Appendix H: Warwick Evidence Diagnosis of LTBI Report

Please note note that this document will undergo external peer review before it is published in the *Health Technology Assessment* series.

Tuberculosis Clinical Guideline commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence: Final Report

Title of project

Accurate diagnosis of latent Tuberculosis in children, in 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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Declared competing interests of authors:

Aileen Clarke is Professor of Health Sciences, Warwick Medical School, University of Warwick, UK and is on the editorial board of HTA and NIHR Journals Library.

Professor Lalvani is inventor for several patents underpinning T cell-based diagnosis. The ESAT-6/CFP-10 IFN-gamma ELISpot assay (IGRA) was commercialised by an Oxford University spin-out company (T-SPOT.TB®, Oxford Immunotec Ltd, Abingdon, UK) in which the University of Oxford and Professor Lalvani have minority shares of equity and royalty entitlements. Professor Lalvani commented on the draft protocol and no further input was provided thereafter

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

TBC

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Paul Sutcliffe (Associate Professor) co-ordinated the review. Farah Seedat (PhD medical student), Alexander Tsertsvadze (Senior Research Fellow) and Clare Walker (Visiting Academic

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AFB	Acid fast bacilli
BCG	Bacillus Calmette–Guérin
BTS	British Thoracic Society
CD4	Cluster of differentiation 4
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CFP	Culture filtrate protein
CG	Clinical guideline
CI	Confidence interval
CIR	Cumulative incidence ratio
CRF	Compound risk factor
CT	Computerised tomography
CXR	Chest X-ray
DARE	Database of Abstracts of Reviews of Effects
DMARD	Disease-modifying anti-rheumatic drug
DOH	Department of Health
DOT	Direct observed therapy
DOTS	Directly observed therapy short course
DORa	Adjusted diagnostic odds ratio
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-Linked Immunospot
EMBASE	Excerpta Medica dataBASE
EQ-5D	European Quality of Life-5 Dimensions
ESAT-6	Early secretion antigen target-6
ESLD	End-stage liver disease
ESRD	End stage renal disease
ETS	Enhanced tuberculosis surveillance
FPR	False positive rate
FNR	False negative rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

H	Hour
HC	Hepatitis C
HCT	Hematopoietic stem cell transplant
HIV	Human immunodeficiency virus
HRQL	Health related quality of life
HTA	Health technology assessment
ICTRP	International Clinical Trials Registry Platform
ICER	Incremental cost-effectiveness ratio
IDRR	Incidence density rate ratio
IFN-γ	Gamma interferon
IGRAs	Interferon-gamma (IFN-γ) release assays
IQR	Interquartile range
JSNA	Joint Strategic Needs Assessment
IBD	Inflammatory bowel disease
IMID	Immune-mediated inflammatory disease
KTP	Kidney transplantation patient
KTR	Kidney transplant recipients
LE	Lupus erythematosus
LTBI	Latent tuberculosis infection
LT	Liver transplant
MEDLINE	Medical Literature Analysis and Retrieval System Online
MDR-TB	Multi-Drug Resistant Tuberculosis
MeSH	Medical subject heading
Mos	Months
MRC	Medical Research Council
MTB	Mycobacterium tuberculosis
MTX	methotrexate
N	Number
NA	Not applicable
NR	Not reported
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NOID	Notification of infectious diseases
NPV	Negative predictive value
NTM	Non tuberculous mycobacteria
OR	Odds ratio
PHE	Public health England
PKT	Post kidney transplant
PPD	Purified protein derivative
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
P-Y	Person year
QALY	Quality adjusted life-year
QFT	QuantiFERON-TB
QFT-G	QuantiFERON-Gold
QFT-GIT	QuantiFERON-Gold in Tube
QUIPS	Quality in Prognosis Studies
R-CIR	Ratio of cumulative incidence ratio
R-DORs	Ratio of diagnostic odds ratios
R-IDRR	Ratio of incidence density rate ratio
RCT	Randomised controlled trial
REPEC	Research Papers in Economics
ROB	Risk of bias
ROC	Receiver operated characteristic
RTR	Renal transplant recipient
SA	Sensitivity analysis
SCI-EXPANDED	Science Citation Index Expanded
SD	Standard deviation
SN	Sensitivity
SOTC	Solid organ transplantation candidate
SP	Specificity
TB	Tuberculosis
TNF	Tumor necrosis factors
TST	Tuberculin skin test

XDR-TB	Extensively drug-resistant TB
Yrs	Years
WHO	World Health Organization
WHO ICTRP	WHO International Clinical Trials Registry Platform
WTP	Willingness-to-pay

Glossary

Acid fast bacilli

Bacteria which, having been stained with a dye, retain their colour in acid alcohol. Used as a technique for microscopic detection of mycobacteria.

Active tuberculosis

Infection with mycobacteria of the *M. tuberculosis* complex, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent TB, where 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 TB disease depend on where in the body the bacteria are growing. If TB is in the lungs (pulmonary TB), the symptoms may include a cough, pain in the chest, and coughing up blood. (Source: www.hpa.org.uk).

Adherence

The term 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, where decision points are represented with boxes, linked by arrows.

Atypical mycobacteria

Mycobacteria other than those of the *M. tuberculosis* complex.

Bacille Calmette-Guerin vaccine

A vaccine for TB named after the French scientists Calmette and Guerin. (Source: www.hpa.org.uk).

Cochrane Review

A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare 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 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 due to its connotations of patient subservience. (See "Concordance" and "Adherence").

Concordance

Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.

Concordance

The percentage of agreement between two tests.

Confidence interval

A range of values which 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, then 95% of the calculated intervals will actually

Contact (domestic, close, casual, and workplace)

A person who has spent time with a person with infectious TB. (Source: www.hpa.org.uk).

Cost-effectiveness analysis

An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, 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

(QALYs).

Culture

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

Discordance

The percentage of disagreement between two tests.

Gamma-interferon test (correctly, Interferon-gamma)

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

High-incidence country

Following the widely used threshold, any country with an incidence equal to or greater than 40 cases per 100,000 population per year. A similar definition is made for areas within countries and may be used o decide on local need for vaccination, for instance for neonatal BCG vaccination.

Immunocompromised

Immunocompromised refers to an individual who has a significantly impaired immune system. For instance this may be due to prolonged steroid use, TNF-α antagonists, anti-rejection therapy, the use of immunosuppression-causing medication or co morbid states that affect the immune system, for example HIV, chronic renal disease, many haematological and solid cancers and diabetes.

Infectious TB

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

Latent tuberculosis

Infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. Also known as latent TB infection, or LTBI.

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. (Also see "Tuberculin skin test" and "Heaf test").

Multidrug-resistant TB

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

Mycobacterium tuberculosis complex (M. TB Complex)

The related mycobacterial species *M. tuberculosis*, *M. bovis* and *M. africanum* 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, see above) Sputum is examined for TB 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', AFB) have been seen in a stained smear of sputum examined under a microscope. (Source: www.hpa.org.uk).

Abstract

Background

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) with an annual incidence of nine million new cases and two million deaths worldwide.

Objectives

To investigate the clinical effectiveness and cost-effectiveness of screening tests (IGRAs and TST) in latent tuberculosis infection (LTBI) diagnosis in three population groups: children, immunocompromised people, and those who have recently arrived to the UK from high incidence countries. All these groups are at higher risk of progression from LTBI to active TB.

Data sources

Electronic databases including MEDLINE, EMBASE, The Cochrane Library, Current Controlled Trials, and others were searched and updated in December 2014.

Review methods

English language studies evaluating head-to-head effectiveness of commercially available tests used for identifying LTBI in children, immunocompromised people, and recent arrivals to the UK were eligible for inclusion. The two included interventions were IGRAs (QuantiFERON-TB Gold-In-Tube (QFT-GIT) and T-SPOT.TB) and the comparator was TST 5mm or 10mm alone or plus IGRA. Two independent reviewers screened all identified records, undertook quality assessment and data synthesis. A de novo model, structured in two stages was developed to compare the cost-effectiveness of diagnostic strategies.

Results

A total of 6,687 records were screened of which 54 (53 unique studies) were included and a further 37 additional studies from CG117. The majority of included studies compared strength of association for QFT-GIT/G IGRA vs. TST (5mm or 10mm) in relation to incidence of active TB or prior TB exposure. Ten studies reported evidence on decision analytical models to determine the cost-effectiveness of IGRAs compared with TST for the diagnosis of LTBI.

In the children population, TST (≥ 5mm) negative followed by QFT-GIT strategy was the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of £18,900 per QALY gained. In the immunocompromised population, the QFT-GIT negative followed by TST (≥ 5mm) strategy was the

most cost-effective strategy with an ICER of approximately £18,700 per QALY gained. In the recently arrived population, the TST (≥ 5mm) alone strategy was less costly and more effective than TST (≥ 5mm) positive followed by QFT-GIT, T-SPOT.TB and QFT-GIT alone testing strategies.

Limitations

The limitations in evidence (e.g., absence of gold standard in LTBI diagnosis, risk of bias in individual studies, scarcity of evidence, test administration/interpretation, variation in the exposure-based definitions of LTBI construct, limitations of the screening tests) and heterogeneity in IGRA performance relative to TST limits the extent of applicability of the review findings.

Conclusions

Given the current evidence available, the cost-effectiveness results showed that TST (≥ 5mm) negative followed by QFT-GIT was the most cost-effective strategy in children, QFT-GIT negative followed by TST (≥ 5mm) in an immunocompromised population and TST (≥ 5mm) for recent arrivals in diagnosing LTBI that progresses to active TB. These results should be interpreted with caution, given the limitations identified.

Study registration

This study is registered as PROSPERO 32014000500.

Funding

The National Institute for Health Research Health Technology Assessment programme.

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 (5mm and 10mm) and 2) the interferon gamma (IFN-γ) release assays (IGRAs).

In this review we updated a previous clinical guideline (CG117) 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 to the UK from high incidence countries. All these groups are at higher risk of progression from LTBI to active TB.

This review addressed the following questions: Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB

- in children?
- in people who are immunocompromised?
- in people who are recent arrivals from countries with a high incidence of TB?

Methods

Clinical effectiveness

Search strategy

Search strategies comprised the following main elements: a) search of electronic bibliographic databases (MEDLINE, EMBASE, the Cochrane Library, the Science Citation Index and Conference Proceedings, HEED, etc.) (updated on 2 December 2014); b) contact with experts in the field; c) scrutiny of references of included studies and systematic reviews; and d) screening of manufacturers' and other relevant websites.

Study eligibility criteria

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

Populations

- Children (both genders, age < 18 years, immunocompetent)
- Immunocompromised or at risk of immunosuppression (both genders, any age, transplant recipients, HIV, renal disease, haematological disease, autoimmune disease, recipients of anti-TNF-α treatment, steroids, or cyclosporins)
- People recently arrived from regions with a high incidence/prevalence of TB (both genders, any age, immunocompetent, areas with estimated incidence 40 per 100,000 or greater)

Intervention

Two IGRAs:

- QuantiFERON-TB Gold In Tube (QFT-GIT) (old version: QuantiFERON-TB Gold [QFT-G])
- T-SPOT.TB

Comparator

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

Outcome

Associations between test results and validity constructs for LTBI:

- Progression to active TB
- Prior exposure to *Mycobacterium tuberculosis* (MTB; defined by proximity, duration, geographic location, or dose-response gradient)
- People at low risk of MTB or healthy populations

Study

- Randomised controlled trials, retrospective or prospective cohort studies
- Cross sectional or case-control studies

Economics

- Decision-analytic models investigating cost-effectiveness
- Costs studies

Exclusions

- Studies using test results as proxies for LTBI

- Non-commercial/in-house IGRAs, 1st generation QFT, or tests unavailable in 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 resolved by recourse to a third reviewer. For each test, summary parameters (e.g., sensitivity, specificity, diagnostic odds ratios, cumulative incidence ratios, percent concordance, kappa statistic) with corresponding measures of variability (95% CIs, p-value) were extracted or calculated (e.g., using construct validity categories of exposure levels or progression to active TB, where data permitted).

Risk of bias and methodological quality were also assessed independently using QUIPS and a modified tool by Dinnes et al. (2007) for incidence and exposure studies and CHEERS and Philips' checklists for economics studies.

Data synthesis and analysis

Predictive values for IGRAs and TST for progression to active TB (incidence studies), degree of association of IGRAs and TST results with prior exposure to MTB (defined by proximity, duration, or dose-response gradient), and compared 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-square 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 MetaDisC version 1.4 (Madrid, Spain) and Stata.

Cost-effectiveness

A de novo model structured in two stages (decision tree and infectious disease model) was developed in R (version 3.1.1) to compare the cost-effectiveness of diagnostic strategies. The first stage included pathways following testing for one-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 MCMC 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 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 from clinical experts. Costs were adjusted to 2012/2013 prices. The simulation was run for 100 years, with 3.5% discount rates and with an NHS and PSS 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 (ICER) 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 6,687 records. After removing duplicates, 3,757 records were screened, of which fifty-four (53 unique studies) were included. We included 37 additional studies from CG117.

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

Children

Results of 27 studies were:

- Incidence studies:
    - TST-5mm: there was no difference with QFT-GIT (2 studies; pooled ratio of cumulative incidence ratio (R-CIR) = 1.12, 95% CI: 0.72, 1.75)
    - TST-10mm: QFT-GIT was better (3 studies; pooled R-CIR = 4.33, 95% CI: 1.32, 14.23)
- Sensitivity and specificity:
    - TST-5mm: IGRA (QFT-GIT/G) had a similar range of sensitivity (48%-100% vs. 57%-100%) and slightly better specificity (49%-90% vs 45%-65%)
    - TST 10mm: IGRA had a higher range of sensitivity (48%-100% vs 30%-56%), and a slightly lower specificity (49%-90% vs. 63%-93%)
- Exposure studies IGRA performed better compared to TST 5mm/10mm in 14 studies:
    - Pooled ratio of diagnostic odds (R-DOR) = 1.98, 95% CI: 1.19, 3.28; I^2 = 89%
- Subgroup analyses (stratified by TB burden setting):
    - In low TB burden settings: IGRAs were superior to TST 5mm/10mm (6 studies: pooled R-DOR = 4.74, 95% CI: 2.15, 10.44)
    - In high TB burden settings there was no difference (8 studies; pooled R-DOR = 1.13, 95% CI: 0.78, 1.65)

Immunocompromised people

The 48 studies were stratified into: HIV, solid organ transplantation candidates, post kidney transplantation, hemodialysis (end stage renal disease), immune-mediated inflammatory diseases before anti-TNF-α therapy, Hepatitis C, and lupus erythematosus.

- 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 5mm/10mm in people with

        - Hemodialysis (4 studies; pooled R-DOR = 2.53, 95% CI: 1.48, 4.34)
        - Hepatitis C (R-DOR = 8.45, 95% CI: 3.71, 19.24)
    - TST 10 mm performed significantly better for people with
        - HIV/AIDS compared to QFT-GIT (2 studies; pooled R-DOR = 0.35, 95% CI: 0.15, 0.83)
    - Sub-group analysis (stratified by condition): R-DOR estimates were non-significant/inconclusive with wide 95% CI in people with
        - lupus erythematosus
        - immune-mediated inflammatory diseases before anti-TNF-α therapy,
        - solid organ transplantation candidates
        - kidney transplant recipients

Recently arrived people from high TB burden areas

Results of 15 studies were:

- Incidence studies:
    - TST 5mm/10mm showed no significant difference with QFT-GIT (2 studies; pooled R-CIR = 1.57, 95% CI: 0.52, 4.76)
    - TST 10mm showed no significant difference with T.SPOT.TB (R-CIR=0.37, 95% CI: 0.10, 1.41)
- Exposure studies:
    - TST 10mm: there was no significant difference with QFT-GIT (3 studies; pooled R-DOR = 0.96 CI: 0.69, 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 for use in the models:

	Sensitivity, % **(95% credible interval)**	**Specificity, %** **(95% credible interval)**
Children		
TST (≥ 5mm)	72.80 (60.59 – 72.94)	49.03 (47.96 – 50.08)
TST (≥ 10mm)	53.51 (38.21 – 67.69)	74.81 (34.34 – 76.18)

QFT-GIT	68.84 (58.56 – 78.20)	61.03 (60.30 – 61.76)
T-SPOT.TB	50.00 (2.45 – 97.64)	77.58 (67.38 – 86.40)
Immunocompromised		
TST (≥ 5mm)	32.42 (11.19 – 58.48)	74.22 (72.88 – 75.57)
TST (≥ 10mm)	16.82 (2.52 – 38.99)	83.97 (78.99 – 88.31)
QFT-GIT	55.48 (24.73 – 83.73)	82.27 (80.52 – 83.96)
T-SPOT.TB	66.65 (35.17 – 0.9144)	68.46 (63.46 – 73.37)
Recently arrived		
TST (≥ 5mm)	93.56 (77.86 – 99.77)	50.11 (47.90 – 52.29)
QFT-GIT	59.15 (35.84 – 81.42)	79.29 (77.80 – 80.73)
T-SPOT.TB	70.01 (39.78 – 92.42)	39.92 (34.39 – 45.54)

Model outputs - ICERS: cost per QALY and cost per diagnostic error avoided

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

Discussion

Summary of results

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

IGRAs appeared to outperform TST in low versus high TB burden countries, a finding which is consistent with a growing body of evidence showing reduced sensitivity and specificity of IGRAs in these settings. This type of effect modification could be explained by higher frequency of exposure to MTB, different transmission dynamics, malnutrition, co-morbidity, co-infection with HIV or helminthic infection.

For immunocompromised people most of the evidence was insufficient and inconsistent. There was large variation in the performance of IGRA compared to TST across different clinical subgroups. QFT-GIT and T-SPOT.TB performed better than TST 5mm/10mm for people undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT was 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 evidence was inconclusive due to high uncertainty around statistically non-significant effect estimates. The QFT-GIT negative followed by TST (≥ 5mm) strategy was the most cost effective in this group with an ICER of approximately £18,700 per QALY.

Amongst recently arrived people from countries with a high TB burden, there was no significant difference in the performance of IGRAs compared to TST in identifying LTBI. The TST (≥ 5mm) 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 due to 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 inadequate definition of construct validity for LTBI (e.g., definitions of prior 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, prior BCG vaccination, and the limitations of screening tests (inter-/intra-rater variability in 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 due to lack of blinding, selection bias, partial verification bias due to incomplete outcome data assessment, and incorporation bias.

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

Implications

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 amongst different populations.

Research priorities

1. Is the inconsistent performance of IGRAs in high vs. low TB settings replicable?
2. Prospective studies are needed for people at high risk for TB to assess progression to active TB.
3. The relative benefits of two-step vs. single testing with different combinations of IGRAs and TST should be investigated.
4. For retrospective or cross-sectional studies a standard set of component exposures to aid classification into high vs. low risk for LTBI is needed, alongside identification of more accurate markers of LTBI.

Plain English summary

Tuberculosis (TB) is one of the biggest causes of illness and death worldwide. The majority of people with TB are not infectious and have no symptoms; they are considered to have latent tuberculosis infection (LTBI). People with LTBI are at 5%-10% risk for developing active TB during their lifetime. The risk of LTBI getting worse is higher in young children and in people co-infected with human immunodeficiency virus (HIV) or in those who are immunocompromised due to other conditions or long-term use of immunosuppressant medications.

There are two types of tests used to identify LTBI in the UK: 1) the tuberculin skin test (TST) which can be read at 5mm or 10 mm and 2) the interferon gamma release assays (IGRAs: one type of which is QFT-GIT). This review examines the clinical and cost effectiveness of TST and IGRAs to detect LTBI in children, in people who have low or compromised immunity either due to disease such as HIV or due to medications for other conditions, and in recent arrivals from countries with a high incidence of TB.

We undertook systematic reviews and we updated and analysed the clinical evidence about the different tests since the last clinical guideline (CG117, 2009), was produced and we built a model to determine the most cost-effective approach for identifying LTBI.

We identified 53 new studies plus 37 studies from CG117. There were twenty on-going studies. For the cost effectiveness review we found 10 published models, almost all related to people with compromised immunity with very little data on children and recent arrivals.

The studies that compared IGRAs with TST in children showed no difference between IGRAs (QFT-GIT) and TST-5mm. However, QFT-GIT performed better than TST-10mm in identifying LTBI or predicting the risk of active TB and our meta-analysis confirmed this.

In people with low immunity, the IGRA and TST performed better at identifying people who didn't have LTBI than people who did have LTBI. There was a wide range of results from different tests between individual studies.

For people recently arrived in the UK from high incidence countries, there was no evidence to suggest that IGRAs performed better than TST at identifying LTBI.

The economic model takes into account costs as well as effectiveness and these varied between the different populations. The model showed that in children the TST (5mm) used sequentially and followed by QFT-GIT if negative had the highest probability of being cost-effective. For people with compromised immunity, the QFT-GIT test used sequentially and followed by TST (5mm) if negative was the most cost-effective. For the recently arrived population, the TST (5mm) alone was the most cost-effective.

The evidence for each subgroup of patients was limited and future research needs to be devoted to defining LTBI more clearly so that measures to detect and deal with it can be strengthened.

1 Background

1.1 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) with an annual incidence of nine million new cases and two million deaths 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 last 20 years, especially in ethnic minorities born in places with high TB prevalence.[4, 5] Between 1998 and 2009, annual tuberculosis notifications rose in the UK by 44%, from 6,167 to 8,900 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 US[7] thereby posing a major public health challenge. The re-emergence has been largely driven by recently arriving immigrants through re-activation of latent infection and/or acquiring new infection as a result of their maintaining links with high prevalence countries.

