Sensitivity of QFT-G
specQFTG	Specificity of QFT-G
ATBposQFTG	Number of active TB cases given a positive result on QFT-G
pATBposQFTG	Probability of active TB given a positive result on QFT-G
ATBnegQFTG	Number of active TB cases given a negative result on QFT-G
pATBnegQFTG	Probability of active TB given a negative result on QFT-G
pposQFTGIT	Probability of a positive QFT-GIT result
sensQFTGIT	Sensitivity of QFT-GIT
specQFTGIT	Specificity of QFT-GIT
ATBposQFTGIT	Number of active TB cases given a positive result on QFT-GIT
pATBposQFTGIT	Probability of active TB given a positive result on QFT-GIT
ATBnegQFTGIT	Number of active TB cases given a negative result on QFT-GIT
pATBnegQFTGIT	Probability of active TB given a negative result on QFT-GIT
pposTSPOTTB	Probability of a positive T-SPOT.*TB* result
sensTSPOTTB	Sensitivity of T-SPOT.*TB*
specTSPOTTB	Specificity of T-SPOT.*TB*
ATBposTSPOTTB	Number of active TB cases given a positive result on T-SPOT.*TB*
pATBposTSPOTTB	Probability of active TB given a positive result on T-SPOT.*TB*
ATBnegTSPOTTB	Number of active TB cases given a negative result on T-SPOT.*TB*
pATBnegTSPOTTB	Probability of active TB given a negative result on T-SPOT.*TB*
pposTST5	Probability of a positive TST5 result
sensTST5	Sensitivity of TST5
specTST5	Specificity of TST5
ATBposTST5	Number of active TB cases given a positive result on TST5
pATBposTST5	Probability of active TB given a positive result on TST5
ATBnegTST5	Number of active TB cases given a negative result on TST5
pATBnegTST5	Probability of active TB given a negative result on TST5
pposTST10	Probability of a positive TST10 result
sensTST10	Sensitivity of TST10

continued

TABLE 66 Variables and descriptions used in the WinBUGS model (*continued*)

Variable name	Description
specTST10	Specificity of TST10
ATBposTST10	Number of active TB cases given a positive result on TST10
pATBposTST10	Probability of active TB given a positive result on TST10
ATBnegTST10	Number of active TB cases given a negative result on TST10
pATBnegTST10	Probability of active TB given a negative result on TST10
pposTST15	Probability of a positive TST15 result
sensTST15	Sensitivity of TST15
specTST15	Specificity of TST15
ATBposTST15	Number of active TB cases given a positive result on TST15
pATBposTST15	Probability of active TB given a positive result on TST15
ATBnegTST15	Number of active TB cases given a negative result on TST15
pATBnegTST15	Probability of active TB given a negative result on TST15
TST5QFTGIT	Probability of positive QFT-GIT following a positive result on TST5
TST10QFTGIT	Probability of positive QFT-GIT following a positive result on TST10

WinBUGS code used in the child population

```
model{

for (study in 1:Nstudy){

prev[study] <- mprev

#Binomial link between the number of positive results and probability of a positive result

rplusTST10[study] ~dbin(pposTST10[study],Npats[study,1])

rminusTST10[study] <- Npats[study,1] - rplusTST10[study]
```

```
pposTST10[study] <- prev[study]*sensTST10 + (1-prev[study])*(1-specTST10)

ATBposTST10[study]~dbin(pATBposTST10[study],rplusTST10[study])

pATBposTST10[study] <- prev[study]*sensTST10/pposTST10[study]

ATBnegTST10[study]~dbin(pATBnegTST10[study],rminusTST10[study])

pATBnegTST10[study] <- prev[study]*(1-sensTST10)/(prev[study]*(1-sensTST10)+specTST10*(1-prev[study]))


rplusTST10IT[study] ~dbin(pposTST10IT[study],Npats[study,2])

rminusTST10IT[study] <- Npats[study,2] - rplusTST10IT[study]


pposTST10IT[study] <- prev[study]*sensTST10IT + (1-prev[study])*(1-specTST10IT)

ATBposTST10IT[study]~dbin(pATBposTST10IT[study],rplusTST10IT[study])

pATBposTST10IT[study] <- prev[study]*sensTST10IT/pposTST10IT[study]

ATBnegTST10IT[study]~dbin(pATBnegTST10IT[study],rminusTST10IT[study])

pATBnegTST10IT[study] <- prev[study]*(1-sensTST10IT)/(prev[study]*(1-sensTST10IT)+specTST10IT*(1-prev
[study]))


rplusTSPOTTB[study] ~dbin(pposTSPOTTB[study],Npats[study,3])

rminusTSPOTTB[study] <- Npats[study,3] - rplusTSPOTTB[study]


pposTSPOTTB[study] <- prev[study]*sensTSPOTTB + (1-prev[study])*(1-specTSPOTTB)

ATBposTSPOTTB[study]~dbin(pATBposTSPOTTB[study],rplusTSPOTTB[study])

pATBposTSPOTTB[study] <- prev[study]*sensTSPOTTB/pposTSPOTTB[study]

ATBnegTSPOTTB[study]~dbin(pATBnegTSPOTTB[study],rminusTSPOTTB[study])

pATBnegTSPOTTB[study] <- prev[study]*(1-sensTSPOTTB)/(prev[study]*(1-sensTSPOTTB)+specTSPOTTB*
(1-prev[study]))
```

```
rplusTST10[study] ~ dbin(pposTST10[study],Npats[study,4])

rminusTST10[study] <- Npats[study,4] - rplusTST10[study]


pposTST10[study] <- prev[study]*sensTST10 + (1-prev[study])*(1-specTST10)

ATBposTST10[study]~dbin(pATBposTST10[study],rplusTST10[study])

pATBposTST10[study] <- prev[study]*sensTST10/pposTST10[study]

ATBnegTST10[study]~dbin(pATBnegTST10[study],rminusTST10[study])

pATBnegTST10[study] <- prev[study]*(1-sensTST10)/(prev[study]*(1-sensTST10)+specTST10*(1-prev[study]))


rplusTST10[study] ~dbin(pposTST10[study],Npats[study,5])

rminusTST10[study] <- Npats[study,5] - rplusTST10[study]


pposTST10[study] <- prev[study]*sensTST10 + (1-prev[study])*(1-specTST10)

ATBposTST10[study]~dbin(pATBposTST10[study],rplusTST10[study])

pATBposTST10[study] <- prev[study]*sensTST10/pposTST10[study]

ATBnegTST10[study]~dbin(pATBnegTST10[study],rminusTST10[study])

pATBnegTST10[study] <- prev[study]*(1-sensTST10)/(prev[study]*(1-sensTST10)+specTST10*(1-prev[study]))


rplusTST15[study] ~dbin(pposTST15[study],Npats[study,6])

rminusTST15[study] <- Npats[study,6] - rplusTST15[study]


pposTST15[study] <- prev[study]*sensTST15 + (1-prev[study])*(1-specTST15)

ATBposTST15[study]~dbin(pATBposTST15[study],rplusTST15[study])

pATBposTST15[study] <- prev[study]*sensTST15/pposTST15[study]

ATBnegTST15[study]~dbin(pATBnegTST15[study],rminusTST15[study])

pATBnegTST15[study] <- prev[study]*(1-sensTST15)/(prev[study]*(1-sensTST15)+specTST15*(1-prev[study]))
```

```
}

for (i in 1:N.cs){

rplusTST10TST10IT[i]~dbin(pplusTST10TST10IT[i],rplusTST10[cs.index[i]])

pplusTST10TST10IT[i] <-prev[cs.index[i]]*sensTST10*cpos.sensTST10IT5+((1-specTST10)*(1-prev[cs.index[i]])