1.2 Aetiology and pathology of TB

TB infection is transmitted to a healthy person through the air by inhaling respiratory fluids/sputum droplets with 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 bacterium is 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 the bones, lymph nodes, or brain.[8] In over 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. The immune system keeps the bacteria inactive resulting in latent tuberculosis infection (LTBI). These cases who have 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 this process can also involve other organs of the human body (extra-pulmonary 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 eight weeks to decades. The greatest chance of progressing to a disease is within the first two years after infection, where approximately 50% of the 5-10 per cent lifetime risk occurs.[15] The risk of infection and progression to active TB disease depends mostly on the host's immune functioning as well as 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 or coming from countries of high prevalence of TB, infants, children, HIV-infected persons, 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 re-activate, and explain the trends observed for TB in UK.[17]

1.3 Active TB

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 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 X-ray examination, and microscopy of tissue biopsy or sputum samples. 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 takes several weeks for a definitive result.

TB 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 the duration of six months.[18] Although patients start to feel better after two 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 effectiveness, requires longer than six months, and causes greater side effects.[10, 26]

1.4 Measurement of latent TB infection

Unfortunately, there is no diagnostic gold standard for identification of individuals with LTBI. Instead, the available screening tests for LTBI provide 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 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 gamma interferon (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 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 to 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 amongst commonly used cut-off values (e.g., diameter of induration ≥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, persons who have 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, patients with diabetes, malignancies, or renal failure).[16] The administration of the TST is relatively cheap and does not require a laboratory, but does require a skilled operator.

IGRAs have been recently developed as alternative screening tests for LTBI. There are two types of IGRAs: QuantiFERON-TB Gold In Tube (QFT-GIT; Cellestis/Qiagen, Carnegie, Australia) [old version: QuantiFERON-TB Gold (QFT-G)] and T-SPOT.TB (Oxford Immunotec, Abingdon, UK). Both tests are commercially available in UK. The QFT is a whole-blood test based on an enzyme-linked immunosorbent assay (ELISA), whereas T-SPOT.TB test uses peripheral blood mononuclear cells and is

based on an enzyme-linked immunosorbent spot (ELISPOT) assay.[11] Both tests measure CD4 cell-released gamma interferon (IFN-γ) response to MTB-specific antigens (early secretion antigen target-6 [ESAT-6], culture filtrate protein-10 [CFP-10], and tb7.7) in vitro blood samples.[12, 13, 16]

1.4.1 Treatment of LTBI

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 for between three to six months depending upon treatment regime. For individuals affected by HIV treatment has to be for six months. Rifampicin for four months is the second line drug that can be used as an alternative in individuals who are resistant to isoniazid or at high risk of side effects from isoniazid.[16]

1.5 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 in England and Wales. It first became a statutory requirement to notify TB cases in 1913. Known as the Notifications of Infectious Diseases system (NOIDs), 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. [28]

In 1999, the Enhanced Tuberculosis Surveillance system (ETS) was established to collect more detailed information of annual TB cases including patient information of age, sex, ethnic group, country of birth, and site of disease, NHS region, and treatment outcomes. It has been reported that the enhanced TB surveillance system reflects the true incidence of TB better than the NOIDs as many measures are used to ensure quality standards are met annually, thereby providing a corrected analysis of TB cases.[29] 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,[28] and is therefore robust.

There is no national system that collects data for latent TB infection. 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.

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 13.6-14.4 per 100,000 since 2005.[5] The most recent figures in 2012 report a total of 8,751 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 8,130 cases of active TB, a rate of 15.2 per 100,000 whereas 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]

1.5.1 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 constitute 73% of reported TB cases.[5] It is reported there is a 98% increase in the number of TB cases from individuals born overseas.[4, 6, 30] The rate of TB amongst the non UK-born population is 80 per 100,000, which is almost 20 times the rate in the UK-born. Almost half of the cases born outside the UK were diagnosed within five years of coming to the UK with another 30% diagnosed within two years.[5] Sixty per cent of foreign-born cases originated from South Asia, followed by 22% from Sub-Saharan Africa. With respect to countries of origin, India (31%), Pakistan (18%) and Somalia (6%) are the most common. Similarly, a higher proportion of non-UK born cases (above 50%) present with extra-pulmonary TB compared to UK born cases (31%).[31]

Among UK-born individuals, the highest rate of TB is in ethnic minority groups. The largest proportion of cases is from the Indian ethnicity (27%), followed by White (21%) and then Pakistani (17%). The highest rates of TB are found in Indian, Pakistani and Black ethnic groups.[5] It has been indicated that recently arriving immigrants and ethnic minorities are vulnerable as a result of re-activation of latent infection once in the country or acquiring new infection as a result of their maintaining links with high prevalence countries (e.g., may visit rural Pakistan or may have relatives from high prevalence areas visit them).[32] Also having diabetes increases the likelihood of reactivation of TB, and is more common in individuals from South East Asia , including the ethnic groups highlighted above.[33]

1.5.2 Geographical difference

Since the establishment of the enhanced TB surveillance system, it has been 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 amongst all high-income European countries.[34, 35] London is followed by West Midlands with 12% of the burden and a rate of 19.3 per 100,000.[5] Both London and West Midlands have high rates of immigration.[36]

Within London, there is great variation between boroughs. Twelve of the 33 local authorities have a rate of 40 per 100,000. The boroughs with the highest rates of TB are Newham at 122 per 100,000 and Brent at 100 per 100,000. However, other boroughs such as Havering and Richmond-upon-Thames have an annual incidence rate lower than 10 per 100,000.[37] 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.[38]

A similar picture is seen in Birmingham. Rates for Birmingham as a whole have fluctuated between 33.7 and 44.8 cases per 100,000 between 2009 and 2013. In the 4th quarter of 2013 Sandwell and West Birmingham CCG had a rate of 49.6 per 100,000 (43.5-56.4). In Solihull it was 1.9 (0.5-4.9). Again this reflects the ethnic make-up of the areas (expert personal communication).

1.5.3 Age and gender difference

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

1.5.4 Immunosuppression and TB

In addition to young children, the risk of progression from LTBI to active TB is higher in people co-infected with human immunodeficiency virus (HIV), immunocompromised patients due to co-morbidity (e.g., diabetes, malignancy, renal disease) and/or long-term use of immunosuppressant medications (e.g., corticosteroids, tumor necrosis factor-alpha antagonists).[11, 16, 39] The co-infection between HIV and TB infection has been internationally well documented.[40-42] In the UK, there has been a decrease in the number of co-infected HIV-TB cases from 9% in 2003/04 to 3.6% of TB cases in 2013.[5] This has been in line with general downward trends in HIV and TB in migrants from Sub-Saharan Africa.[31]

1.5.5 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%), drug (2.8%) and alcohol misuse (3.2%).[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%) compared to foreign-born cases (5.4%). Within UK-born cases, almost half with at least one factor are from the White ethnic group (46%).[5]

1.6 Impact of health problem

1.6.1 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.[43] Similarly, extra-pulmonary TB can have serious complications for the bones, brain, liver, kidneys, and heart.[43] Tissue damage can be permanent if tuberculosis is not treated early.[44] As 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 treatment of TB. This can include anxiety, depression, disorientation, feelings of loss of control, and mood swings.[45, 46] A diagnosis of TB can also bring related stigma through which individuals face social and economic consequences.[47]

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 no 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 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, drug-resistant, and come with treatments with greater side effects.[16, 48] 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. 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.

1.6.2 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 decreasing in the US. It has been estimated that in two to five years the burden of TB in the UK will be higher than 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 in the UK.

The healthcare costs associated with active TB include the cost of diagnosing and treating pulmonary TB, extra-pulmonary TB, MDR-TB and XDR-TB. In the UK, the normal cost of treating a case of active TB is £5,000 but is between £50,000-£70,000 for MDR-TB and can be up to £100,000 for XDR-TB.[49] Taking 2012 figures, it is estimated that annually TB treatment would cost more than £50 million. Given that LTBI represents a reservoir of potential TB epidemic, it is important to identify and, if appropriate, treat people with LTBI in order to reduce the spread and burden of TB disease.[13, 18]

1.7 Current service provision

1.7.1 Management of LTBI

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 only be assessed 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 at risk.[10, 50]

Active case finding is recommended for recently arrived migrants who have recently arrived in the UK from countries with a TB incidence of 40 per 100,000 or greater. 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. Healthcare professionals responsible for new migrant screening are advised to coordinate a programme to detect and treat active

and latent TB, provide Bacillus Calmette–Guérin (BCG) vaccination where appropriate and provide relevant referrals and information. Active case finding is also recommended for street homeless, new NHS employees, and prison and remand centres. Commissioners 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.[51]

A simplified care pathway for LTBI screening derived from the National Collaborating Centre for Chronic Conditions[10, 50] is presented in Figure 1 and further details about testing strategies for people being screened for LTBI are provided in Box 1.

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 and if this is positive they are treated for active TB and if negative then treated for LTBI. If the results for LTBI are negative, the individual is offered a BCG if under the age of 16 or 16-35 and from sub Saharan Africa or from an area with an incidence of over 500/100 000. 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, 50]
- TST is recommended for contacts above the age of five years for the diagnosis of LTBI. IGRA is recommended for individuals whose TST shows positive results (≥6 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 to be referred to specialist TB care. For contacts who are aged two to five years old, 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 for excluding the possibility of active disease and consideration of LTBI treatment or treatment of active TB disease 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 IGRA should be offered after six weeks alongside a repeat TST to increase sensitivity.[10, 50]
- For child contacts of a with sputum smear positive disease aged four weeks to two years who has not been vaccinated, isoniazid should be started and 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 they should then be offered full treatment for latent TB. If the TST is negative (<6 mm induration), isoniazid should be continued for six 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 considered. On the other hand, contacts of a person with sputum-smear positive disease aged four weeks to two years who has been vaccinated, TST should be performed and if positive (≥15 mm) the child should be assessed for active TB. If active TB is excluded then the child should be given a regimen of either 3 months of rifampicin and isoniazid or six months of isoniazid. If TST is negative (<15 mm), the TST should be performed with an IGRA after six weeks. If both repeats are negative no further action is needed. If either is positive, active TB has to be excluded, and treatment for LTBI followed.[10, 50]

- To diagnose LTBI in recently arriving migrants from high incidence countries, for children 5-15 years, TST should be offered and if positive an IGRA should be performed. For individuals 16-35 years, either IGRA alone or in a dual strategy with a TST should be offered. For those older then 35, individual risk and benefits of treatment should be considered before testing. For children under five, TST should be offered and if initial test if positive taking BCG history into account then active TB disease should be excluded and LTBI treatment considered.[10, 50]
- Regarding those who are immunocompromised, children should be referred to a TB specialist. For people with HIV and CD4 counts less than 200 cells/mm3, or between 200-500 cells/mm3, an IGRA should be offered with concurrent TST. If either is positive active TB should be ruled before LTBI treatment is given. For other people who are immunocompromised, an IGRA should be offered alone or with TST.[10, 50]
- Once active TB has been excluded by chest x-ray and examination, individuals should be offered treatment. Individuals 35 years or older who do not have HIV should be assessed further and counselled about treatment because of the increasing risk of hepatotoxicity from medication. Treatment should include either six months of isoniazid or three months of rifampicin and isoniazid for people aged 16-35 not known to have HIV; six months of isoniazid or three months rifampicin and isoniazid.[10, 50]
- Neonates who have been in close contact with people who have sputum-smear positive TB who have not received at least two weeks anti-tuberculosis drug treatment should be started on isoniazid for three months and then TST performed after three months treatment. If the TST is positive, active TB should be assessed and if found negative then isoniazid should be continued for a total of six months. If TST is negative then it should be repeated with IGRA and if both are negative isoniazid should be stopped and BCG vaccination performed. In children above two years of age, three months of rifampicin and isoniazid or six months isoniazid should be given.

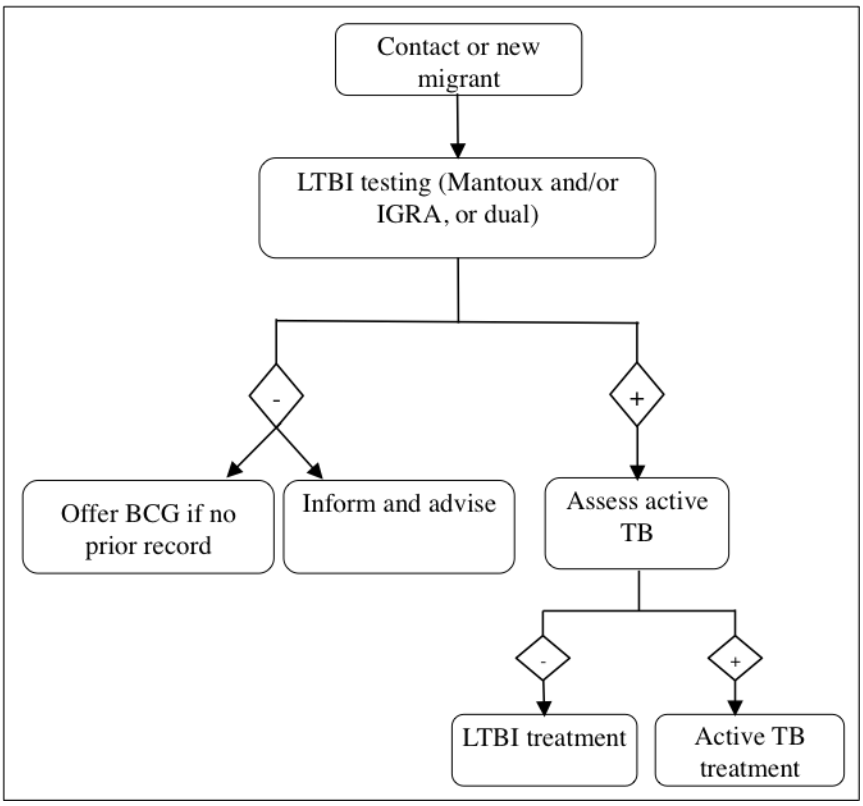


Figure 1. Care pathway of LTBI screening[50]

1.8 Current service cost

Estimates for the cost of diagnosing and treating LTBI have been provided by NICE. These costs are based on NICE guidelines in 2006,[50] and the partial update in 2011.[10] Costs shown include the unit costs of the disposables, time to administer and read tests, and the cost of collecting a blood sample per patient for the tests, which were calculated in 2011. The cost of chemoprophylaxis includes the cost of drugs, active TB tests, consultations, and nurse visits, which was calculated in 2006. BCG costs are also from 2006. Compared to the cost of treating active TB (£5,000 and above), diagnosing and treating LTBI per patient is less costly (see Table 1).

Table 1. Unit costs for LTBI diagnosis and treatment[10]

Description	Test type	Unit cost (£)
Cost of tuberculin skin tests	-	16.42
Cost of interferon gamma testing	-	30.34
Household and other close contacts 5 years and older	TST	16.42
New entrants from high incidence countries Children under 5 Children 5-15 years Adults 16-34: IGT test alone or dual strategy People over 35 - consider individual risk	 TST TST IGRA or dual	 16.42 16.42 30.34
Household contacts, aged 2-5 Contacts 5 years and older - outbreak	TST IGRA If contact with sputum smear positive and TST is negative IGRA	16.42 30.34 30.34
Immunocompromised HIV CD4 count < 200	TST IGRA test Total	16.42 30.34 46.76
Immunocompromised HIV CD4 count 200-500	IGRA test or IGRA with concurrent TST	30.34 46.76
Cost of complete chemoprophylaxis treatment	-	483.74
BCG Vaccination	-	11.71

1.9 Variation in services and/or uncertainty about best practice

1.9.1 Limitations of LTBI screening tests

The main limitation of TST is its inability to distinguish between reactions caused by MTB vs. BCG vaccination or non-tuberculosis mycobacteria (NTM).[11] The BCG vaccination is routinely used in countries with 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 TST, may also lead to false positives, thereby limiting 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, 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 TST, which results in missed diagnoses in 10% of cases.[52] Measurement of TST is also dependent on inter-observer variability, which therefore requires adequate training to reduce variability.[53, 54]

Because the antigens in the IGRA tests are not present in 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 to TST.[55] IGRAs also have the advantage of requiring a single patient visit versus the sequential two-step testing required with TST. Automated testing 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.[56] The IGRAs, however, have their own limitations; specifically, they are more costly and labour-intensive than TST. Moreover, care in blood sampling is required and the time for blood sample storage and analysis is restricted to 8 to 12 hours after collection.[12]

1.9.2 Diagnostic accuracy of LTBI tests

Since the introduction of IGRAs evidence on estimating and comparing the performance of 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, 39, 56-58] Most studies have instead determined associations (e.g., diagnostic odds ratios 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 or progression from LTBI to active TB (e.g., sensitivity, diagnostic odds ratios, positive and negative predictive values, incidence rate ratios, cumulative incidence ratios).[18, 57, 59]

Some studies have assessed and compared specificity of these tests in people at very low risk for MTB (e.g., healthy individuals, residents of low incidence countries)[56] or compared sensitivity in culture-confirmed individuals with active TB (taken as a surrogate reference standard for LTBI).[39, 56, 58] Using suboptimal reference standards for diagnostic accuracy testing can lead to overestimation or underestimation of the true accuracy of a test. The degree of concordance (inter-rater or intra-rater 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 IGRAs and TST were similarly high in people who are not vaccinated with BCG (> 90%), however the pooled specificity of TST in BCG-vaccinated populations was much lower compared to IGRAs (about 56% vs. 96%).[11, 52, 56] In contrast, prospective longitudinal studies showed that neither IGRAs nor TST had high prognostic values in predicting risk of progression to active TB.[11, 18]

1.9.3 Treatment of LTBI

Once patients are diagnosed with LTBI through any of the tests, there are claims of low adherence to chemotherapy treatment.[60] As a result of low adherence, an alternative therapy recommended in the US[61] 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.[60] Suitability is based on certain criteria including normal renal and liver function, 16 years of age or above, not pregnant, HIV patients not on antiretroviral treatment, agreeable to direct observations, and direct observations are feasible. If suitable, it 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 nine-month daily isoniazid regime used in the US, with higher completion rates, as only 12 doses are needed.[60]

1.10 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 clinical guideline on the clinical diagnosis and management of tuberculosis, and measures for its prevention and control in 2006,[50] with a partial update in 2011,[10] as well as public health guidance to identify and manage tuberculosis among hard to reach groups in 2012.[51] The Department of Health (DOH) has also published guidelines for the planning, commissioning and delivery of TB services,[62] guidelines for testing health care workers,[63] a wider action plan for stopping TB in England,[64] and guidance for the prevention and control of HIV-related and drug resistant TB.[65] Finally, the British Thoracic Society has published guidelines on the prevention, risk assessment, and management of TB in

adult patients with chronic kidney disease [66] and in patients due to start anti-TNF-a treatment,[67] management of air travel passengers,[68] and the management of opportunist mycobacterial infections.[69]

1.11 Description of technology under assessment

1.11.1 Summary of intervention

As noted above, screening for LTBI is crucial to curb the re-emergence of TB as the majority of TB cases have latent TB which has been re-activated.[70] Testing and treating high-risk individuals for LTBI would not only prevent active TB illness for the individual but also reduce the transmission of TB, thus reducing the pool of infection.[71]

There is much interest in using IGRA to identify individuals at high risk of LTBI due to the advantages it has over traditional TST particularly that it only requires one visit and that previous BCG status does not interfere with results. For IGRA to replace TST in the current care pathway, it would have to show improved cost-effectiveness relative to TST although in the absence of a gold standard, this is difficult.[72] Otherwise IGRA may have to be used as complementary to TST as is currently recommended in the national guidelines.[10]

The IGRA test takes at least 24 hours, although it can take days depending on the laboratory.[73] TST takes two to three 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 TST and shifts the cost and labour from clinic to laboratory.[74] Both TST and IGRA require specific equipment either for administering the injection or taking a blood sample. In addition, IGRA requires advanced laboratory facilities.[74] Skilled personnel are needed to administer both tests and in the case of TST, are needed to read the result, whereas for IGRA laboratory personnel are needed to process the result.[72] In both cases, patients follow a common pathway where nurses provide the patient with the result, follow up for testing of active TB, and offer treatment and advice.[10] IGRAs can be used in settings similar to TST so long as there is access to a laboratory and pathways are negotiated so the sample can be analysed within 12 hours.[45]

1.11.2 Screening tests for LTBI in special sub-groups at risk

It has been suggested that screening tests applied to presumably healthy populations or persons at low risk for progression to active TB may not be justified given the potential harms due to unnecessary treatment.[16, 75] It is also not feasible or cost effective to universally screen the population as the administrative and clinical costs outweigh the benefits of the TB cases that would be identified.[45] The

benefits of screening for LTBI using these tests are likely to be maximal in individuals at high risk of contracting MTB (e.g., recently arrived persons from countries with high TB incidence, close contacts with active TB) and those with suspected LTBI who are at high risk of progression to active TB disease and complications associated with the infection (e.g., immunocompromised patients, young children). Since these sub-groups are at higher risk of developing active TB, it is of public health importance to identify LTBI in them.

Studies comparing TST and IGRAs for detecting LTBI in children have mostly demonstrated better specificity for IGRAs as compared to TST.[58] As for sensitivity, it has been shown to be comparable between TST and 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 persons has been too scarce to draw definitive conclusions. One systematic review showed suboptimal but comparable performance between TST and IGRAs for identifying LTBI in HIV-infected patients.[39] In general, based on limited data, the accuracy indices for 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 TST and the two IGRAs (QFT-GIT and T-SPOT) for detecting LTBI in migrants to the UK.[76] However, comparison of the tests was done 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 was estimated. Authors found that TST was positive in 30.3% of individuals who completed screening, QFT-GIT was positive in 16.6% and T-SPOT in 22.5%. The higher rate for TST could be due to the effect of BCG. Although NICE recommends that recently arriving migrants from countries with a TB incidence of 40 per 100,000 should be screened, the report found this would require 97-99% of the cohort to be screened and would identify 98-100% whereas screening migrants from countries with an incidence of 150 per 100,000 would identify 49-71% of LTBI but would only require screening half of the cohort. The two most cost-effective options were to screen recently arriving migrants from countries with a TB incidence greater than 250 per 100,000 with one QFT-GIT (£21,565.3 per case prevented) but as this would miss many cases, and a rate of 150 per 100,000 was recommended as it is 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 the groups of new migrants in the UK that should be screened for LTBI.[6] Despite these

findings, it is difficult to draw firm conclusions on the accuracy of identifying LTBI in immigrants, as there was no reference test 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 and recently arrived immigrants from high endemic countries). This will aid in the decision as to whether or not IGRAs should replace or complement TST, and if yes, in which circumstances. There is an on-going large multi-centre cohort study assessing the efficacy and cost-effectiveness of IGRAs compared to TST for predicting active TB in recently arriving migrants to the UK and people who have been in contact with TB cases; results from this study will be available in 2017.[77]

1.12 Current usage in the NHS

The UK National Screening Committee decided that TB screening should be organised locally rather than as a national programme. Therefore the implementation of NICE guidelines on LTBI testing through TST and IGRA 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.[49]

More recently in March 2014, the Triborough Joint Strategic Needs Assessment (JSNA) reports "*However, GP screening has to date been inconsistent and no clear assessment and patient pathway exists for latent TB*".[78] Leicester, Leicestershire and Rutland's TB Summary Needs Assessment from December 2013 mentions expanding numbers of cases of LTBI through IGRA testing but calls for a more systematic testing process for testing new entrants to make an impact on active TB cases.[79] Kirklees's JSNA mentions exploring funding to develop IGRA testing,[80] Manchester reports needing to improve LTBI screening.[81]

Commissioners are currently looking at models for local service provision. This is in line with the TB Control Board's suggested approach in the recent Public Health England (PHE) consultation document Collaborative TB strategy for England.[7] There is not one agreed service model and PHE has recently sponsored several pilot projects ongoing at present looking at the feasibility of screening in different settings. These include the identification of eligible individuals from GP practice lists with invitation for screening at the GP surgery by IGRA, and a more innovative approach where screening for latent TB was carried out by IGRA in a college of further education among self-selected individuals taking part in ESOL classes [82] following a campaign of education. Neither of these studies have reported yet, but are expected to show positive result rates of between 17-20% (personal communication from our clinical advisor).

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[83] teams list testing new entrants for LTBI as part of their remit and give a contact number or email address. Birmingham & Solihull Tuberculosis services[84] has a full page on their website with eligibility criteria, whereas Liverpool Community Health NHS Trust Tuberculosis service[85] 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 which cares for refugees and asylum seekers, offers IGRA testing to all registered patients (practice manager, Meridian Centre). The Coventry and Warwickshire TB service reports they "*indirectly try to identify high TB risk individuals other than identified contacts and offer screening*". Apart from supporting the work at the Meridian centre, they also support the Warwickshire programme for looked after children who have an established TB screening programme incorporated into their medical review, and have plans to discuss their programme with Coventry. In addition the Coventry and Warwickshire Partnership Trust commenced a TB screening programme for HIV infected individuals in July 2013 and support 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 sub-groups of interest: children, immunocompromised and recently arrived immigrants from high endemic countries. This evidence will aid in the decision-making process on whether IGRAs should be used as a replacement or as an adjunct to 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.

2 Definition of decision problem

Tuberculosis (TB) 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 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 tuberculin skin test (TST) and 2) the gamma interferon (IFN-γ) release assays (IGRAs).

In light of newly emerged 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 are:

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

3 Clinical effectiveness methods

3.1 Identification and selection of studies

3.1.1 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 included studies of the NICE clinical guideline CG117[10] and methods manuals.[86, 87] The bibliographic database search strategies focussed on the diagnosis of LTBI using IGRAs compared to other methods and were limited to articles in English that have been added to databases since searches for the equivalent questions in the NICE clinical guideline CG117 were run (7 – 14 December 2009; Appendix 1).[10] The searches automatically picked up comparisons in performance between IGRAs and TSTs, 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 comprised 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

Bibliographic databases searched:
MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); Cochrane Library incorporating Cochrane Database of Systematic Reviews, CENTRAL, DARE and HTA databases (Wiley); Science Citation Index and Conference Proceedings (Web of Science); and Medion.

ClinicalTrials.gov and 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 five years. The online resources of relevant organisations were 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).

3.1.2 Inclusion and exclusion of relevant studies

3.1.2.1 Inclusion criteria

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

- IGRAs, e.g.,:
    - QuantiFERON-TB Gold In Tube (QFT-G-IT) [old version: QuantiFERON-TB Gold (QFT-G)]
    - T-SPOT.TB
- TST (i.e., Mantoux test)

Head to head studies involving direct comparison of IGRA and TST only were included.

3.1.2.1.1 Type and language of publication:

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

3.1.2.1.2 Study design:

- Longitudinal studies (randomized controlled trial, retrospective or prospective cohort study)
- Cross sectional studies, case-control studies

3.1.2.1.3 Population:

- Children (both genders, age < 18 years, immunocompetent) – **Research Question #1**
- People (both genders, any age) who are immunocompromised or at risk from immunosuppression (e.g., transplant recipients or those with HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, or who are on or about to start anti-TNF-α treatment, steroids, or cyclosporins) – **Research Question #2**
- People (both genders, 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 per 100,000 or greater e.g. those in Africa, Central/South America, Eastern Europe, and Asia) – **Research Question #3**

3.1.2.1.4 Intervention:

- Two IGRAs [one- or two-step testing]:
    - QuantiFERON-TB Gold In Tube (QFT-G-IT) [old version: QuantiFERON-TB Gold (QFT-G)]
    - T-SPOT.TB

3.1.2.1.5 Comparator:

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

3.1.2.1.6 Construct validity measures (as a proxy for Outcomes):

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

3.1.2.2 Exclusion criteria

- Studies not comparing IGRAs to TST in regards to the pre-specified construct validity (i.e., incidence of TB, exposure to MTB defined by proximity, duration, geographic location, dose-response gradient)
- Studies which do not compare the accuracy of tests (IGRAs with TSTs) in head to head comparison in identifying people with LTBI
- Studies (involving children, recently arrived immigrants, or immunocompromised people) which do not report subgroup data separately for each relevant population
- Studies comparing the IGRAs to each other (e.g., QFT-G-IT vs. T-SPOT.TB) in identifying people with LTBI
- Studies which have applied non-commercial IGRAs, in-house IGRAs, older generation IGRAs (e.g., PPD-based 1st generation QuantiFERON-TB), or tests unavailable in UK
- Studies which assess effects of TB treatment on IGRA/TST test results
- Studies which have evaluated and/or compared reproducibility (test and retest) of tests for identifying LTBI
- Studies which do not focus specifically on LTBI (e.g., studies in which the presence of blood culture-positive TB [active TB] is used to estimate sensitivity. 'Active TB' is assumed as the reference standard for '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 which use serial testing of IGRAs (or TST) to detect LTBI
- Studies which focus on a specific biomarker (e.g., IP-10)

- Systematic/narrative reviews, meta-analyses, case reports, case-series, abstracts (see above 'type of publication'), commentaries, letters, or editorials

3.1.2.3 Review outcomes

3.1.2.3.1 Diagnostic accuracy measures:

- Measures of association between test (IGRAs, TST) results and construct validity-I (i.e., prognostic value of tests in predicting development/risk of active TB [sensitivity, specificity, false-negative and false-positive rates, positive and negative predictive values, incidence density rate ratios, cumulative incidence ratios]
- Measures of association between test (IGRAs, TST) results and construct validity-II (i.e., exposure status/level to MTB defined by proximity, length of time, type of contact) including dose-response gradient, if applicable [sensitivity, specificity, false-negative and false-positive rates, diagnostic odds ratios, regression-based odds ratios 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, residents of low incidence countries) [specificity and false-positive rate]

3.1.2.3.2 Measures of concordance and discordance:

- Agreement (inter-rater, intra-rater) [Kappa statistic, 95% CI]
- Concordance between tests [%, 95% CI]
- Discordance between tests [%, 95% CI]

3.1.2.3.3 Other outcomes:

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

3.2 Study selection strategy

Two independent reviewers, using a pre-specified and piloted questionnaire form, screened all identified bibliographic records for title/abstract (screening level I). Afterwards, full text reports of all potentially relevant records passing screening level I were 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.

3.3 Data extraction strategy

Two reviewers independently extracted relevant data using an a priori defined pre-piloted extraction sheet (Appendix 3). Data extracted was cross-checked and any disagreements were resolved by discussion or by recourse to a third party reviewer. Data extracted included study (e.g., author, country, publication year, design, setting, sample size, follow-up duration, risk of bias items such as blinding, incomplete outcome data), participant (e.g., age, sex, study eligibility criteria, co-morbidity, BCG vaccination status/time, immune status), intervention test/comparator test (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 derivation of test results, repeating 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 population, type of summary effect measure).

For individual studies, two by two 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 proportion 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-value) were ascertained or calculated, if reported data permits. All relevant summary parameters were entered into the data extraction sheets, evidence and summary tables. Calculated parameters are marked as 'calculated'.

3.4 Study quality assessment

The methodological quality of the studies included in the current review was assessed against the Quality in Prognosis Studies (QUIPS)[88] and a modified tool used by Dinnes et al. (2007)[43] for the incidence and exposure studies, respectively (Appendix 4).

The Quality In Prognosis Studies (QUIPS;[88] also referred to as the "Methodology checklist: prognostic studies" developed by Hayden and colleagues in the NICE Guidelines Manual 2012)[87] was used to assess studies reporting diagnostic performance/validation of tests (e.g., sensitivity, specificity, incidence density rate/cumulative incidence ratios, positive/negative predictive values, diagnostic odds ratios, regression-based odds ratios). The QUIPS tool includes assessment of risk of bias (ROB) for 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 are rated as high, moderate, or low ROB. Then, the overall summary ROB rating for each study is derived based on the domain-specific ROB ratings.

We used a modified tool reported by Dinnes et al. (2007)[43] to assess the quality of retrospective/cross sectional studies reporting associations between test results and exposures. The QUIPS tool would not be directly applicable to assessing 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: Studies with 0 to 2 satisfied [yes response] quality features are classified low quality
- Moderate: Studies with 3 satisfied [yes response] quality features are classified moderate quality
- High: Studies with 4-5 satisfied [yes response] quality features are classified high quality

Study quality was assessed independently by two reviewers (PS and KF). Any disagreements were resolved by discussion or by a third reviewer.

3.5 Data synthesis and analysis

Given the absence of a gold standard for diagnosing LTBI, the performance of tests was compared using alternative methodologies which rely on validation of test results against pre-determined validity constructs (i.e., proxies for a reference standard). Thus, our analyses focussed on the following recommended approaches: we a) evaluated and compared predictive values of IGRAs and TST in relation to construct validity I (i.e., progression rate to active TB), b) evaluated and compared the degree of association/correlation of IGRAs and TST results with construct validity II (i.e., exposure to MTB defined by proximity, duration, or dose-response gradient), c) estimated and compared specificity (or false-positives) of IGRAs and TST in relation to construct validity III (i.e., low risk of MTB or healthy populations), and d) measured the degree of concordance/discordance between IGRAs and TST.[43, 89-92]

For each index test (TST, IGRAs), if data permitted (either directly reported; 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 test results (one test negative, the other test positive or vice versa) are

presented, or calculated, if data permitted. Moreover, where possible, likelihood of indeterminate test results was calculated.

The performance of tests (in terms of diagnostic accuracy and concordance) was compared (e.g., IGRA vs. TST) using sensitivity, specificity, positive/negative predictive values, ratio of diagnostic odds ratios (R-DORs), ratio of incidence density rate ratios (or cumulative incidence ratios), regression-based odds ratios, kappa statistic, percent discordance, and likelihood of indeterminate test results. Note that since 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 pre-determined 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 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, diagnostic odds ratios, ratio of diagnostic odds ratios, ratios of cumulative incidence) 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 test threshold effect on the diagnostic odds ratio) using univariate[93] 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 OR and R-DOR estimates and degree of overlap across 95% CIs) and Chi-square test (two tailed, $p \leq 0.10$).[94, 95] A series of subgroup and sensitivity analyses (see below) were undertaken to explore potential reasons for statistical heterogeneity, if present. Where pooling was not feasible, due to the lack of sufficient data or important clinical/statistical heterogeneity across studies (e.g., significant test threshold effect),[96] the findings from individual studies were summarised qualitatively.

Data synthesis for the summary outcome measures is presented in evidence/summary tables and text as overall and/or stratified by demographic characteristics (e.g., age), TST thresholds (≥5mm, ≥10mm, ≥15mm), T-Spot vs. QFT, and prevalence/burden of TB in country of origin (high burden vs. low burden).[1] In addition, for people who are immunocompromised or at risk from immunosuppression (**Research Question #2**), where possible, outcomes have been stratified by type of immunosuppression, use of immunosuppressive drugs (e.g., steroids, anti-TNF-α treatment, anti-rheumatic drugs), and co-

morbidity condition (e.g., HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, transplant recipients).

Subgroup analysis was planned to be conducted according to BCG vaccination status, TST thresholds (≥5mm, ≥10mm, ≥15mm), and prevalence of TB in country of origin, if data permitted. For **Research Questions #2**, the comparison of test performance was examined across the subgroups of type of immunosuppression, use of immunosuppressive drugs (e.g., steroids, anti-TNF-α treatment, anti-rheumatic drugs), and co-morbidity condition (e.g., HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, transplant recipients).

Calculations were performed with MetaDisC version 1.4 (Madrid, Spain)[97] and Stata.[98]

3.6 Overall quality of evidence

There is no formally accepted and validated approach for the assessment of the overall quality of evidence which would be appropriate to the type of evidence synthesized in this review. The work on the formulation of this approach is still ongoing (Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).[99]

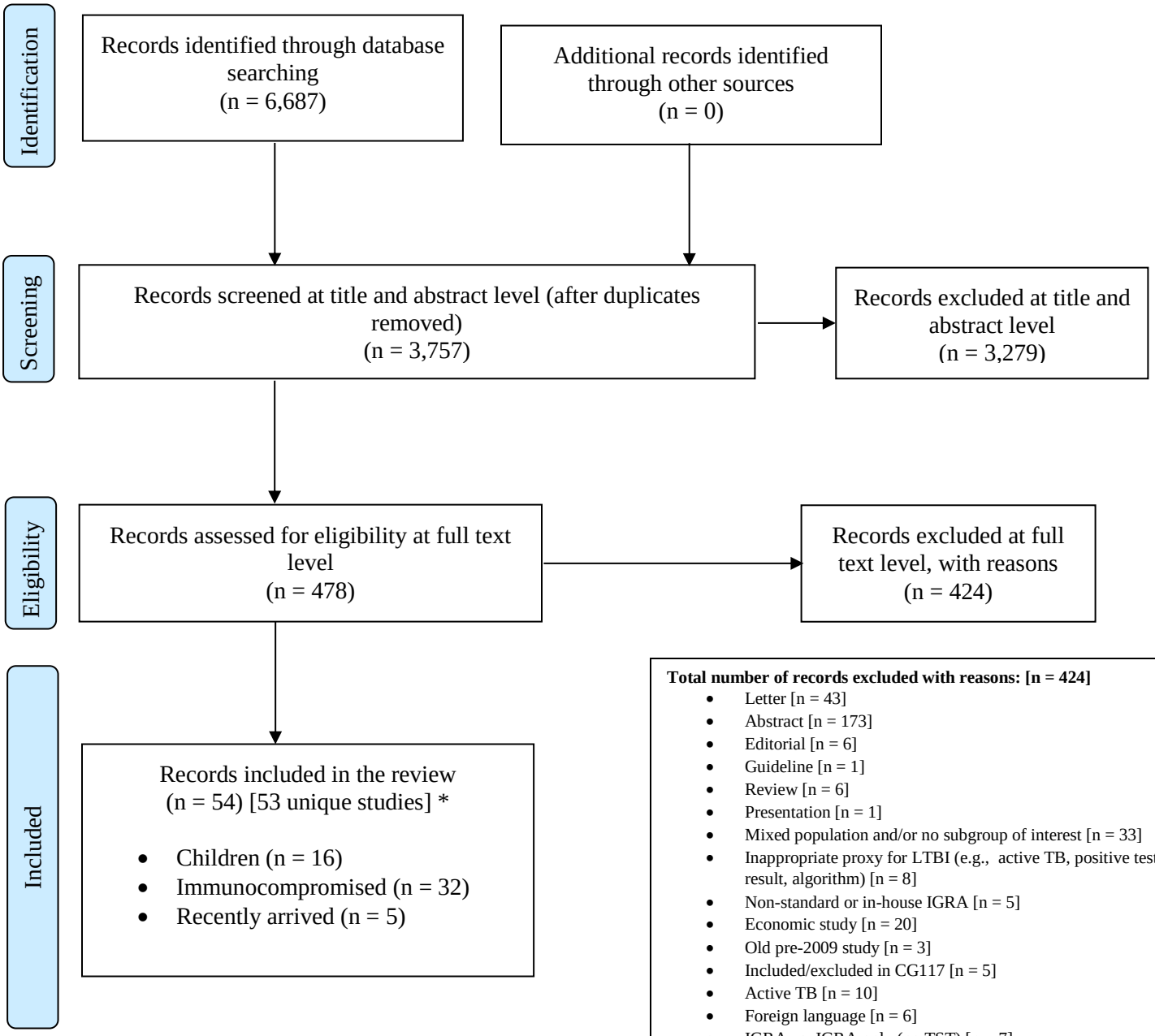
3.7 Derivation of summary measures of diagnostic accuracy

We used Bayesian meta-analysis to derive sensitivity and specificity for various testing strategies for LTBI in the various population subcategories. The methods and results for this are reported in the Section 6.

4 Clinical effectiveness results

4.1 Number of studies identified

A total of 6,687 bibliographic records were identified through electronic database searches. After removing duplicates, 3,757 records were screened for inclusion. On the basis of title/abstract, 3,279 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 (53 unique studies) were considered relevant to the review since the previous NICE clinical guidance work in 2011 (CG117) in[100-153] One study by Rutherford et al. (2012a,b)[108, 109] was presented in two publications. In addition, 37 studies[154-189] were included from CG117 within the current evidence synthesis (see Appendix 6). The study flow and the reasons for exclusion are shown in Figure 2 and Appendix 6. A search of on-going trials was undertaken in different databases (Clinical Trials.gov, WHO ICTRP) up to August 2014. A total of 51 on-going trials were identified. From these, 31 trials were excluded, and the reasons for exclusion are presented in Appendix 7. Twenty on-going trials were considered relevant for inclusion in our synthesis (see Appendix 8).



Total number of records excluded with reasons: [n = 424]

- Letter [n = 43]
- Abstract [n = 173]
- Editorial [n = 6]
- Guideline [n = 1]
- Review [n = 6]
- Presentation [n = 1]
- Mixed population and/or no subgroup of interest [n = 33]
- Inappropriate proxy for LTBI (e.g., active TB, positive test result, algorithm) [n = 8]
- Non-standard or in-house IGRA [n = 5]
- Economic study [n = 20]
- Old pre-2009 study [n = 3]
- Included/excluded in CG117 [n = 5]
- Active TB [n = 10]
- Foreign language [n = 6]
- IGRA vs. IGRA only (no TST) [n = 7]
- IGRA only (no TST) [n = 8]
- Case report [n = 1]
- No relevant outcomes [n = 6]
- Combined test positive result (either TST + or IGRA +) [n = 1]
- Serial testing, conversion and reversion rates [n = 6]
- Comparing antigens [n = 1]
- Case-control study of test results [n = 1]
- Inclusion of TST + patients [n = 1]
- Irrelevant non-TB study [n = 1]
- Irrelevant - no tests [n = 1]
- QFT used as confirmatory test on subgroup of TST + patients [n = 1]
- Studies without the pre-specified construct validity (exposure, active TB incidence) [n = 69]

Figure 2. PRISMA study flow diagram of newly identified studies since 2011 (CG117)[10]
* An additional 37 studies were included from CG117[10]

4.2 Description of included studies and synthesis

In the following sections we describe the baseline characteristics and study quality of the new studies for the three populations of interest: 1) children, 2) immunocompromised and 3) recently arrived for the incidence and exposure studies. Full data extraction sheets including baseline characteristics for all recently identified studies since CG117 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.

4.3 Children

4.3.1 Description of baseline characteristics

This section included 27 studies (in 28 publications) in children and adolescents,[100-111, 146, 148-150, 152, 154-164] of which 11 studies[154-164] had already been reviewed in CG117 (Appendix 6). Our searches identified 16 additional studies (in 17 publications),[100-111, 146, 148-150, 152] five of which investigated the incidence of active TB following testing for LTBI (incidence studies)[100-102, 148, 150] and 11 studies (in 12 publications) investigated levels of exposure in relationship to LTBI test outcomes (exposure studies).[103-111 146, 149, 152] Two publications[108, 109] reported data on the same population and were therefore considered as one study. See Appendix 9 for full data extraction sheets of all new included studies.

4.3.1.1 Incidence studies

Three of the five incidence studies described their population as close contacts of TB cases[100, 102, 150] and one study included only TST positive (≥15mm) children with no history of close contact with TB case.[148] Mahomed et al. (2011a)[101] recruited low risk high school students in a high TB burden country, of whom 25% had current or past household contact of TB. Four studies were carried out in countries with TB vaccination such as South Africa,[102] Iran,[101] Turkey,[148] and South Korea.[150] One study was carried out in Germany in which only 35.7% of participants were BCG vaccinated.[100] Four studies investigated the agreement of a QFT test with the TST test.[100, 101, 102, 150] Four studies compared QFT-GIT with TST in community settings,[100,101, 148, 150] whereas, Noorbakhsh et al. (2011)[102] investigated the agreement between IGRA QFT-G and TST (≥10mm) in a hospital setting. Follow-up to confirm active TB across the five studies ranged from 1 year[102] to 3.8-4 years.[100,101] See Table 2 for further details on these studies.