*(1-cpos.specTST10IT5))/pposTST10[cs.index[i]]

rnegTST10TST10IT[i]~dbin(pnegTST10TST10IT[i],rminusTST10[cs.index[i]])

pnegTST10TST10IT[i] <-((1-prev[cs.index[i]])*specTST10*cneg.specTST10IT5+(1-sensTST10)*prev[cs.index[i]]
*(1-cneg.sensTST10IT5))/((1-prev[cs.index[i]])*specTST10+prev[cs.index[i]]*(1-sensTST10))

}

for (i in 1:N.cs2){

rplusTST10TST10IT[i]~dbin(pplusTST10TST10IT[i],rplusTST10[cs2.index[i]])

pplusTST10TST10IT[i] <-prev[cs2.index[i]]*sensTST10*cpos.sensTST10IT10+((1-specTST10)*(1-prev
[cs2.index[i]])*(1-cpos.specTST10IT10))/pposTST10[cs2.index[i]]

rnegTST10TST10IT[i]~dbin(pnegTST10TST10IT[i],rminusTST10[cs2.index[i]])

pnegTST10TST10IT[i] <-((1-prev[cs2.index[i]])*specTST10*cneg.specTST10IT10+(1-sensTST10)*prev
[cs2.index[i]]*(1-cneg.sensTST10IT10))/((1-prev[cs2.index[i]])*specTST10+prev[cs2.index[i]]*(1-sensTST10))

}
```

```
sensTST10IT <- cpos.sensTST10IT5*sensTST10 + cneg.sensTST10IT5*(1-sensTST10)

specTST10IT <- cpos.specTST10IT5*(1-specTST10) + cneg.specTST10IT5*(specTST10)


#Prior at baseline


sensTST10~dunif(0,1)

specTST10~dunif(0,1)

logit(sensTST10)<-logit(sensTST10)-dsens510

dsens510~dunif(0,5)

logit(specTST10)<-logit(specTST10)+dspec510

dspec510~dunif(0,5)

sensTST15~dunif(0,1)

specTST15~dunif(0,1)

sensTST10~dunif(0,1)

specTST10~dunif(0,1)

sensTSPOTTB~dunif(0,1)

specTSPOTTB~dunif(0,1)

cpos.sensTST10IT5~dunif(0,1)

cpos.specTST10IT5~dunif(0,1)

cneg.sensTST10IT5~dunif(0,1)

cneg.specTST10IT5~dunif(0,1)

cpos.sensTST10IT10~dunif(0,1)

cpos.specTST10IT10~dunif(0,1)

cneg.sensTST10IT10~dunif(0,1)

cneg.specTST10IT10~dunif(0,1)
```

```
mprev ~ dbeta(1,1)

}

#Sample data from the clinical evidence

list(Nstudy=13,Npats=structure(.Data=c(84,84,73,84,84,84,306,306,306,306,306,306,104,104,104,104,
104,104,5244,5244,5244,5244,5244,5244,59,59,59,59,59,59,69,69,69,69,69,69,204,204,204,204,204,
204,195,195,195,195,195,195,184,184,184,184,184,184,1073,1073,1073,1073,1073,1073,104,104,
104,104,104,104,50,50,50,50,50,50,2982,2966,2982,2982,2982,2982),.Dim=c(13,6)),N.cs=6,cs.index=
c(1,4,6,9,10,11),N.cs2=4,cs2.index=c(7,8,12,13), rplusTST10=c(NA,6,NA,NA,18,NA,NA,NA,NA,NA,NA,
NA,NA),rplusTST10IT=c(20,NA,21,2669,NA,10,31,33,61,331,21,30,317),rplusTSPOTTB=c(16,NA,NA,NA,
NA,NA,NA,NA,NA,NA,NA,NA,NA), rplusTST10=c(38,200,40,2894,NA,42,NA,NA,84,645,27,NA,NA),
rplusTST10=c(NA,90,40,NA,8,NA,115,47,NA,NA,NA,32,663),rplusTST15=c(NA,NA,NA,NA,NA,NA,NA,NA,
NA,NA,NA,NA,231),ATBposTST10=c(NA,0,NA,NA,10,NA,NA,NA,NA,NA,NA,NA,NA),ATBposTST10IT=c(NA,
NA,6,39,NA,NA,NA,NA,NA,NA,NA,NA,11),ATBposTSPOTTB=c(NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,
NA,NA),ATBposTST10=c(NA,0,6,40,NA,NA,NA,NA,NA,NA,NA,NA,NA),ATBposTST10=c(NA,0,4,NA,3,NA,NA,
NA,NA,NA,NA,NA,13),ATBposTST15=c(NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,13),ATBnegTST10=
c(NA,0,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA),ATBnegTST10IT=c(NA,NA,0,13,NA,NA,NA,NA,NA,NA,NA,
NA,12),ATBnegTSPOTTB=c(NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA),ATBnegTST10=c(NA,0,0,12,NA,
NA,NA,NA,NA,NA,NA,NA,NA), ATBnegTST10=c(NA,0,2,NA,7,NA,NA,NA,NA,NA,NA,NA,10),ATBnegTST15=
c(NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,10),rplusTST10TST10IT=c(18,2383,10,51,266,19),
rnegTST10TST10IT=c(44,2064,27,90,363,75), rplusTST10TST10IT=c(27,28,30,231),rnegTST10TST10IT=
c(85,143,18,2219))

#Sample initial values

list(dsens510=0.5,dspec510=0.5)
```