Table 2. Baseline characteristics of studies in children and adolescents (incidence studies)

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Diel, 2011[100] Germany [Low]	**Study aim:** To compare the 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 **Study design:** Prospective cohort study **Follow up:** 2-4 years **Funding source:** NR (None of the authors has a financial relationship with a commercial entity that has an	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 months) was considered	**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 h indoors with shared air) **Exclusion criteria:** Contacts with an exposure time of < 40 h to the source	**Type of tests:** IGRA (QFT-GIT) TST **Cut-off values/thresholds:** IGRA: IFN-g ≥ 0.35 IU/ml TST: >5mm or >10mm	**Mean (range or SD) age:** 10.4 (4.3) years **Female (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 [%]):**	**Total N or recruited patients:** 141 **Total N of excluded patients:** 15	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

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	interest in the subject of this manuscript)	sufficient to confirm the diagnosis of TB			NR **Co-morbidity (n [%]):** NR		
Mahomed, 2011a[101] South Africa [High]	**Study 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) **Study design**: Longitudinal cohort study **Follow up:** 3.8 years **Funding source:**	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	**Inclusion criteria:** Adolescents aged 12 to 18 years **Exclusion criteria:** NR	**Type of tests:** IGRA-GIT TST (≥5mm) **Cut-off values/thresholds:** IGRA: ≥ 0.35 IU/mL TST: ≥ 5mm	**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 anti-TB treatment (n [%]):** NR **Total incidence of active TB (n [%]):** 52 [1.0] **Chest radiography (yes/no):** yes	**Total N or recruited patients:** 6,363 **Total N of excluded patients:** 1,119	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

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	The Aeras Global TB Vaccine Foundation with some support from the Gates Grand Challenge 6 and Gates Grand Challenge 12 grants for the QFT testing				**Clinical examination (yes/no):** yes **Morbidity (n [%]):** NR **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** NR		
Metin Timur, 2014[148] Turkey [Intermediate]	**Study aim:** To compare QFT-GIT and TST as a diagnosis of LTBI in the children with Bacille Calmette-Guerin (BCG) vaccine **Setting:** community based **Study design:** prospective cohort study **Follow up:** 3 years as outpatients with	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.	**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	**Type of tests:** QFT-GIT and TST **Cut-off values/thresholds:** ≥ 15mm (TST) NR (QFT-GIT)	**Mean (range or SD) age (years):** 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 anti-TB treatment (n [%]):** NR	**Total N or recruited patients:** NR **Total N of excluded patients:** NR	

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	3 months intervals **Funding source:** NR		**Exclusion criteria:** 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		

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					TST^{+}/QFT^{+} results with symptoms –with TB)		
Noorbakhsh, 2011[102] Iran [Intermediate]	**Study 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 **Study design:** Cross-sectional	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	**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 center 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	**Type of tests:** IGRA (QFT-G) TST (≥10mm) **Cut-off values/thresholds:** IGRA: NR TST: Induration diameter of ≥10mm	**Mean (range or SD) age (years):** NR **Female (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	**Total N or recruited patients:** NR **Total N of excluded patients:** NR	

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	study **Follow up:** 1 year **Funding source:** Research Centre of Paediatric Infectious Diseases, Iran University of Medical Sciences		clinical signs (malignancy, corticosteroid therapy, HIV, etc.)		**Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** NR		
Song 2014,[150] South Korea [High]	**Study aim:** 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 TB in middle and high school students in close contact with tuberculosis patients in South Korea **Setting:** community-	NR	**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	**Type of tests:** QFT-GIT and TST **Cut-off values/thresholds:** 0.35 IU/ml (QFT-GIT) TST (≥10mm, 15mm)	**Mean (range or SD) age (years):** 15.1 (1.3) **Female (n [%]):** 1,356 [45.5] **Race/ethnicity (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]	**Total N or recruited patients:** 3,202 **Total N of excluded patients:** 220	To eliminate the possibility of false-positive IGRA results due to PPD reagents, blood samples were collected before PPD injection

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	based **Study design:** prospective cohort study **Follow up:** 24 months **Funding source:** Research of Korea Centers for Disease Control and Prevention		antituberculosis drugs or chemoprophylaxis earlier		**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)		

Abbreviations: AFB = acid-fast bacilli; BCG = Bacille de Calmette et Guérin; CXR = chest X ray; h = hour; HIV = human immunodeficiency virus; IFN = interferon; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; MTB = Mycobacterium tuberculosis; N = number; NR = not reported; QFT-GIT = QuantiFERON-TB Gold In-Tube; SD = standard deviation; TB = tuberculosis; TST = tuberculosis skin test

4.3.1.2 *Exposure studies*

Eleven studies (in 12 publications) compared one or more QFT test with the TST test in children and adolescents by relating test results to prior levels of exposure (exposure studies).[103-111, 146, 149, 152] Five studies were carried out in countries of high TB incidence (Gambia,[103] South Africa[105, 106] and Indonesia (1 study in 2 publication)[108, 109] and Thailand[152]), two studies in countries of intermediate incidence (Mexico,[146] Brazil[149]) and four studies in low incidence countries (USA,[104, 110] Croatia[107] and Greece[111]).

The mean and/or median age of the recruited children was reported in eight[104-107, 110, 146, 149, 152] of the 11 studies.[103-111, 146, 149, 152] Namely, the populations in the studies by Pavic et al. (2011)[107] and Perez-Porcuna et al. (2014)[149] had a mean age less than 4 years. The studies by Laniado-Laborın 2014[146] and Tieu et al. (2014)[152] included children whose mean age was about 8 years. Cruz et al. (2011)[104] and Kasambira et al. (2011)[105] recruited children with the median age of 8.6 and 6 years, respectively. Mahomed et al. (2011b)[106] and Talbot et al. (2012)[110] 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[103-106, 110, 146, 149, 152] and 40% in one study.[107] Eight studies compared QFT-GIT with TST (≥5mm)[105, 106, 146] or TST (≥10mm).[107-109, 149, 152] The T-SPOT.TB test was compared with the TST (≥ 10mm or ≥15mm) in three studies.[104, 110, 152] Adetifa et al. (2010)[103] compared three tests (IGRA-GIT, T-SPOT.TB and TST (≥10mm)) while Tsolia et al. (2010)[111] compared QFT-GIT with TST at two different thresholds (≥5mm and ≥10mm).

Exposure to TB was defined as household contacts in one study[106] and was further categorised by four studies to include sleep proximity[103] (same room / different room), time spent with contact[105, 107] (≥40h in closed rooms; <6h/day or >7h/day, respectively) or both[108, 109] (different room / same room / same bed and <2h/day or 2-8h/day or >8h/day). One study described exposure only as contact with a source case[104] or in terms of country of birth, residence, extended visit to high incidence country,[110] and one study distinguished exposure as either non-household but regular contact or household contact.[111] Three studies used a TB contact score,[149, 152] or duration of exposure to TB index case.[146, 149, 152]

The study setting was either community based[103, 105, 106, 110, 149, 152] or hospital based.[104, 107-109, 111, 146] BCG vaccination was high in six studies,[105-107, 146, 149, 152] medium in a further three studies,[103, 104, 108, 109] low in one study[110] and not reported in another.[111] See Table 3 for further details on these studies.

Table 3. Baseline characteristics of studies in children and adolescents (exposure studies)

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Adetifa, 2010[103] Gambia [High]	**Study aim:** To compare T-SPOT.TB, QFT-GIT, and TST for diagnosis of LTBI in Gambian childhood contacts of TB patients **Setting:** Community-based **Study design:** Retrospective cohort/cross-sectional study Study **Funding source:** Medical Research Council (MRC) labs 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:** IGRA (T-SPOT.TB) IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** 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): ≥0.35 IU/ml TST: ≥10mm induration	**Mean (range or SD) age:** NR **Female (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**	**Recruited (N):** 285 **Excluded (N):** NR	None

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					(yes/no): Yes **Morbidity (n [%]):** HIV positive (3 [1.1]) **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** NR		
Cruz, 2011[104] US [Low]	**Study aim:** To compare the performance of T-SPOT.TB with TST in children with different epidemiologic risk factors for tuberculosis **Study setting:** Pediatric tuberculosis clinics **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Cellestis, Ltd, Oxford	**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 tuberculosis **Exclusion criteria:** Children on any TB medication for 2 or more months were not eligible for enrollment	**Type of tests:** IGRA (T-SPOT.TB) TST (≥15mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥ 8 spots TST: ≥15mm induration	**Mean (range or SD) age:** Median 8.6 (range: 1 month to 18 years) **Female (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]	**Recruited (N):** NR **Excluded (N):** NR	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

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Immunotec, Inc				**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		
Kasambira, 2011[105] South Africa [High]	**Study aim:** 1) To determine and compare the prevalence of M. tuberculosis infection	*Adult index case type of TB diagnosis* **Non exposed:** Smear-positive	**Inclusion criteria:** Children aged 6-16 years whose parents and guardians were TB index cases aged	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm) **Cut-off**	**Mean (range or SD) age (years):** Median 6 [3–9] **Women (n [%]):**	**Recruited (N):** NR **Excluded (N):** NR	None

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	as assessed by TST and by QFT-GIT; 2) To assess agreement between the two test methods and identify factors associated with various patterns of test results **Study setting:** Community based **Study design:** Retrospective cohort/cross-sectional study (with limited follow-up of 6mos) **Funding source:** The United States Agency for International Development	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 h) **Exposed:** Majority of day (> 7 h)	⩾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	**values/thresholds** **Definition of test+:** IGRA: NR TST: Induration of ≥5mm	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-**		

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					study treatment (n [%]): active TB treatment 37 [19] and LTBI treatment 19 [10]		
Laniado-Laborın, 2014 [146] Mexico [intermediate]	**Study aim:** To compare the prevalence of LTBI between paediatric contacts of drug-resistant cases and drug susceptible cases **Setting:** TB clinic **Study design:** Cross-sectional/retrospective cohort study **Funding source:** NR	**Non exposed:** NR **Exposed:** Exposure to source Hours/day exposure # of cohabitants # of rooms	**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	**Type of tests:** QFT-GIT TST **Cut-off values/thresholds Definition of test+:** QFT-GIT≥0.35 IU/ml TST≥5mm	**Mean (range or SD) age:** drug susceptible 7.79 (4.28) years; drug resistant 7.36 (4.46) years **Women (n [%]):** 86/173 [50.0] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination (n [%]):**164 [95] H**istory of anti-TB treatment (n [%]):** none **Total incidence of active TB (n [%]):**	**Recruited (N):** NR **Excluded (N):** NR	

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					NR **Chest radiography (yes/no):** yes **Clinical examination (yes/no):** yes **Morbidity (n [%]):** NR **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** 77/173 [44.5] contacts of multidrug susceptible index cases were treated for LTBI with INH or rifampicin. 96/173 [55.5%] contacts of multidrug resistant cases did not receive treatment for LTBI		

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Mahomed, 2011b[106] South Africa [High]	**Study aim:** To determine the prevalence of and predictive factors associated with latent TB infection in adolescents **Study setting:** High school **Study design:** Retrospective cohort/cross-sectional study **Funding source:** The 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 prior TB household contact **Exposed :** Current or prior TB household contact	**Inclusion criteria:** All adolescents aged 12-18 years **Exclusion criteria:** Diagnosed with active TB	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm) **Cut-off values/thresholds Definition of test+:** IGRA: QFT-GIT ≥ 0.35 IU TST: Induration ≥ 5mm	**Mean (range or SD) age:** 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] **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	**Recruited (N):** 6,363 enrolled, 5,244 enrolled for analysis **Excluded (N):** 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)	None

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					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		
Pavic, 2011[107] Croatia [Low]	**Study aim:** To evaluate an IGRA for diagnosis of LTBI in BCG –vaccinated children up to 5 years of age, with documented exposure to active TB **Study setting:** Children hospital and general hospital	**Non exposed:** Distant contact was defined as occasional or unclear exposure time or <40 h during the presumed period of infectiousness **Exposed:** Close contact was	**Inclusion criteria:** Pediatric patient's ≤5 years with 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 h in closed room and	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥ 0.35 IU/mL as recommended by the manufacturer	**Mean (range or SD) age:** 29 ± 16 months **Women (n [%]):** 57[40.1] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination**	**Recruited (N):** 142 **Excluded (N):** 1	Blood samples for QFT-GIT were drawn under standardized condition in our hospital at the same day as TST. The test was considered

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Study design: Retrospective cohort/cross-sectional study **Funding source:** None	defined as household contact with aggregate exposure to a patient with active TB ≥40 h in closed rooms	distant contact (occasional or unclear exposure time of <40 h during the presumed period of infectiousness) **Exclusion criteria:** Children >5 years, immunocompromised children, inadequate blood sampling and diagnosis of active TB	TST: ≥10mm induration	**(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		indeterminate if the value of the +ve control well was less than 0.5 IU/mL, and/or nil -ve control was more than 8 IU/L.
Perez-Porcuna, 2014 [149] Brazil [intermediate]	**Study aim:** To evaluate the response of the QFT-GIT and TST tests in young children with recent exposure to an index	*Time of exposure to the index case* **Non exposed:** NR	**Inclusion criteria:** children from 0–6 years of age with recent contact with an adult symptomatic TB index case within	**Type of tests:** QFT-GIT TST **Cut-off values/thresholds**	**Mean (range or SD) age:** 46 (28.0-64.5) months **Women (n [%]):** 74 [54.8]	**Recruited (N):** 140 **Excluded (N):** 3	Experienced laboratory technicians who were unaware of the data of the

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	case **Setting:** community-based **Study design:** cross-sectional/retrospective study **Funding source:** the Brazilian National Counsel of Technological and Scientific Development, the Foundation of Research Support of the State of Amazonas, and the University of Barcelona. Cellestis Ltd. donated QFT kits.	**Exposed**: # months (continuous scale covariate) *Mycobacterium tuberculosis 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 hours per day (0–4), the relationship to the index case (0–4) and the type of exposure (0–3**)**	the last 12 months **Exclusion criteria:** Children receiving treatment or prophylaxis for TB	**Definition of test+:** **QFT-**GIT ≥0.35 IU/mL TST≥ 10mm	**Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination (n [%]):** 118 [90.8] H**istory 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		study subjects

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Type of during-study treatment (n [%]): NR		
Rutherford, 2012a-b[108, 109] Indonesia [High]	**Study aim:** To quantify M. TB infection in children living with a smear-positive adult TB case and identify risk factors for TST and QFT-GIT positivity **Study setting:** Out-patient-based clinic **Study 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*	**Inclusion criteria:** Child contacts living for more than 3 months with newly diagnosed TB cases (index case) 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 (≥10mm) **Cut-off values/thresholds Definition of test+** IGRA: NR TST: Induration of ≥10mm	**Mean (range or SD) age:** Median [IQR] 58 [31–81] months **Women (n [%]):** 152 [50.7] **Race/ethnicity (n [%]):** Sudanese 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	**Recruited (N):** 320 **Excluded (N):** 16	None

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
		child (# h/day) **Non exposed:** <2 **Exposed 1:** 2-8 **Exposed 2:** >8			**Chest radiography (yes/no):** Yes **Clinical examination (yes/no):** Yes (Children who were symptomatic and test-ve (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		
Talbot, 2012[110] US [Low]	**Study aim:** To test the specificity of TST and the T-SPOT.TB assay among students at low risk for TB	**Non exposed:** Low-TB exposure risk group	**Inclusion criteria:** Students with history of exposure to TB **Exclusion criteria:**	**Type of tests**: IGRA (T-SPOT.TB) TST (≥15mm)	**Mean (range or SD) age:** Median 20 (17-47) years **Women (n [%]):**	**Recruited (N):** 184 **Excluded (N):** 4	None

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	exposure **Study setting:** College health setting **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Oxford Immunotec	**Exposed:** 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)	NR	**Cut-off values/thresholds Definition of test+:** IGRA: 5–7 spots borderline, and results with a low mitogen response or a high nil control response are indeterminate TST: Induration > 15mm for students with no risk factors for TB exposure	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		

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Co-morbidity (n [%]): NR **Type of during-study treatment (n [%]):** NR		
Tieu, 2014[152] Thailand [high]	**Study 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 recent exposure to an adult index case with TB **Setting:** community-based **Study 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)	**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	**Type of tests:** QFT-GIT TST **Cut-off values/thresholds Definition of test+:** QFT-GIT, TSPOT (NR) TST (10mm or ≥15mm)	**Mean (range or SD) age:** 7.6 (4.3) years **Women (n [%]):** 67 [49.3] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination (n [%]):** 132 [96.4] H**istory of anti-TB treatment (n [%]):** NR **Total incidence of active TB (n [%]):** NR **Chest radiography**	**Recruited (N):** 137 [TB-exposed] **Excluded (N):** NR	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

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
		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:**	isoniazid [INH] for latent TB), or if they had recently been diagnosed with active TB		**(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]		

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
		0-7 hours **Exposed:** ≥8 hours *Duration of contact with TB index case in last 12 months* **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[111] Greece [Low]	**Study aim:** To evaluate and compare the performance of the QFT-GIT assay	**Contact with an adult TB** **Non exposed :**	**Inclusion criteria:** Adolescents ≤ 15 years	**Type of tests:** IGRA (QFT-GIT) TST (≥ 5mm or ≥10mm)	**Mean (range or SD) age:** NR **Women (n [%]):**	**Recruited (N):** 295 **Excluded**	Indeterminate results on the QFT-GIT were excluded

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	and the TST among children with active TB or possible latent TB infection in a low endemic country **Setting:** TB clinic **Study design:** Retrospective cohort/cross sectional study **Funding source:** The Bienmoyo Foundation	Non household occasional contact **Exposed 1:** Non household regular contact **Exposed 2:** Household contact	**Exclusion criteria:** NR	**Cut-off values/thresholds Definition of test+:** IGRA: > 10 IU/mL TST: ≥ 10mm for BCG immunized children ≥ 5mm for non-BCG immunized children	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	**(N):** 9 (refusal, lost specimen, sample processing delay)	from the analysis

Subgroup of interest – children and adolescents							
Study ID (Author name, year, and country) [burden]	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Type of during-study treatment (n [%]): NR		

Abbreviations: +ve = positive; BCG = Bacille de Calmette et Guérin; ESAT-6 and CFP-10 = Mycobacterium tuberculosis T-cell antigens; h = hour; HIV = human immunodeficiency virus; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; N = number; NR = not reported; QFT-GIT = QuantiFERON-TB Gold In-Tube; SD = standard deviation; TB = tuberculosis; TST = tuberculosis skin test; -ve = negative

4.3.2 Study quality

4.3.2.1 Incidence of active TB (n = 5)

Of the five newly identified active TB incidence studies in children[100, 101, 102, 148, 150] three were rated as having a moderate risk of bias (Diel 2011,[100] Mahomed 2011a,[101] Song 2014[150]) and two as having a high risk of bias (Noorbakhsh 2011,[102] Metin Timur 2014[148]). Most studies had moderate risk of bias 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. See Table 4 for further details.

Table 4. Summary assessment of risk of bias (ROB) for included incidence studies in children (adapted from Hayden et al., 2013)[89]

First author, Year, Study ID	**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** *risk of bias in misclassification of individuals in relation to construct validity groups*	**Study Confounding** *risk of bias due to confounding*	**Statistical Analysis and Reporting** *risk of bias due to analysis and selective reporting*	**Total ROB** *high, moderate, low*
Diel, 2011[100] [Low]	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate ROB
Mahomed, 2011a[101] [High]	Low	Moderate	Moderate	Moderate	Moderate	High	Low	Moderate ROB
Metin Timur, 2014[148][Intermediate]	Low	High	High	Moderate	Moderate	High	High	High ROB
Noorbakhsh 2011[102] [Intermediate]	Moderate	High	High	High	Moderate	High	High	High ROB
Song, 2014[150][High]	Low	Low	Moderate	Low	High	Moderate	Low	Moderate ROB

4.3.2.2 Exposure levels (n = 11)

The majority of the 11 included exposure studies in children (in 12 publications)[103-111, 146, 149, 152] identified since CG117 were rated as low quality and only three studies were rated as high quality.[149, 152, 190] One study was of moderate quality.[146] See Table 5 for further details.

Table 5. Summary of quality assessment for the included children exposure studies (adapted from Dinnes et al., 2007)[43]

First author, Year, Study ID	**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]#, inadequate or unreported [no]*	**Overall quality score of satisfactory features** [£]
Adetifa, 2010[103] [High]	No	No	Yes	Yes	No	Low quality
Cruz, 2011[104] [Low]	No	No	No	No	Yes	Low quality
Kasambira, 2011[105] [High]	No	No	No	Yes	Yes	Low quality
Laniado-Laborın, 2014[146] [intermediate]	Yes	Yes	Yes	No	No	Moderate quality
Mahomed, 2011b[106] [High]	No	No	No	No	No	Low quality
Pavic, 2011[107] [Low]	Yes	No	Yes	Yes	Yes	High quality
Perez-Porcuna, 2014[149] [intermediate]	Yes	Yes	Yes	Yes	No	High quality
Rutherford, 2012 a[108] b[109] [High]	No	No	No	Yes	Yes	Low quality
Talbot, 2012[110] [Low]	No	No	Yes	No	No	Low quality
Tieu, 2014[152] [high]	Yes	Yes	No	Yes	Yes	High quality
Tsolia, 2010[111] [Low]	Yes	No	No	No	Yes	Low quality

[#] ≥ 90% of participants were included in the follow-up analysis [yes response] and < 90% were classified as "no response"

[£] Studies with 1 or 2 "yes" ratings = Low quality; studies with 3 "yes" ratings = Moderate quality; studies with 4 or 5 "yes" ratings = High quality

Please note the following item has been removed from the original Dinnes et al., (2007)[43] checklist: "study design" (as all studies were considered are retrospective), this item has been removed. Furthermore, the following item has been added: "sample attrition"

4.3.3 Comparative performance of tests (diagnostic accuracy indices for identifying LTBI) - children

4.3.3.1 Incidence of active TB

4.3.3.1.1 Ratios of cumulative incidence ratios (R-CIRs):

This section included seven studies: two studies reviewed in CG117[159, 160] (see Appendix 6) and five more recent studies, three of them published in 2011,[100-102] and two studies published in 2014.[148, 150] (see Appendix 9). For 3 studies (out of the 5 recent studies), ratios of cumulative incidence ratios (R-CIRs) could not be calculated because none of the children developed active TB.[148, 159, 160] The R-CIRs in the remaining 4 studies (see summary Table 6)[100-102, 150] were pooled in which one analysis compared QFT-GIT to TST 5mm and the other QFT-GIT to TST 10mm (they were pooled separately because TST performance differs according to its threshold). The pooled estimates indicated no significant difference between QFT-GIT and TST 5mm performance (pooled R-CIR = 1.12, 95% CI: 0.72, 1.75),[100, 101] (see Figure 3) whereas QFT-GIT was better than TST 10mm in identifying/predicting LTBI (pooled R-CIR = 4.33, 95% CI: 1.32, 14.23)[100, 102, 150] (see Figure 4).

Table 6. Comparison of the test performance - diagnostic accuracy indices for identifying LTBI (incidence studies)

Subgroup of interest – children and adolescents						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
Diel, 2011[100] Germany [Low]	**N test results** QFT-GIT: 106 T-SPOT: NA TST: 106 **Test (+/-)** QFT-GIT (23/83) T-SPOT (NA) TST≥ 5mm (40/66) TST ≥ 10mm (20/86) **N indeterminate** QFT-GIT: NR T-SPOT: NA TST: NR **N lost to follow-up** NR	**QFT (GIT)** SN: 100 (60.97, 100) SP: 84.69 (76.27, 90.5) PPV: 28.57 (13.81, 49.96) NPV: 100 (95.58, 100)	**TST ≥ 5mm** SN: 100 (60.97, 100) SP: 65.31 (55.47, 73.99) PPV: 15.00 (7.06, 29.07) NPV: 100 (94.34, 100) **TST ≥ 10mm** SN: 66.67 (30.00, 90.32) SP: 63.27 (53.39, 72.14) PPV: 10.00 (3.96, 23.05) NPV: 96.88 (89.3, 99.14)	**QFT (GIT)** CI (+): 28.57 (13.81, 49.96) CI (-): 1.20 (0.03, 6.53) CIR: 23.7 (2.57, 110.3)	**TST ≥ 5mm** CI (+): 15.00 (7.06, 29.07) CI (-): 1.55 (0.04, 8.4) CIR: 9.6 (1.08, 448.2) **TST ≥ 10mm** CI (+): 10.00 (3.95, 23.05) CI (-):3.12 (0.22, 11.33) CIR: 3.20 (0.61, 16.67)	**R-CIR [QFT (GIT)] vs. TST ≥ 5mm** 2.47 (0.40, 15.12) **R-CIR [QFT (GIT)] vs. TST ≥ 10mm** 7.41 (2.06, 26.57)
Mahomed, 2011a[101] South Africa [High]	**N test results** QFT-GIT: 5244 T-SPOT: NA TST: 5244 **Test (+/-)** QFT-GIT (2669/2575)	**QFT (GIT)** SN: 75.00 (61.79, 84.77) SP: 49.35 (47.99, 50.71) PPV: 1.46 (1.07, 1.99) NPV: 99.50 (99.14,	**TST ≥ 5 mm** SN: 76.92 (63.87, 86.28) SP: 45.03 (43.68, 46.39) PPV: 1.38 (1.02, 1.88) NPV: 99.49 (99.11,	**QFT (GIT)** CI (+): 1.46 (1.07, 1.99) CI (-): 0.50 (0.28, 0.87) CIR: 2.89 (1.55, 5.40) IDR (+): 0.64/100 p-y (0.45, 0.87)	**TST ≥ 5 mm** CI (+): 1.38 (1.02, 1.87) CI (-): 0.51 (0.28, 0.90) CIR: 2.71 (1.42, 5.14) IDR (+): 0.60/100 p-y (0.43, 0.82)	**R-CIR [QFT (GIT)] vs. TST ≥ 5mm** 1.07 (0.68, 1.68) **R-IDRR [QFT (GIT)] vs. TST ≥ 5mm**

Subgroup of interest – children and adolescents						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	T-SPOT (NA) TST≥ 5 mm (2894/2350) **N indeterminate** QFT-GIT: NR T-SPOT: NA TST: NR **N lost to follow-up** 18%	99.7)	99.71)	IDR (-): 0.22/100 p-y (0.12, 0.38) IDRR: 2.92 (1.58, 5.67)	IDR (-): 0.22/100 p-y (0.11, 0.39) IDRR: 2.73 (1.45, 5.42)	1.07 (0.67, 1.71)
Metin Timur, 2014[148] Turkey [Intermediate]	**N test results** QFT-GIT: 81 T-SPOT: NA TST: 81 **Test (+/-)** QFT-GIT (12/69) T-SPOT (NA) TST≥ 15 mm (81/0) **N indeterminate** QFT-GIT: 0 T-SPOT: NA TST: 0	**QFT (GIT)** SN: NA SP: 100 (95% CI: NR) PPV: NA NPV: 100 (95% CI: NR)	**TST ≥ 15 mm** SN: NA SP: 0.0 (95% CI: NR) PPV: 0.0 (95% CI: NR) NPV: NA	**QFT (GIT)** CI (+): NA CI (-): 0.0 (95% CI: NR) CIR: NA	**TST ≥ 15 mm** CI (+): 0.0 (95% CI: NR) CI (-): NA CIR: NA	**R-CIR [QFT (GIT)] vs. TST ≥ 15mm** NA

Subgroup of interest – children and adolescents						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	N lost to follow-up NR					
Noorbakhsh, 2011[102] Iran [Intermediate]	**N test results** QFT-G: 59 T-SPOT: NA TST: 58 **Test (+/-)** QFT-G (18/41) T-SPOT (NA) TST≥ 10 mm (8/50) **N indeterminate** QFT-G: NR T-SPOT: NA TST: 1 **N lost to follow-up** NR	**QFT (G)** SN: 100 (72.25, 100) SP: 83.67 (70.96, 91.49) PPV: 55.56 (33.72, 75.44) NPV: 100 (91.43, 100)	**TST ≥ 10 mm** SN: 30.00 (10.78, 60.32) SP: 89.58 (77.83, 95.47) PPV: 37.50 (13.68, 69.43) NPV: 86.00 (73.81, 93.05)	**QFT (G)** CI (+): 55.56 (33.72, 75.44) CI (-): 2.41 (0.06, 12.9) CIR: 22.78 (2.75, 101.1)	**TST ≥ 10 mm** CI (+): 37.5 (13.49, 69.62) CI (-): 14.00 (6.63, 26.50) CIR: 2.68 (0.86, 8.27)	**R-CIR [QFT (G)] vs. TST ≥ 10 mm** 8.50 (2.87, 25.17)
Song, 2014[150] South Korea [High]	**N test results** QFT-GIT: 2966 T-SPOT: NA TST: 2982 **Test (+/-)** QFT-GIT (317/2649)	**QFT (GIT)** SN: 47.83 (95% CI: 29.24, 67.04) SP: 89.6 (95% CI: 88.45, 90.65) PPV: 3.47 (95% CI:	**TST ≥ 10 mm** SN: 56.52 (95% CI: 36.81, 74.37) SP: 78.03 (95% CI: 76.51, 79.49) PPV: 1.96 (95% CI:	**QFT (GIT)** CI (+): 3.47 (95% CI: 1.87, 6.17) CI (-): 0.45 (95% CI: 0.24, 0.79) CIR: 7.66 (95% CI:	**TST ≥ 10 mm** CI (+): 1.96 (95% CI: 1.11, 3.36) CI (-): 0.43 (95% CI: 0.22, 0.80) CIR: 4.55 (95% CI:	**R-CIR [QFT (GIT)] vs. TST ≥ 10 mm** 1.68 (95% CI: 0.94, 3.03) **R-OR [QFT**

Subgroup of interest – children and adolescents						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	T-SPOT (NA) TST≥ 10 mm (663/2319) TST≥ 15 mm (231/2751) **N indeterminate** QFT-GIT: 16 T-SPOT: NA TST: 0 **N lost to follow-up** NR	1.94, 6.10) NPV: 99.55 (95% CI: 99.21, 99.74)	1.14, 3.32) NPV: 99.57 (95% CI: 99.21, 99.77) **TST ≥ 15 mm** SN: 56.52 (95% CI: 36.81, 74.37) SP: 92.63 (95% CI: 91.64, 93.52) PPV: 5.62 (95% CI: 3.31, 9.38) NPV: 99.64 (95% CI: 99.33, 99.80)	3.41, 17.21) OR=7.90 (95% CI: 3.46, 18.06)	2.00, 10.32) OR=4.62 (95% CI: 2.02, 10.58) **TST ≥ 15 mm** CI (+): 5.62 (95% CI: 3.23, 9.47) CI (-): 0.36 (95% CI: 0.18, 0.67) CIR: 15.48 (95% CI: 6.86, 34.92) OR=16.35 (95% CI: 7.08, 37.71)	**(GIT)]** **TST ≥ 10 mm** 1.71 (95% CI: 0.94, 3.11) **R-CIR [QFT (GIT)] vs. TST ≥ 15 mm** 0.49 (95% CI: 0.28, 0.89) **R-OR [QFT (GIT)] vs. TST ≥ 15 mm** 0.48 (95% CI: 0.27, 0.88)

Abbreviations: 95% CI = 95 percent confidence interval; CI = cumulative incidence; CIR = cumulative incidence ratio; GIT = Gold In-Tube; IDR = incidence density rate; IDRR = incidence density rate ratio; N = number; NPV = negative predictive value; PPV = positive predictive value; P-Y = person-year(s); QFT = QuantiFERON-TB; R-CIR = ratio of cumulative incidence ratio; R-IDRR = ratio of incidence density rate ratio; SN = sensitivity; SP = specificity; TB = tuberculosis; TST = tuberculin skin test

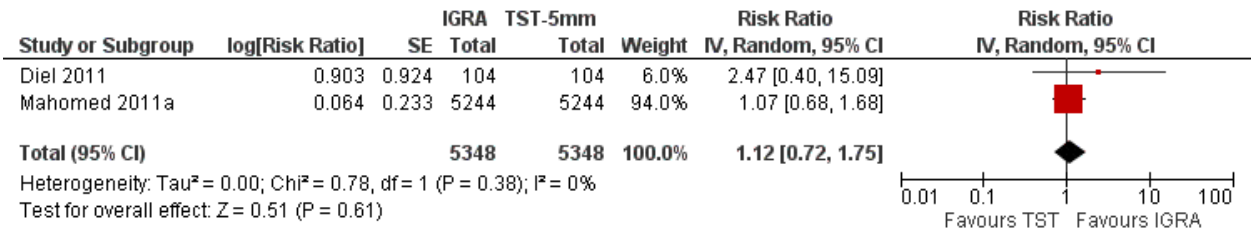


Figure 3. Pooled ratio of cumulative incidence ratios (QFT-GIT vs. TST 5mm) in children

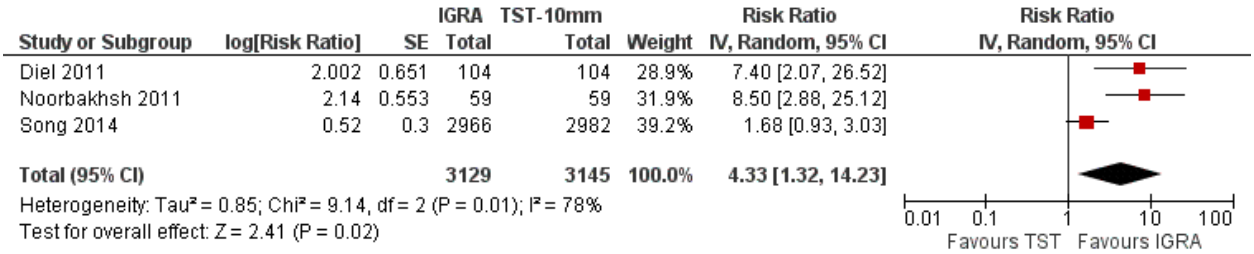


Figure 4. Pooled ratio of cumulative incidence ratios (QFT-GIT vs. TST 10mm) in children

4.3.3.1.2 Sensitivity and specificity:

There was a wide variability in sensitivity and specificity of IGRA (QFT-GIT/G) and TST (5mm or 10mm) across newly identified studies.[100-102, 148, 150] The TST sensitivity was higher at 5mm compared to 10mm/15mm, and vice versa, specificity was better at 10mm/15 mm than at 5mm. IGRA (QFT-GIT/G) demonstrated similar sensitivity (range: 48%-100%) and slightly better specificity (range: 49%-90%) compared to TST 5mm (sensitivity range: 57%-100%; specificity range: 45%-65%). Although, sensitivities of IGRA and TST 5mm were higher than that for TST 10mm/15mm (range: 30%-56%), the corresponding specificities of these tests were lower compared to TST 10mm/15mm (63%-93%). The forest plots of sensitivities and specificities were generated and due to high unexplained heterogeneity (not explained by IGRA type and TST threshold, similar diagnostic methods of active TB), no meta-analysis could be performed (see Figure 5, Figure 6, Figure 7, Figure 8).

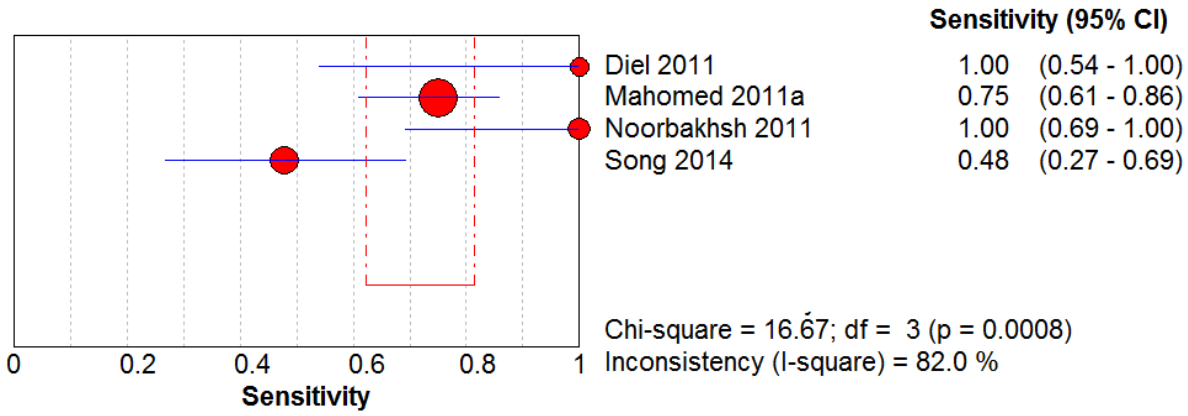


Figure 5. Forest plot of sensitivity based on incidence of active TB (QFT-GIT/G) in children

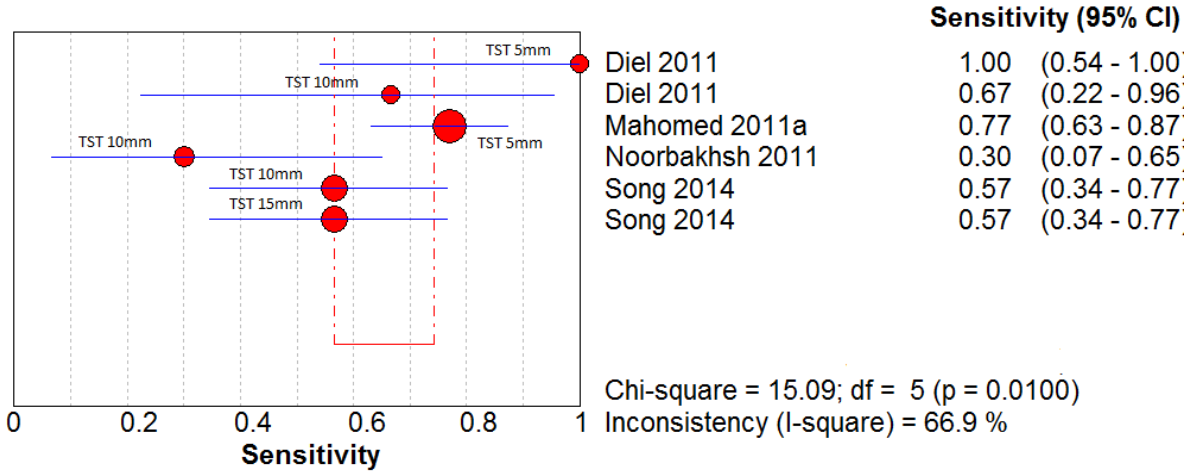


Figure 6. Forest plot of sensitivity based on incidence of active TB (TST) in children

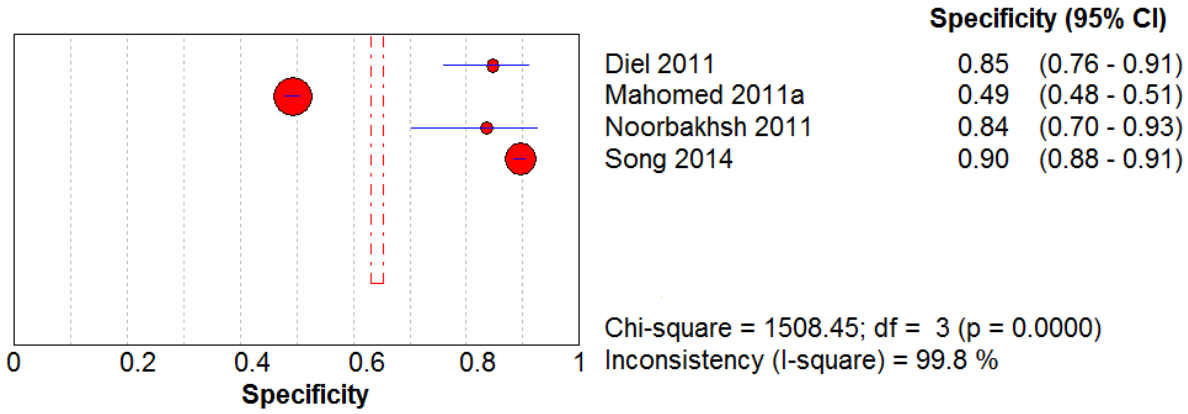


Figure 7. Forest plot of specificity based on incidence of active TB (QFT-GIT-G) in children

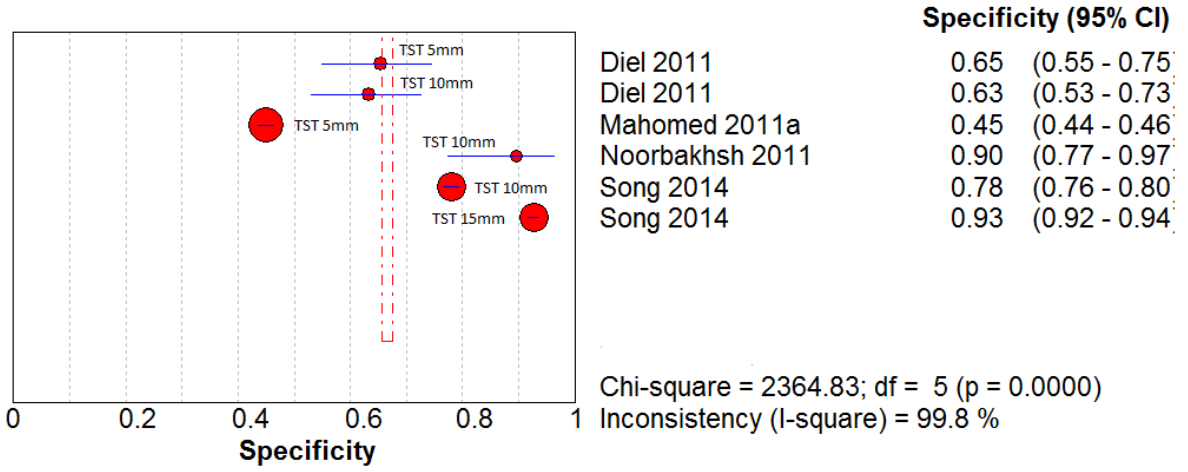


Figure 8. Forest plot of specificity based on incidence of active TB (TST) in children

4.3.3.2 Exposure levels

4.3.3.2.1 Ratios of diagnostic odds ratios (R-DORs):

This section included 17 studies: six studies from CG117[154, 155, 158, 160-162] (see Appendix 6) and 11 in more recent studies[103-111, 146, 149, 152] (see Appendix 9). The association between the screening test results and the risk of LTBI/exposure level measured using the ratio of diagnostic odds ratios (R-DOR; IGRA vs. TST) in individual studies ranged from 0.27[103] to 11.01.[111] See summary Table 7 for exposure studies in children.