The robustness of the model was assessed by examining the convergence diagnostics for evidence of when the simulation appeared to mix. This was examined based on visual inspection of the sample trace plots. A burn-in period of 30,000 simulations was used followed by a further 30,000 simulations.

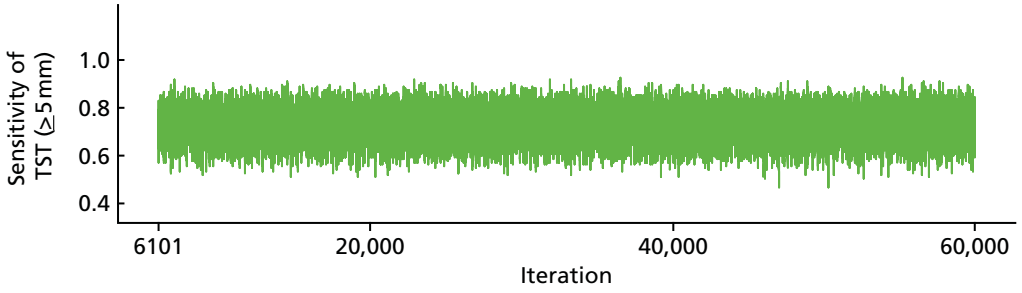

FIGURE 75 Sample traces of chains for sensitivity of TST (≥ 5 mm) where convergence/mixing looks reasonable.

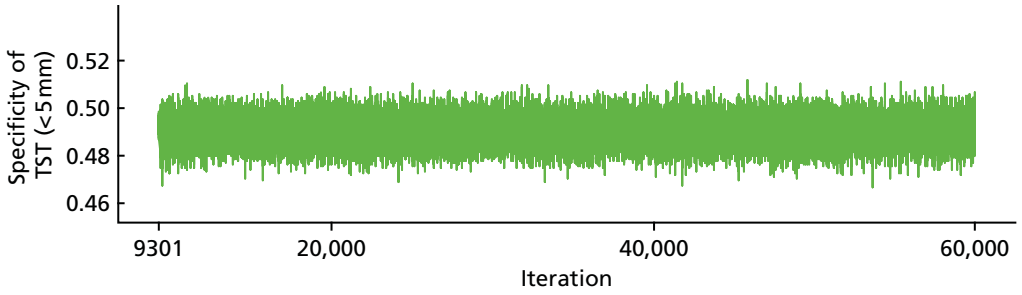

FIGURE 76 Sample traces of chains for specificity of TST (< 5 mm) where convergence/mixing looks reasonable.

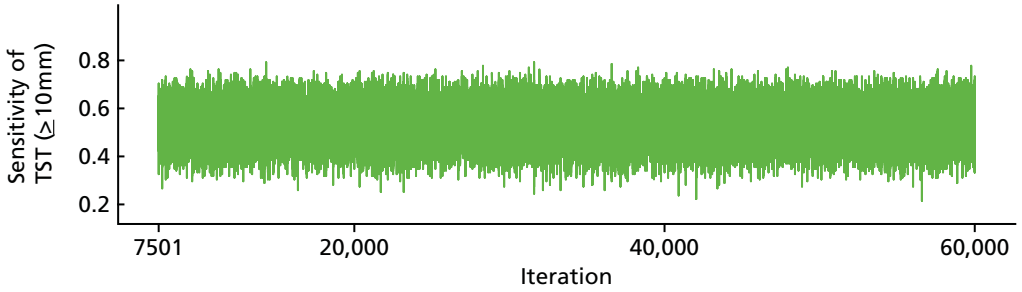

FIGURE 77 Sample traces of chains for sensitivity of TST (≥ 10 mm) where convergence/mixing looks reasonable.

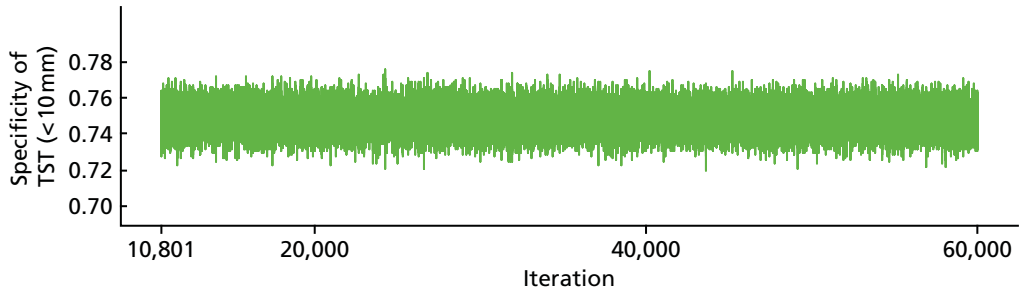

FIGURE 78 Sample traces of chains for specificity of TST (< 10 mm) where convergence/mixing looks reasonable.

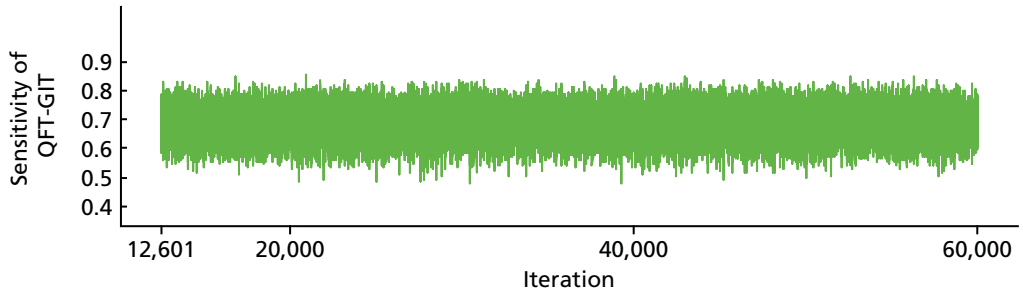

FIGURE 79 Sample traces of chains for sensitivity of QFT-GIT where convergence/mixing looks reasonable.

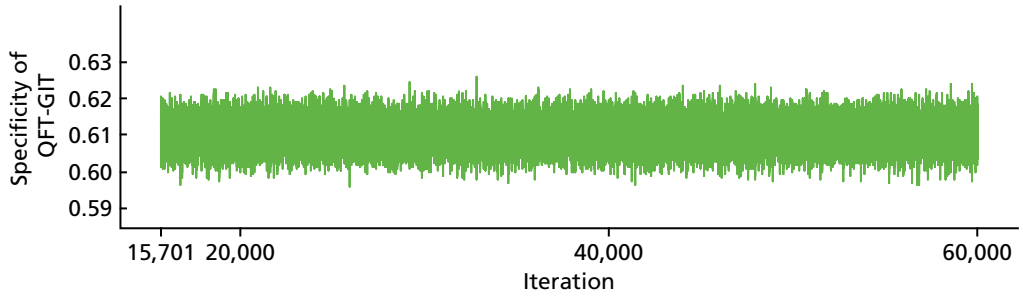

FIGURE 80 Sample traces of chains for specificity of QFT-GIT where convergence/mixing looks reasonable.

Appendix 18 Information required to derive the diagnostic accuracy of various testing strategies by population

Children and adolescents

TABLE 67 Information used to derive sensitivity in the child and adolescent population

Test	Total tested	Number of positives	Number of positives who developed active TB	Length of follow-up (years)	Source
QFT-G	306	6	0	3	Higuchi *et al.*[161]
TST (≥ 5 mm)	306	200	0		
TST (≥ 10 mm)	306	90	0		
QFT-GIT	104	21	6	2–4	Diel *et al.*[102]
TST (≥ 5 mm)	104	40	6		
TST (≥ 10 mm)	104	40	4		
QFT-GIT	5244	2669	39	3.8	Mahomed *et al.*[103]
TST (≥ 5 mm)	5244	2894	40		
QFT-G	59	18	10	1	Noorbakhsh *et al.*[104]
TST (≥ 10 mm)	59	8	3		
QFT-GIT	2966	317	11	2	Song *et al.*[152]
TST (≥ 10 mm)	2982	663	13		
TST (≥ 15 mm)	2982	231	13		