Table 7. Comparison of the test performance – diagnostic accuracy indices for identifying LTBI (exposure studies)

Subgroup of interest – children and adolescents						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
Adetifa, 2010[103] Gambia [High]	**N test results** QFT-GIT: 215 T-SPOT: 215 TST: 215 **Test (+/-)** QFT-GIT (72/143) T-SPOT (71/144) TST≥ 10 mm (57/158) **N indeterminate** QFT-GIT/G: 2 T-SPOT: 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** Same house/ different room vs. different house SN: NR SP: NR PPV: NR NPV: NR Same house/same	**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, 2.60) DORa: 1.50 (0.70, 3.10) Same house/same room vs. different house DOR: 3.20 (1.20, 9.10) DORa: 4.00 (1.40, 11.40) **T-SPOT** Same house/different room vs. different house DOR: 2.00 (0.80, 5.10) DORa: 2.60 (0.90, 7.10) Same house/same	**TST ≥ 10 mm** Same house/different room vs. different house DOR: 2.40 (1.00, 5.80) DORa: 2.90 (1.30, 6.70) Same house/same room vs. different house DOR: 10.10 (3.20, 32.10) DORa: 15.00 (4.70, 47.20) **T-SPOT** Same house/different room vs. different house DOR: 2.40 (1.00, 5.80) DORa: 2.90 (1.30, 6.70) Same house/same	**QFT-GIT vs. TST ≥ 10 mm** Same house/different room R-DOR: 0.58 (0.28, 0.90) R-DORa: 0.52 (0.29, 0.91) Same house/same room R-DOR: 0.32 (0.14, 0.69) R-DORa: 0.27 (0.12, 0.59) **T-SPOT vs. TST ≥ 10 mm** Same house/different room R-DOR: 0.83 (0.43, 1.60) R-DORa: 0.90 (0.46, 1.76) Same house/same

		room vs. different house SN: NR SP: NR PPV: NR NPV: NR		room vs. different house DOR: 5.30 (1.50, 18.50) DORa: 6.60 (1.70, 25.20)	room vs. different house DOR: 10.10 (3.20, 32.10) DORa: 15.00 (4.70, 42.20)	room R-DOR: 0.52 (0.22, 1.25) R-DORa: 0.44 (0.18, 1.09)
Cruz, 2011[104] US [Low]	**N test results** T-SPOT: 163 TST: 163 **Test (+/-)** T-SPOT (94/69) TST≥ 15 mm (94/69) **N indeterminate** T-SPOT: 22 TST: 22	**T-SPOT** 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** Contact with an identifiable source case vs. no such contact DOR: NR DORa: 4.41 (1.78, 10.94)	**TST ≥ 15 mm** Contact with an identifiable source case vs. no such contact DOR: NR DORa: 0.48 (0.26, 0.91)	**T-SPOT vs. TST ≥ 15 mm** Contact with an identifiable source case R-DOR: NA R-DORa: 9.19 (5.23, 16.3)
Kasambira, 2011[105] South Africa [High]	**N test results** QFT-GIT: 251 TST: 254 **Test (+/-)** QFT-GIT (79/172) TST≥ 5 mm (71/183) **N indeterminate** QFT-GIT: 19 TST: 16	**QFT (GIT)** Exposure to index case during the majority of day (> 7 hrs) vs. minority of day (< 6 hrs) SN: 29.87 (23.2, 37.52) SP: 71.68 (62.77, 79.17) PPV: 58.97 (47.89, 69.22) NPV: 42.86 (36.01, 49.99)	**TST ≥ 5 mm** Exposure to index case during the majority of day (> 7 hrs) vs. minority of day (< 6 hrs) SN: 29.79 (22.86, 37.79) SP: 73.64 (64.71, 80.97) PPV: 59.15 (47.54, 69.83) NPV: 45.00 (37.91, 52.30)	**QFT (GIT)** Exposure to index case during the majority of day (> 7 hrs) vs. minority of day (< 6 hrs) DOR: 1.10 (0.63, 1.80) DORa: 1.30 (0.69, 2.30) Adult index case smear grade (vs. negative) <u>Scanty</u> DOR: 0.30 (0.05, 1.60) DORa: NR <u>1+</u>	**TST ≥ 5 mm** Exposure to index case during the majority of day (> 7 hrs) vs. minority of day (< 6 hrs) DOR: 1.20 (0.67, 2.10) DORa: 1.10 (0.58, 2.10) Adult index case smear grade (vs. negative) <u>Scanty</u> DOR: NR DORa: NR <u>1+</u>	**QFT-GIT vs. TST ≥ 5 mm** Exposure to index case during the majority of day (> 7 hrs) R-DOR: 0.92 (0.62, 1.36) R-DORa: 1.18 (0.75, 1.85) Adult index case smear grade (+3) R-DOR: 0.78 (0.40, 1.52) R-DORa: 0.97 (0.27, 3.47)

				DOR: 1.50 (0.70, 3.60) DORa: 5.50 (0.89, 34.70) 2+ DOR: 1.50 (0.50, 4.90) DORa: 8.70 (1.20, 62.00) 3+ DOR: 3.20 (1.40, 7.40) DORa: 11.40 (1.80, 72.00)	DOR: 2.81 (1.20, 6.70) DORa: 7.90 (1.50, 41.00) 2+ DOR: 2.90 (0.80, 10.60) DORa: 15.70 (2.60, 92.0) 3+ DOR: 4.10 (1.50, 11.10) DORa: 11.70 (2.20, 62.00)	
Laniado-Laborın, 2014[146] Mexico [intermediate]	**N test results** QFT-GIT: 172 TST: 172 **Test (+/-)** QFT-GIT (71/101) TST≥ 5 mm (136/36) **N indeterminate** QFT-GIT: 1 TST: 1	**QFT (GIT)** Exposure to source Hours/day exposure # of cohabitants # of rooms SN: NR SP: NR PPV: NR NPV: NR	**TST ≥ 5 mm** Exposure to source Hours/day exposure # of cohabitants # of rooms SN: NR SP: NR PPV: NR NPV: NR	**QFT (GIT)** Exposure to source: DORa: 0.91 (95% CI 0.57, 1.45) Hours/day exposure: DORa: 1.03 (95% CI 0.96, 1.10) # of cohabitants: DORa: 0.91 (95% CI 0.79, 1.05) # of rooms: DORa: 1.12 (95% CI 0.77, 1.61)	**TST ≥ 5 mm** 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)	**QFT-GIT vs. TST ≥ 5 mm** R-DORa: NA
Mahomed, 2011b[106] South Africa [High]	**N test results** QFT-GIT: 5244 TST: 5244 **Test (+/-)** QFT-GIT (2669/2562)	**QFT (GIT)** Current or prior TB household contact vs. no such contact SN: 66.67 (64.09, 69.15) SP: 54.32 (52.75,	**TST ≥ 5 mm** Current or prior TB household contact vs. no such contact SN: 71.32 (68.83, 73.69) SP: 50.31 (48.74,	**QFT (GIT)** Current or prior TB household contact vs. no such contact DOR: 2.40 (2.11, 2.74) DORa: 1.90 (1.70,	**TST ≥ 5 mm** Current or prior TB household contact vs. no such contact DOR: 2.52 (2.20, 2.88) DORa: 2.00 (1.70,	**QFT-GIT vs. TST ≥ 5 mm** Current or prior TB household contact R-DOR: 0.94 (0.86, 1.04) R-DORa: 0.95

	TST≥ 5 mm (2894/2350) **N indeterminate** QFT-GIT: 13 TST: 0	55.88) PPV: 33.27 (31.51, 35.08) NPV: 82.67 (81.16, 84.09)	51.87) PPV: 32.83 (31.14, 34.56) NPV: 83.74 (82.2, 85.18)	2.20)	2.30)	(0.86, 1.05)
Pavic, 2011[107] Croatia [Low]	**N test results** QFT-GIT: 141 TST: 142 **Test (+/-)** QFT-GIT (18/123) TST≥ 10 mm (24/118) **N indeterminate** QFT-GIT: 1 TST: 0	**QFT (GIT)** Close contact (household contact with aggregate exposure to a patient with active TB ≥40 hrs in closed rooms) vs. distant contact (occasional or unclear exposure time or <40 hrs during the presumed period of infectiousness) SN: 19.54 (12.57, 29.08) SP: 98.15 (90.23, 99.67) PPV: 94.44 (74.24, 99.01) NPV: 43.09 (34.68, 51.92)	**TST ≥ 10 mm** Close contact (household contact with aggregate exposure to a patient with active TB ≥40 hrs in closed rooms) vs. distant contact (occasional or unclear exposure time or <40 hrs during the presumed period of infectiousness) SN: 26.44 (18.31, 36.56) SP: 98.18 (90.39, 99.68) PPV: 95.83 (79.76, 99.26) NPV: 45.76 (37.05, 54.74)	**QFT (GIT)** Close contact (household contact with aggregate exposure to a patient with active TB ≥40 hrs in closed rooms) vs. distant contact (occasional or unclear exposure time or <40 hrs during the presumed period of infectiousness) DOR: 12.87 (1.66, 99.80) DORa: NR	**TST ≥ 10 mm** Close contact (household contact with aggregate exposure to a patient with active TB ≥40 hrs in closed rooms) vs. distant contact (occasional or unclear exposure time or <40 hrs during the presumed period of infectiousness) DOR: 19.41 (2.53, 148.40) DORa: NR	**QFT-GIT vs. TST ≥ 10 mm** Close contact (household contact with aggregate exposure to a patient with active TB ≥40 hrs in closed rooms) R-DOR: 0.66 (0.15, 2.89) R-DORa: NA
Perez-Porcuna, 2014[149] Brazil [intermediate]	**N test results** QFT-GIT: 116 TST: 135 **Test (+/-)** QFT-GIT (36/80) TST≥ 10mm (47/88) **N indeterminate** QFT-GIT: 19	**QFT (GIT)** Time of exposure to the index case (# months) SN: NA SP: NA PPV: NA NPV: NA	**TST ≥ 10 mm** Time of exposure to the index case (# months) SN: NA SP: NA PPV: NA NPV: NA	**QFT (GIT)** Time of exposure to the index case (# months) DOR: NR (p=0.024) DORa: NR (p=0.537) Mycobacterium	**TST ≥ 10 mm** Time of exposure to the index case (# months) DOR: NR (p<0.001) DORa: 1.15 (95% CI: 1.04, 1.27; p=0.009) Mycobacterium	**QFT-GIT vs. TST ≥ 10 mm** Time of exposure to the index case (# months) R-DOR: NA R-DORa: NA

	TST: 0	Mycobacterium tuberculosis contact (MTC) score: 0-15 SN: NA SP: NA PPV: NA NPV: NA	Mycobacterium tuberculosis contact (MTC) score: 0-15 SN: NA SP: NA PPV: NA NPV: NA	tuberculosis contact (MTC) score: 0-15 DOR: NR (p=0.021) DORa: 1.16 (95% CI: 1.01, 1.33; p=0.035)	tuberculosis contact (MTC) score: 0-15 DOR: NR (p<0.001) DORa: 1.29 (95% CI: 1.08, 1.54; p=0.005)	Mycobacterium tuberculosis contact (MTC) score: 0-15 R-DOR: NA R-DORa: 0.90 (95% CI: 0.80, 1.01)
Rutherford, 2012a-b[108, 109] Indonesia [High]	**N test results** QFT-GIT: 290 TST: 302 **Test (+/-)** QFT-GIT (152/138) TST≥ 10mm (145/157) **N indeterminate** QFT-GIT: 14 TST: 2	**QFT (GIT)** Characteristics of TB case smear positivity (3+ vs. Scanty/1+) SN: 62.5 (53.58, 70.65) SP: 59.6 (49.75, 68.73) PPV: 65.22 (56.15, 73.3) NPV: 56.73 (47.14, 65.85) Relationship to child (Parent vs. Other) SN: 61.19 (54.59, 67.4) SP: 77.27 (63.01, 87.16) PPV: 93.06 (87.69, 96.18) NPV: 28.57 (21.22, 37.26)	**TST ≥ 10 mm** Characteristics of TB case smear positivity (3+ vs. Scanty/1+) SN: 61.9 (53.19, 69.91) SP: 68.27 (58.81, 76.43) PPV: 70.27 (61.21, 77.98) NPV: 59.66 (50.68, 68.04) Relationship to child (Parent vs. Other) SN: 55.9 (49.42, 62.18) SP: 82.22 (68.67, 90.71) PPV: 94.12 (88.82, 96.99) NPV: 26.81 (20.12, 34.76)	**QFT (GIT)** Characteristics of TB case smear positivity (2+ vs. Scanty/1+) DOR: 1.56 (0.78, 3.11) DORa: NR Characteristics of TB case smear positivity (3+ vs. Scanty/1+) DOR: 2.43 (1.21, 4.86) DORa: 2.28 (1.06, 4.90) Relationship to child (Aunt/Uncle vs. Other) R-DOR: 1.51 (0.44, 5.17) R-DORa: NR Relationship to child (Parent vs. Other) R-DOR: 5.61 (2.40, 13.12) R-DORa: 4.30	**TST ≥ 10 mm** Characteristics of TB case smear positivity (2+ vs. Scanty/1+) DOR: 1.80 (0.89, 3.63) DORa: NR Characteristics of TB case smear positivity (3+ vs. Scanty/1+) DOR: 3.35 (1.81, 6.21) DORa: 2.93 (1.59, 5.39) Relationship to child (Aunt/Uncle vs. Other) R-DOR: 2.31 (0.77, 6.79) R-DORa: NR Relationship to child (Parent vs. Other) R-DOR: 5.85 (2.56, 13.38) R-DORa: 7.04	**QFT-GIT vs. TST ≥ 10 mm** Characteristics of TB case smear positivity (3+) R-DOR: 0.73 (0.45, 1.17) R-DORa: 0.78 (0.47, 1.28) Relationship to child (Parent vs. Other) R-DOR: 0.96 (0.52, 1.61) R-DORa: 0.78 (0.47, 1.28)

				(1.48, 12.45)	(2.23, 22.28)	
		Sleeping proximity to child (same bed vs. different room) SN: 59.24 (51.42, 66.61) SP: 59.05 (49.48, 67.97) PPV: 68.38 (60.15, 75.6) NPV: 49.21 (40.63, 57.83)	Sleeping proximity to child (same bed vs. different room) SN: 51.52 (43.94, 59.02) SP: 56.88 (47.51, 65.79) PPV: 64.39 (55.92, 72.05) NPV: 43.66 (35.78, 51.88)	Sleeping proximity to child (same room vs. different room) R-DOR: 1.87 (0.70, 5.02) R-DORa: NR Sleeping proximity to child (same bed vs. different room) R-DOR: 2.01 (1.12, 3.61) R-DORa: 1.45 (0.70, 2.99)	Sleeping proximity to child (same room vs. different room) R-DOR: 1.21 (0.41, 3.53) R-DORa: NR Sleeping proximity to child (same bed vs. different room) R-DOR: 1.35 (0.79, 2.32) R-DORa: NR	Sleeping proximity to child (same bed) R-DOR: 1.47 (1.05, 2.16) R-DORa: NA
		Time spent with child (# hrs/day; >8 vs. <2) SN: 52.00 (44.06, 59.85) SP: 42.55 (29.51, 56.72) PPV: 74.29 (65.17, 81.68) NPV: 21.74 (14.54, 31.21)	Time spent with child (# hrs/day; >8 vs. <2) SN: 47.47 (39.83, 55.22) SP: 41.67 (28.85, 55.72) PPV: 72.82 (63.52, 80.47) NPV: 19.42 (12.94, 28.1)	Time spent with child (# hrs/day; 2-8 vs. <2) R-DOR: 0.78 (0.33, 1.80) R-DORa: NR Time spent with child (# hrs/day; >8 vs. <2) R-DOR: 0.83 (0.38, 1.79) R-DORa: NR	Time spent with child (# hrs/day; 2-8 vs. <2) R-DOR: 0.55 (0.24, 1.24) R-DORa: Time spent with child (# hrs/day; >8 vs. <2) R-DOR: 0.64 (0.31, 1.36) R-DORa: NR	Time spent with child (# >8 hrs/day) R-DOR: 1.30 (0.75, 2.24) R-DORa: NA
Talbot, 2012[110] US [Low]	**N test results** T-SPOT: 143 TST: 143 **Test (+/-)** T-SPOT (5/138) TST≥ 15 mm (6/137) **N indeterminate** T-SPOT: 15	**T-SPOT** Non-low-TB exposure risk vs. low-TB exposure risk group SN: NR SP: 100 (97.00, 100) PPV: NR NPV: NR	**TST ≥ 15 mm** Non-low-TB exposure risk vs. low-TB exposure risk group SN: NR SP: 98.39 (94.31, 99.56) PPV: NR	**T-SPOT** Non-low-TB exposure risk vs. low-TB exposure risk group DOR: NR DORa: NR	**TST ≥ 15 mm** Non-low-TB exposure risk vs. low-TB exposure risk group DOR: NR DORa: NR	**T-SPOT vs. TST ≥ 15 mm** Non-low-TB exposure risk vs. low-TB exposure risk group R-DOR: NA R-DORa: NA

	TST: 22		NPV: NR			
Tieu, 2014[152] Thailand [high]	**N test results** QFT-GIT: 136 TSPOT: 136 TST: 136 **Test (+/-)** QFT-GIT (40/96) TSPOT (36/100) TST≥10 mm (88/48) TST≥15 mm (48/88) **N indeterminate** QFT-GIT: 0 TSPOT: 0 TST: 0	**QFT (GIT)** **TSPOT** TB contact score SN: NA SP: NA PPV: NA NPV: NA	**TST ≥ 10 mm** **TST ≥ 15 mm** TB contact score SN: NA SP: NA PPV: NA NPV: NA	**QFT (GIT)** TB contact score (≥13 vs. 8-12) DOR: 4.04 (95% CI: 1.81, 8.99) DORa: 1.98 (95% CI: 0.64, 6.11) **TSPOT** TB contact score (≥13 vs. 8-12) DOR: 3.50 (95% CI: 1.57, 7.81) DORa: 3.15 (95% CI: 1.35, 7.34)	**TST ≥ 10 mm** TB contact score (≥13 vs. 8-12) DOR: 2.59 (95% CI: 1.28, 5.23) DORa: 2.21 (95% CI: 0.99, 4.98) **TST ≥ 15 mm** TB contact score (≥13 vs. 8-12) DOR: 2.19 (95% CI: 1.09, 4.43) DORa: 0.83 (95% CI: 0.35, 1.99)	**QFT-GIT vs. TST≥10mm** TB contact score (≥13 vs. 8-12) R-DOR: 1.56 (95% CI: 0.91, 2.69) R-DORa: 0.90 (95% CI: 0.44, 1.82) **QFT-GIT vs. TST≥15mm** TB contact score (≥13 vs. 8-12) R-DOR: 1.84 (95% CI: 1.07, 3.18) R-DORa: 2.39 (95% CI: 1.15, 4.93) **TSPOT vs. TST≥10mm** TB contact score (≥13 vs. 8-12) R-DOR: 1.35 (95% CI: 0.78, 2.33) R-DORa: 1.43 (95% CI: 0.78, 2.59) **TSPOT vs. TST≥15mm** TB contact score (≥13 vs. 8-12)

						R-DOR: 1.60 (95% CI: 0.93, 2.75) R-DORa: 3.80 (95% CI: 2.04, 7.05)
Tsolia, 2010[111] Greece [Low]	**N test results** QFT-GIT: 95 TST: 99 **Test (+/-)** QFT-GIT (32/63) TST≥ 5 mm (55/44) **N indeterminate** QFT-GIT: 4 TST: 0	**QFT (GIT)** Contact with an adult TB (non-household regular vs. non-household occasional) SN: 33.33 (18.64, 52.18) SP: 90.91 (62.26, 98.38) PPV: 90.00 (59.58, 98.21) NPV: 35.71 (20.71, 54.17) Contact with an adult TB (household vs. non-household occasional) SN: 38.6 (27.06, 51.57) SP: 90.91 (62.26, 98.38) PPV: 95.65 (79.01, 99.23) NPV: 22.22 (12.54, 36.27)	**TST ≥ 5 mm** Contact with an adult TB (non-household regular vs. non-household occasional) SN: 64.29 (45.83, 79.29) SP: 36.36 (15.17, 64.62) PPV: 72.00 (52.42, 85.72) NPV: 28.57 (11.72, 54.65) Contact with an adult TB (household vs. non-household occasional) SN: 50.00 (37.73, 62.27) SP: 36.36 (15.17, 64.62) PPV: 81.08 (65.79, 90.52) NPV: 11.76 (4.67, 26.62)	**QFT (GIT)** Contact with an adult TB (non-household regular vs. non-household occasional) DOR: 5.00 (0.55, 45.39) DORa: NR Contact with an adult TB (household vs. non-household occasional) DOR: 6.28 (0.75, 52.56) DORa: NR	**TST ≥ 5 mm** Contact with an adult TB (non-household regular vs. non-household occasional) DOR: 1.03 (0.24, 4.39) DORa: NR Contact with an adult TB (household vs. non-household occasional) DOR: 0.57 (0.15, 2.15) DORa: NR	**QFT-GIT vs. TST ≥ 5 mm** Contact with an adult TB (non-household regular) R-DOR: 4.85 (95% CI: 1.26, 18.69) R-DORa: NA Contact with an adult TB (household regular) R-DOR: 11.02 (3.07, 39.60) R-DORa: NA

Abbreviations: 95% CI = 95 percent confidence interval; DOR = diagnostic odds ratio; DORa = adjusted diagnostic odds ratio; GIT = Gold In-Tube; N = number; NPV = negative predictive value; PPV = positive predictive value; QFT = QuantiFERON-TB; R-DOR = ratio of diagnostic odds ratio; R-DORa = adjusted ratio of diagnostic odds ratio; SN = sensitivity; SP = specificity; TB = tuberculosis; TST = tuberculin skin test

The updated meta-analysis included 14 studies: six studies from CG117[154, 155, 158, 160-162] (see Appendix 6) and eight more recent studies published in 2009 and onwards[103-109, 111, 152] (see Appendix 9). One study[110] did not provide sufficient information to calculate the R-DOR, therefore this study could not be included in the meta-analysis. In a random effects meta-analysis of 14 studies,[103-109, 111, 152, 154, 155, 158, 160-162] of which two studies used T-SPOT.TB[104, 158] and the remaining 12 studies used QFT-GIT (or G), the pooled R-DOR showed a significantly stronger association for IGRAs compared to TST in relation to a risk of LTBI/exposure level (pooled R-DOR = 1.98, 95% CI: 1.19, 3.28; I^2 = 89%) (Figure 9).