TABLE 68 Information used to derive specificity in the child population

Test	Total tested	Number of positives	Number of positives who developed active TB	Length of follow-up (years)	Source
QFT-G	306	300	0	3	Higuchi *et al.*[161]
TST (< 5 mm)	306	106	0		
TST (< 10 mm)	306	216	0		
QFT-GIT	104	83	0	2–4	Diel *et al.*[102]
TST (< 5 mm)	104	64	0		
TST (< 10 mm)	104	64	2		
QFT-GIT	5244	2575	13	3.8	Mahomed *et al.*[103]
TST (< 5 mm)	5244	2350	12		
QFT-G	59	41	0	1	Noorbakhsh *et al.*[104]
TST (< 10 mm)	59	50	7		
QFT-GIT	2966	2649	12	2	Song *et al.*[152]
TST (< 10 mm)	2982	2319	10		
TST (< 15 mm)	2982	2751	10		

Immunocompromised people

TABLE 69 Information used to derive sensitivity in the immunocompromised population

Test	Total tested	Number of positives	Number of positives who developed active TB	Length of follow-up (years)	Source
T-SPOT.*TB*	265	89	4	1.17 (median)	Kim *et al.*[116]
TST (≥ 5 mm)	288	26	1		
QFT-G	30	12	1	2	Lee *et al.*[118]
T-SPOT.*TB*	32	15	0		
TST (≥ 10 mm)	32	20	1		
QFT-GIT	210	40	1	0.8 (median)	Moon *et al.*[115]
TST (≥ 5 mm)	244	39	0		
QFT-GIT	159	26	3	1.3 (median)	Lee *et al.*[149]
TST (≥ 10 mm)	169	19	0		
TST (≥ 15 mm)	169	12	0		
T-SPOT.*TB*	44	6	1	1.75	Sherkat *et al.*[155]
TST (≥ 10 mm)	44	8	1		

TABLE 70 Information used to derive specificity in the immunocompromised population

Test	Total tested	Number of positives	Number of negatives that developed active TB	Length of follow-up (years)	Source
T-SPOT.*TB*	265	176	0	1.17 (median)	Kim *et al.*[116]
TST (< 5 mm)	288	262	3		
QFT-G	30	18	0	2	Lee *et al.*[118]
T-SPOT.*TB*	32	17	2		
TST (< 10 mm)	32	12	1		
QFT-GIT	210	170	1	0.8 (median)	Moon *et al.*[115]
TST (< 5 mm)	244	205	2		
QFT-GIT	159	133	2	1.3 (median)	Lee *et al.*[149]
TST (≤ 10 mm)	169	150	5		
TST (≤ 15 mm)	169	157	5		
T-SPOT.*TB*	44	38	0	1.75	Sherkat *et al.*[155]
TST (≤ 10 mm)	44	36	0		

Recently arrived population

TABLE 71 Information required to derive sensitivity in the recently arrived population

Test	Total tested	Number of positives	Number of positives who developed active TB	Length of follow-up (years)	Source
QFT-GIT	815	238	8	2.67	Harstad *et al.*[143]
TST (≥ 6 mm)	810	415	8		
QFT-GIT	327	178	5	2	Kik *et al.*[144]
T-SPOT.*TB*	299	181	6		
TST (≥ 15 mm)	322	184	7		

TABLE 72 Information required to derive specificity in the recently arrived population

Test	Total tested	Number of positives	Number of positives who developed active TB	Length of follow-up (years)	Source
QFT-GIT	815	577	1	2.67	Harstad *et al.*[143]
TST (≤ 6 mm)	810	395	1		
QFT-GIT	327	149	3	2	Kik *et al.*[144]
T-SPOT.*TB*	299	118	2		
TST (≤ 15 mm)	322	138	1		

EME
HS&DR
HTA
PGfAR
PHR

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