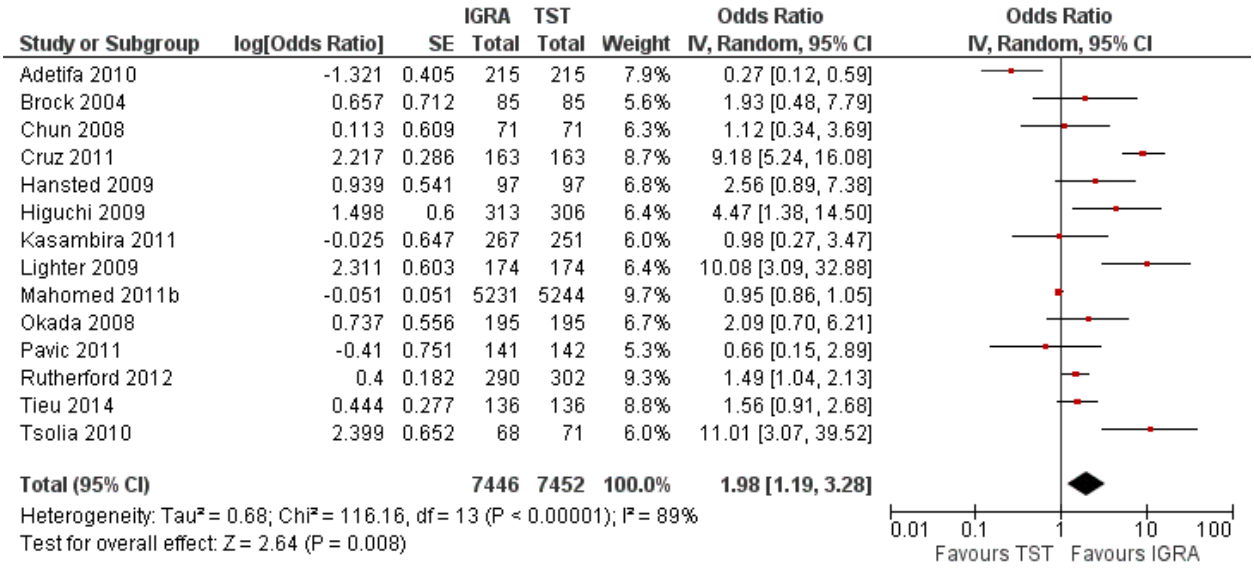


Figure 9. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST based on high risk and low risk exposure in children

Heterogeneity was high (I^2 = 89%) and the sources of heterogeneity were explored through subgroup analyses in regards to burden of TB incidence, IGRA type, TST threshold, and study setting. The simultaneous meta-analytic stratification by IGRA type (QFT-GIT/G and TSPOT) and TST threshold (5mm, 10-15mm) (Figure 10, Figure 11, Figure 12) as well as study setting (community-based contact and hospital-based studies) did not help to explain the presence of heterogeneity (i.e., heterogeneity persisted in these analyses**)** (see Figure 13**,** Figure 14).

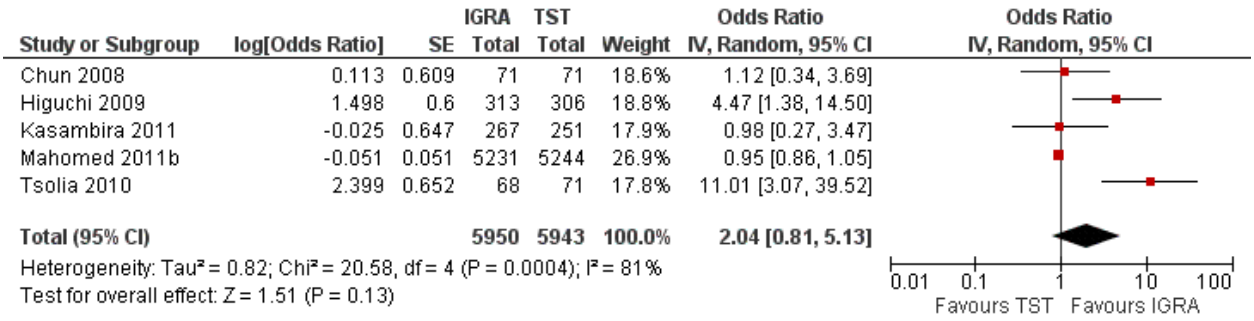


Figure 10. Pooled ratio of diagnostic odds ratio (R-DOR) of QFT vs. TST 5mm based on high risk and low risk exposure in children

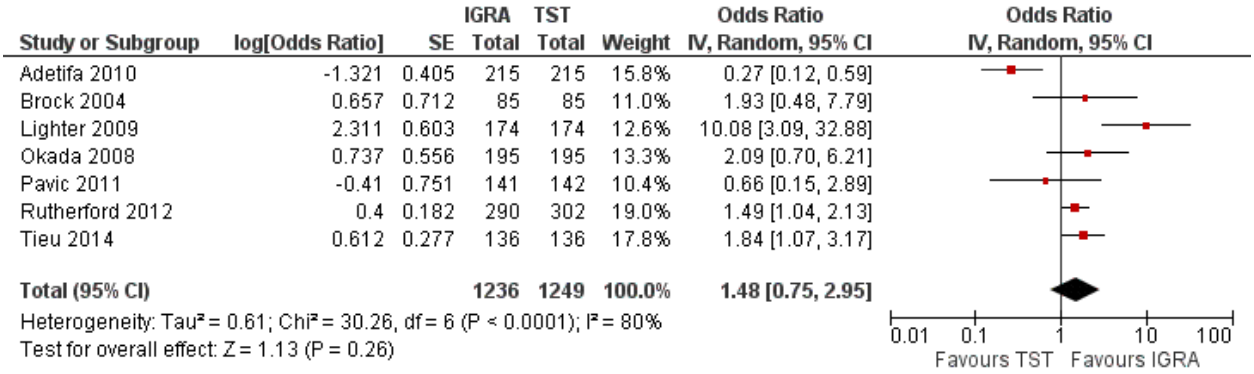


Figure 11. Pooled ratio of diagnostic odds ratio (R-DOR) of QFT vs. TST 10-15mm based on high risk and low risk exposure in children

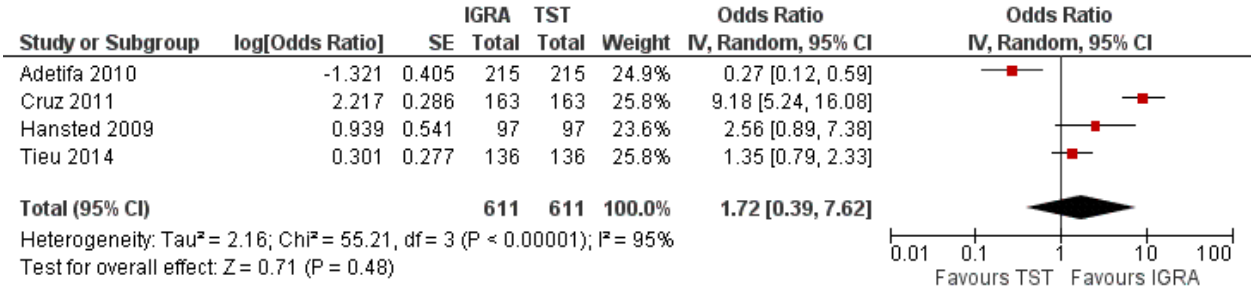


Figure 12. Pooled ratio of diagnostic odds ratio (R-DOR) of TSPOT vs. TST 10-15mm based on high risk and low risk exposure in children

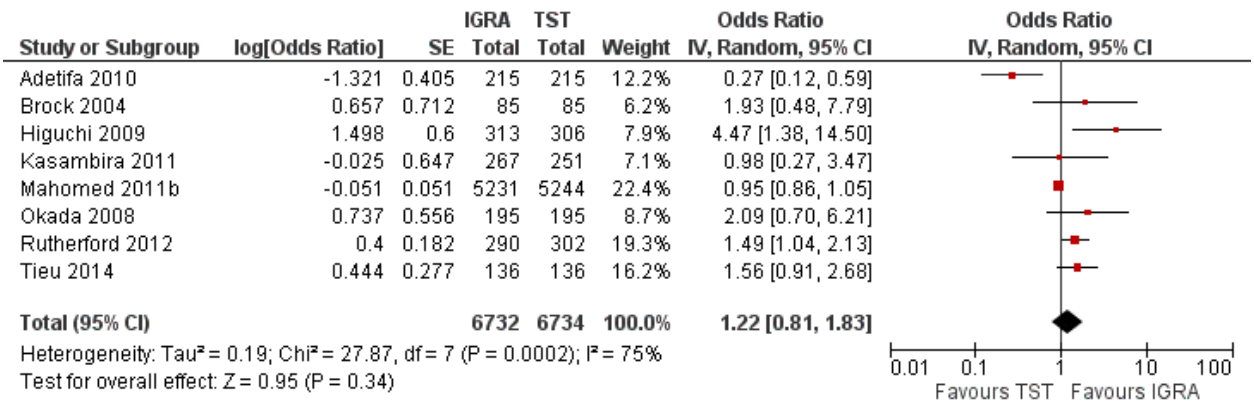


Figure 13. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST based on high risk and low risk exposure (Community based contact studies only) in children

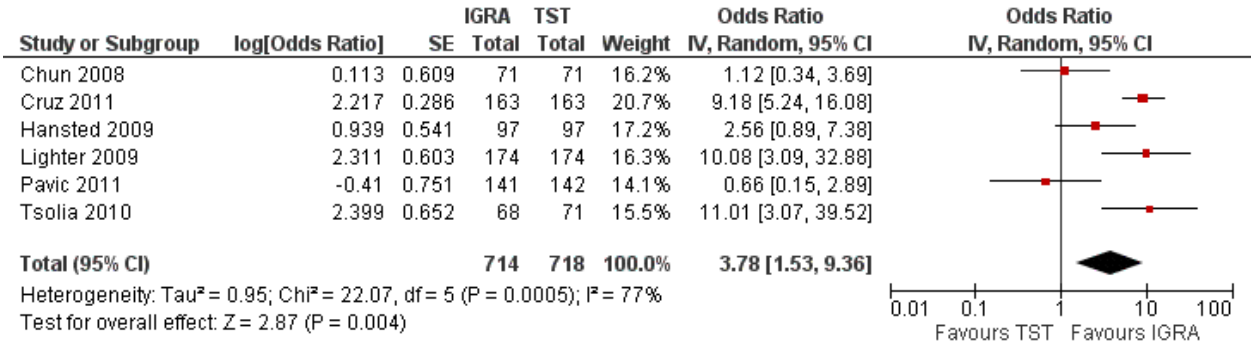


Figure 14. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST based on high risk and low risk exposure (Hospital based studies only) in children

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 TST in identifying LTBI across studies conducted in countries of high TB burden (pooled R-DOR = 1.13, 95% CI: 0.78, 1.65; I^2 = 71**)** (see Figure 15 and Figure 16**)**.

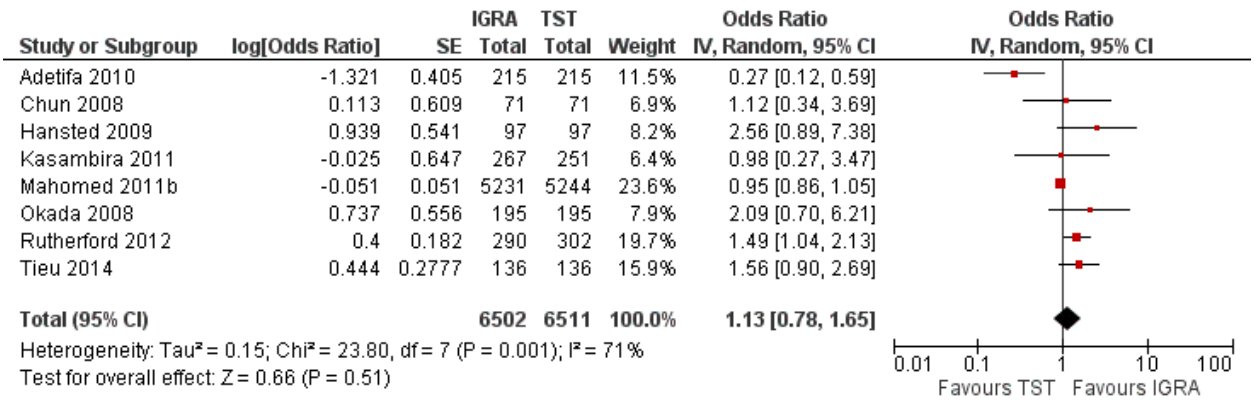


Figure 15. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST based on high risk and low risk exposure (studies conducted in high burden countries) in children

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

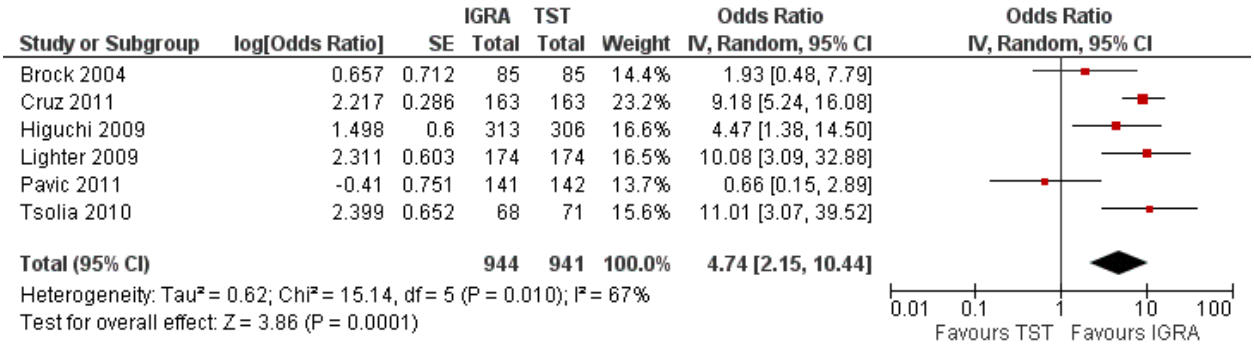


Figure 16. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST based on high risk and low risk exposure (studies conducted in low burden countries) in children

In five studies, trends for exposure gradient (across more than two ordinal exposure groups) for IGRA and TST were explored with respect to sleeping proximity (same house/same room, same house/different room, different house),[103, 108, 109] adult index case type of TB diagnosis,[105] adult index case smear grade (negative, scanty, 1+, 2+, 3+),[105, 108, 109] duration of exposure to index case (time spent with child),[105, 108, 109, 152] relationship to index case (parent, aunt/uncle, other),[108, 109, 152] TB contact score (score-based categories),[152] and type of contact (household, non-household regular, occasional).[111] In general, for both tests IGRA and TST, there was an increasing trend in DORs across the exposure groups. In two studies, this trend was absent for both tests in relation to duration of exposure to index case[108, 109] and for TST in relation to type of contact.[111] See Appendix 9 for full extraction sheets.

4.3.3.2.2 Sensitivity and specificity:

Sensitivity and specificity:

In this analysis, six[103, 104, 110, 146, 149, 152] of the included 11 recent studies[103-111, 146, 149, 152] failed to provide sufficient information for calculating both sensitivity and specificity.[103, 104, 110, 146, 149, 152] There was a wide variability in sensitivity and specificity of IGRA (QFT-GIT/G) and TST (5mm or 10mm) with overlapping values across the five remaining studies[105-109, 111] (see Figure 17, Figure 18, Figure 19, Figure 20, Figure 21, Figure 22, Figure 23, Figure 24).

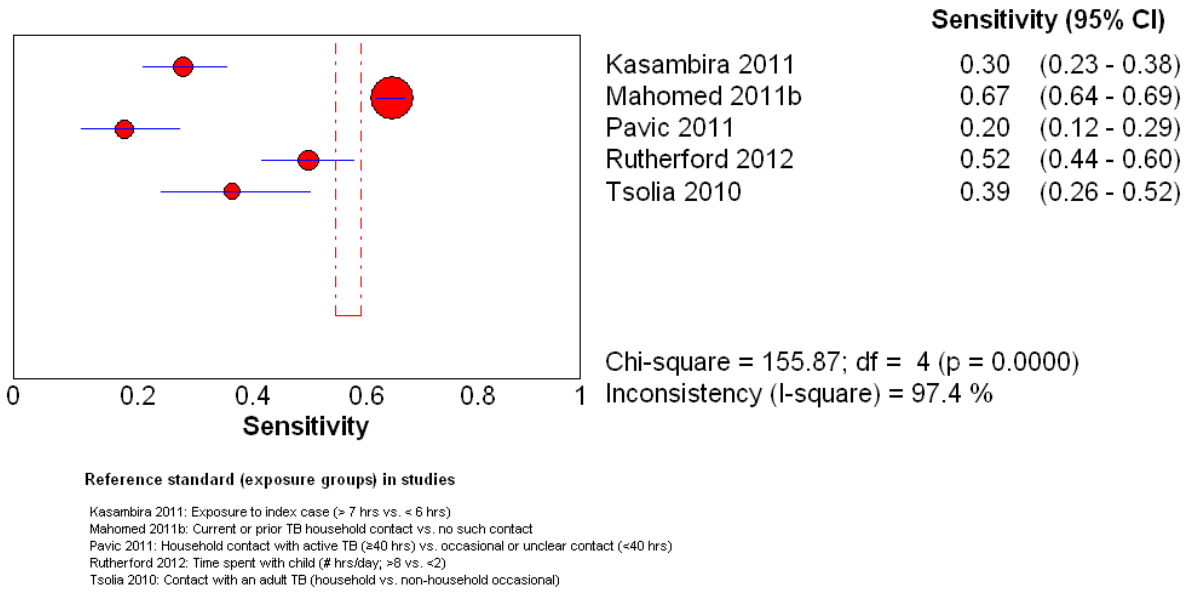


Figure 17. Forest plot of sensitivity based on exposure groups (QFT-GIT) in children

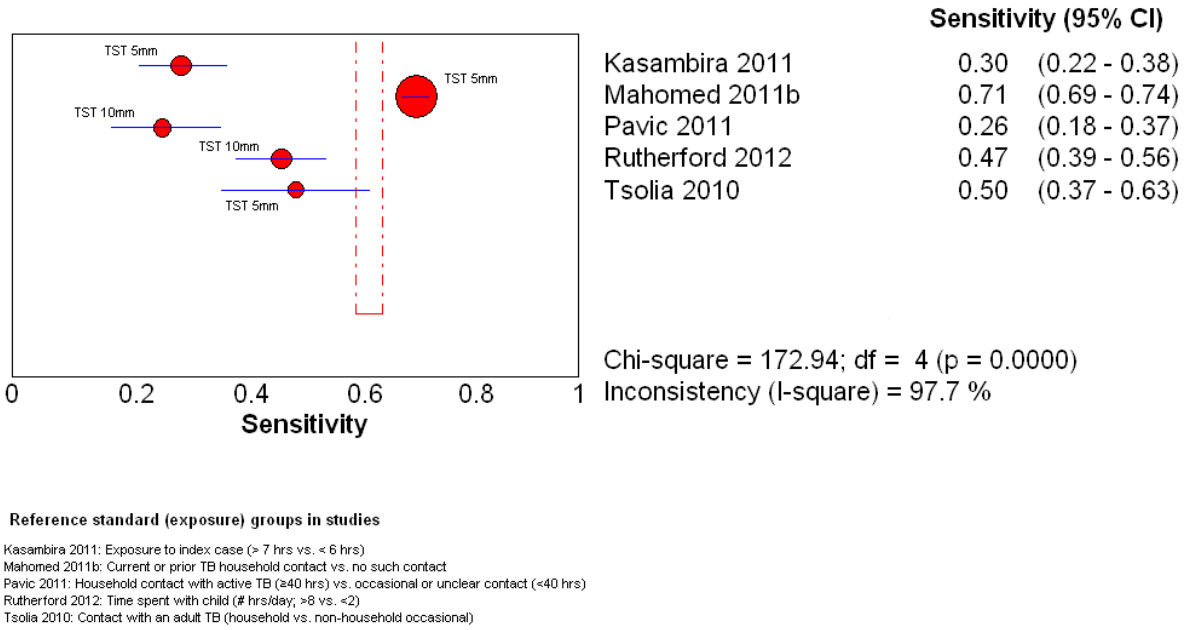


Figure 18. Forest plot of sensitivity based on exposure groups (TST) in children

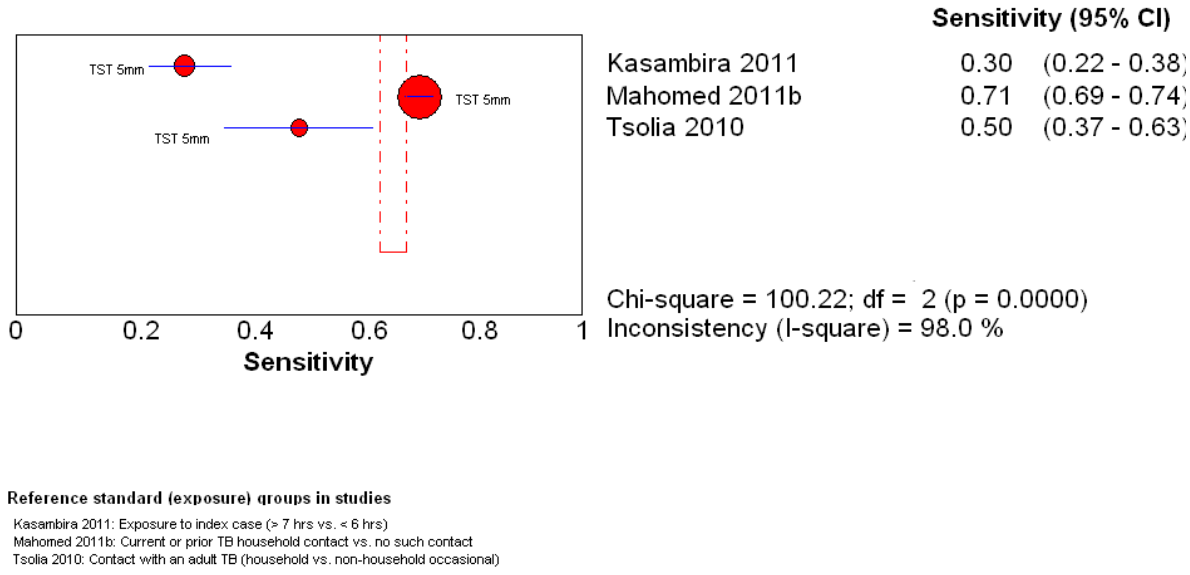


Figure 19. Forest plot of sensitivity based on exposure groups (TST 5mm) in children

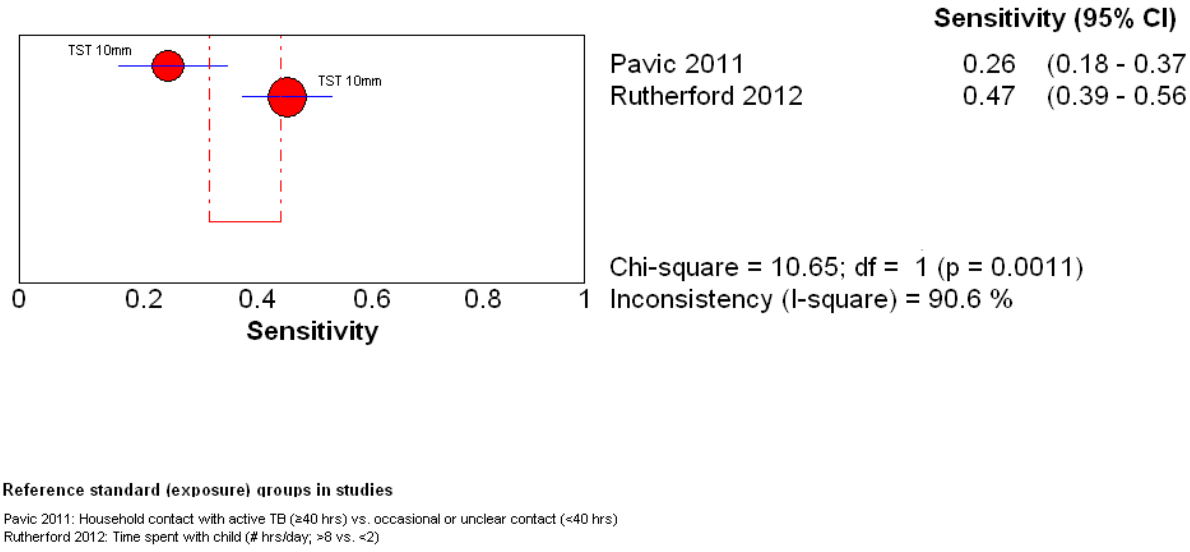


Figure 20. Forest plot of sensitivity based on exposure groups (TST 10mm) in children

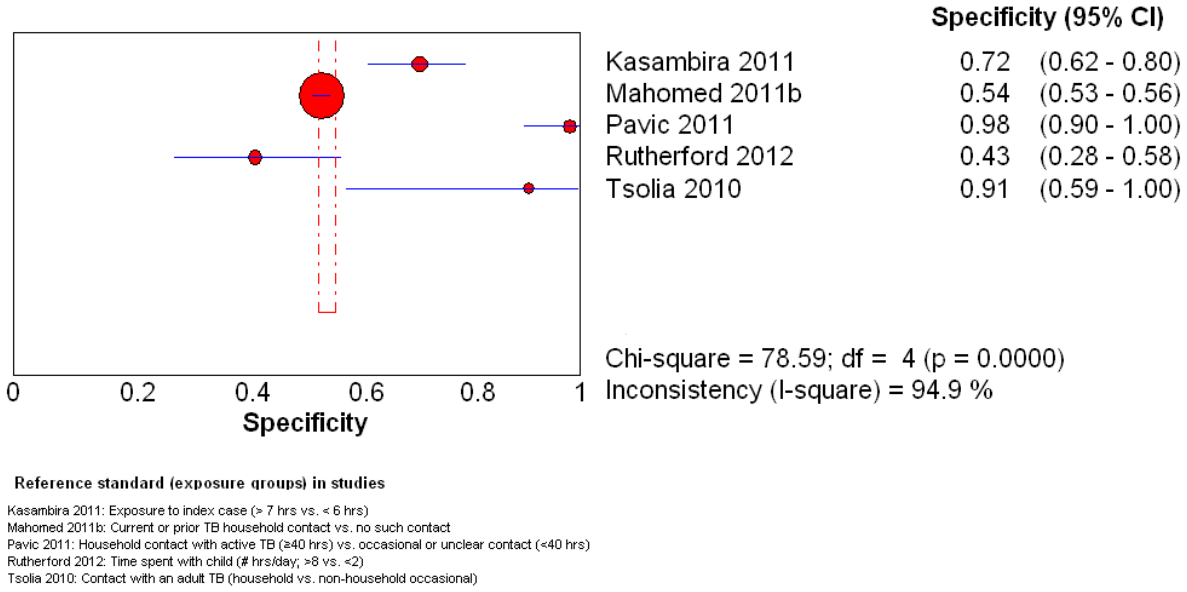


Figure 21. Forest plot of specificity based on exposure groups (QFT-GIT) in children

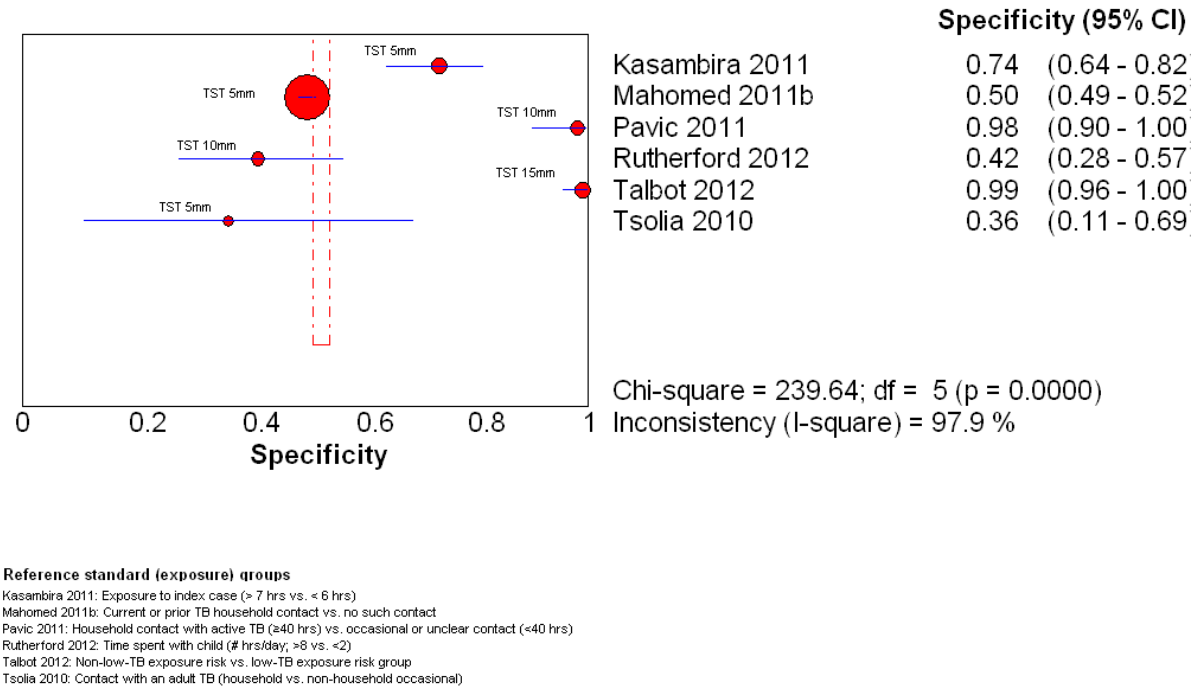


Figure 22. Forest plot of specificity based on exposure groups (TST) in children

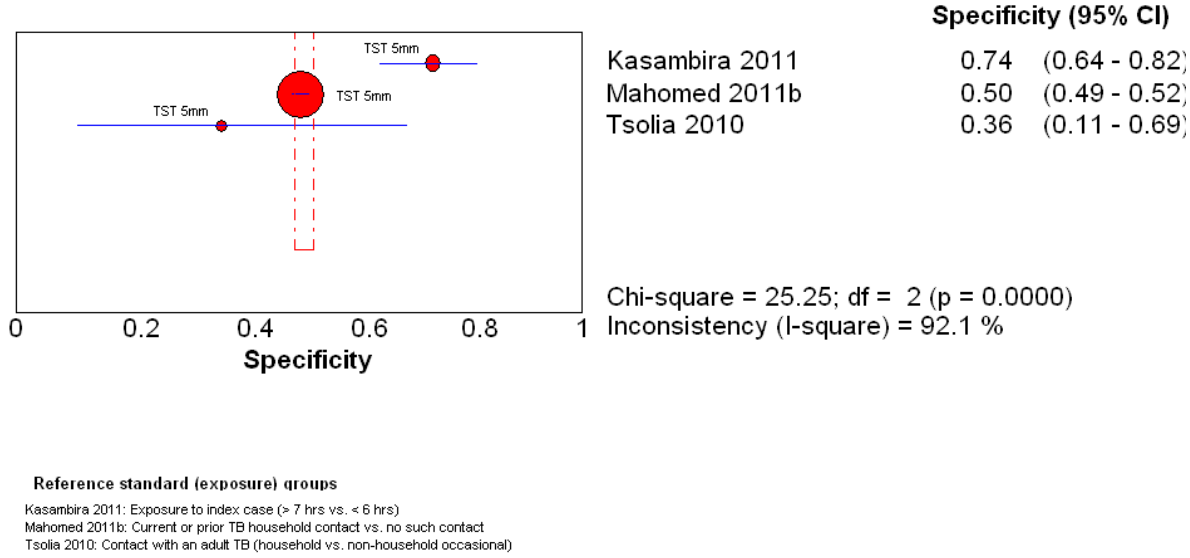


Figure 23. Forest plot of specificity based on exposure groups (TST 5mm) in children

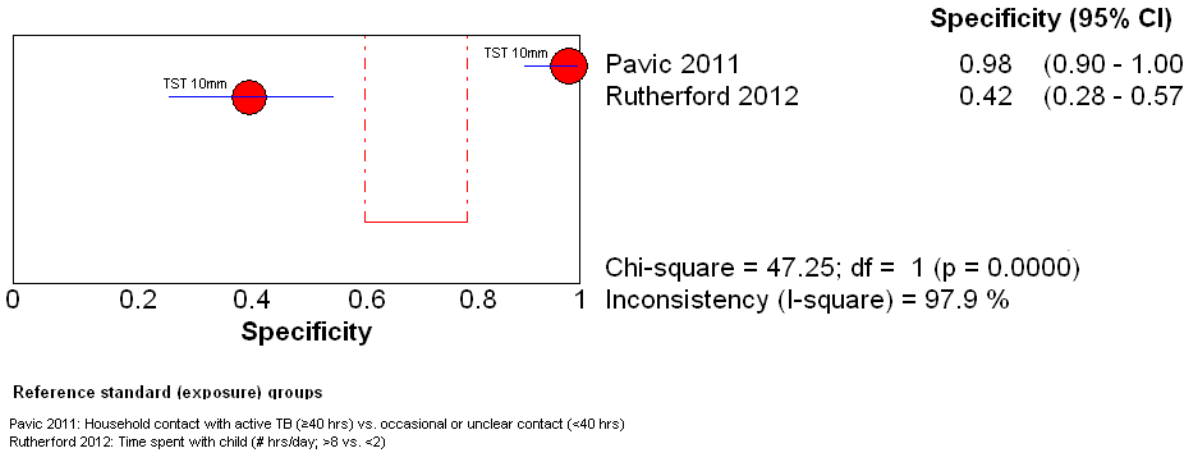


Figure 24. Forest plot of specificity based on exposure groups (TST 10mm) in children

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

4.3.3.2.3 Influence of BCG vaccination status on test positivity:

In this analysis, four[107, 110, 146, 152] of the included 11 recent studies[103-111, 146, 149, 152] did not report any information needed to determine whether or not the BCG vaccination status influenced the odds of test positivity differentially for IGRAs and TST.[107, 110] Of the seven remaining studies reporting this evidence,[103-106, 108, 109, 111, 149] only three demonstrated significantly increased ORs for TST positivity in relation to BCG vaccination status (range of ORs: 1.16-20.34).[104, 106, 111] The odds of test positivity for IGRAs across the seven studies[103-106, 108, 109, 111, 149] were not significantly different between the BCG vaccinated vs. non-vaccinated groups (see summary Table 8). One study with a relatively large sample size and narrow confidence intervals 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, 1.33) but not for IGRA (OR = 0.99, 95% CI: 0.86, 1.12).[106]

Table 8. Association between test positivity and BCG vaccination (exposure studies) subgroup of interest – children and adolescents

Study ID (Author name, year, and 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[103] Gambia [Low]	199	QFT-GIT	1.10 (95% CI: 0.60, 2.00)	NR
	199	T-SPOT	1.10 (95% CI: 0.61, 2.09)	NR
	199	TST-10mm	0.89 (95% CI: 0.50, 1.70)	NR
Cruz, 2011[104] US [Low]	NR	T-SPOT	0.69 (95% CI: 0.37, 1.31)	NR
	NR	TST-15mm	4.32 (95% CI: 1.02, 18.35)	NR
Kasambira, 2011[105] South Africa [High]	262	QFT-GIT	0.62 (95% CI: 0.08, 4.76)	0.83 (95% CI: 0.08, 8.33) adjusted
	247	5mm	0.38 (95% CI: 0.05, 2.85)	0.52 (95% CI: 0.06, 4.00) adjusted
Laniado-Laborın, 2014[146] Mexico [Intermediate]	172	QFT-GIT	NR	NR
	172	TST-5mm	NR	NR
Mahomed, 2011b[106] South Africa [High]	3554	QFT-GIT	0.99 (95% CI: 0.86, 1.12)	NR
	3554	TST-5mm	1.16 (95% CI 1.00, 1.33)	NR
Pavic, 2011[107] Croatia [Low]	NR	QFT-GIT	NR	NR
	NR	TST-10mm	NR	NR
Perez-Porcuna, 2014[149] Brazil [Intermediate]	116	QFT-GIT	3.89 (95% CI: 0.46, 32.33)	NR
	135	TST-10mm	1.85 (95% CI: 0.36, 9.36)	NR
Rutherford, 2012a-b[108, 109] Indonesia [High]	260	QFT-GIT	0.51 (95% CI: 0.26, 1.00)	0.60 (95% CI: 0.26, 1.38) adjusted
	272	TST-10mm	0.68 (95% CI: 0.35, 1.35)	NR
Talbot, 2012[110] US [Low]	NR	T-SPOT	NR	NR
	NR	TST-15mm	NR	NR
Tieu, 2014[152] Thailand [High]	136	QFT-GIT	NR	NR
	136	TST-10mm	NR	NR
	136	T-SPOT	NR	NR
	136	TST-15mm	NR	NR
Tsolia, 2010[111] Greece [Low]	NR	QFT-GIT	0.19 (95% CI: 0.06, 0.60)	NR
	NR	TST-5mm	20.34 (95% CI: 5.60, 73.89)	NR

Abbreviations: 95% CI = 95 percent confidence interval; GIT = Gold In-Tube; N = number; NR = not reported; QFT = QuantiFERON-TB; TB = tuberculosis; TST = tuberculin skin test

4.3.3.3 Between-test concordance, discordance, and agreement

This section included five studies reviewed in CG117[154-157, 162] (see Appendix 6) and 16 more recent studies[100-111, 146, 148-150, 152] (see Appendix 9). The agreement kappa statistic was not available for four studies.[100, 102, 104, 148] There was a wide variation in kappa statistic across 21 studies, ranging from 0.13[111] to 0.91[111] (see summary Table 9). In post-2009 studies,[101, 103, 105-111] the ranges of kappa statistic according to specific TST threshold and IGRA type were as follows: QFT-GIT vs. TST 5mm (range: 0.27-0.91), QFT-GIT vs. TST 10mm (range: 0.13-0.64), and TSPOT vs. TST 10mm (range: 0.53-0.71). According to one study, both between-test percent concordance and kappa statistic were lower amongst participants with BCG vaccination history (concordance: 46.5%, kappa: 0.16) compared to those without such history (concordance: 96.20%, kappa: 0.91).[111]

Table 9. Between-test concordance and discordance (exposure studies and incidence)

Subgroup of interest – children and adolescents					
Study ID (Author name, year, and country) [burden]	**Sample size (N) total or by subgroup**	**Type of IGRA vs. TST induration threshold**	**Concordance (%) 95% CI**	**Discordance (%) 95% CI**	**Agreement kappa 95% CI**
Adetifa, 2010[103] Gambia [Low]	217	QFT-GIT vs. 10mm	80.00 (74.15, 84.80)	20.00 (15.2, 25.85)	0.52 (0.39, 0.65)
	215	T-SPOT vs. 10mm	80.47 (74.65, 85.21)	19.53 (14.79, 25.35)	0.53 (0.40, 0.66)
Cruz, 2011[104] US [Low]	NR	T-SPOT vs. 15mm	NR	NR	NR
Kasambira, 2011[105] South Africa [High]	254	QFT-GIT vs. 5mm	86.86 (81.96, 90.59)	13.14 (9.41, 18.04)	0.68 (0.56, 0.81)
	254	QFT-GIT vs. 10mm	85.59 (80.54, 89.5)	14.41 (10.5, 19.46)	0.64 (0.51, 0.76)
Laniado-Laborın, 2014[146] Mexico [Intermediate]	172	QFT-GIT vs. 5mm	59.88 (52.42, 66.92)	40.12 (33.08, 47.58)	0.27 (0.17, 0.38)
Mahomed, 2011b[106] South Africa [High]	NR	QFT-GIT vs. 5mm	84.8 (NR)	NR	0.70 (0.68, 0.71)
	NR	QFT-GIT vs. 10mm	81.4 (NR)	NR	0.63 (0.61, 0.65)
	NR	QFT-GIT vs. 15mm	64.3 (NR)	NR	0.30 (0.27, 0.32)
Metin Timur, 2014[148] Turkey [Intermediate]	81	QFT-GIT vs. 15mm	NR	NR	NR
Pavic, 2011[107] Croatia [Low]	141	QFT-GIT vs. 10mm	89.36 (83.19, 93.45)	10.64 (6.554, 16.81)	0.59 (0.42, 0.75)
Perez-Porcuna, 2014[149] Brazil [Intermediate]	116	QFT-GIT vs. 10mm	71.55 (62.75, 78.97)	28.44 (21.03, 37.25)	0.35 (0.16, 0.53)
Rutherford, 2012a-b[108, 109] Indonesia [High]	292	QFT-GIT vs. 10mm	80.48 (75.55, 84.62)	19.52 (15.38, 24.45)	0.61 (0.49, 0.72)
Song, 2014[150] South Korea [High]	2982	QFT-GIT vs. 10mm	82.6 (81.2, 83.92)	17.4 (16.08, 18.80)	0.38 (0.34, 0.42)
	2982	QFT-GIT vs. 15mm	92.52 (91.51, 93.41)	7.48 (6.59, 8.48)	0.55 (0.50, 0.61)
Talbot, 2012[110] US [Low]	143	T-SPOT vs. 15mm	97.9 (94.01, 99.28)	2.01 (0.72, 5.99)	0.71 (0.55, 0.88)
Tieu, 2014[152] Thailand [High]	131	QFT-GIT vs. 10mm	59.54 (50.98, 67.56)	40.46 (32.44, 49.02)	0.29 (0.18, 0.40)
	131	QFT-GIT vs. 15mm	79.39 (71.67, 85.43)	20.61 (14.57, 28.33)	0.53 (0.38, 0.69)

Subgroup of interest – children and adolescents					
Study ID (Author name, year, and country) [burden]	**Sample size (N) total or by subgroup**	**Type of IGRA vs. TST induration threshold**	**Concordance (%) 95% CI**	**Discordance (%) 95% CI**	**Agreement kappa 95% CI**
	131	T-SPOT vs. 10mm	55.73 (47.18, 63.95)	44.27 (36.05, 52.82)	0.23 (0.12, 0.34)
	131	T-SPOT vs. 15mm	78.63 (70.84, 84.78)	21.37 (15.22, 29.16)	0.51 (0.35, 0.66)
Tsolia, 2010[111] Greece [Low]	99	QFT-GIT vs. 5mm	71.58 (61.81, 79.67)	28.42 (20.33, 38.19)	0.45 (0.27, 0.63)
	43 with BCG history	QFT-GIT vs. 10mm	46.50 (NR)	NR	0.13 (p = 0.06)
	52 no BCG history	QFT-GIT vs. 5mm	96.20 (NR)	NR	0.91 (p = 0.06)
Diel, 2011[100] Germany [Low]	NR	QFT-GIT vs. 5/10 mm	NR	NR	NR
Mahomed, 2011a[106] South Africa [High]	5244	QFT-GIT vs. 5 mm	84.80 (83.80, 85.75)	15.20 (14.25, 16.20)	0.69 (0.66, 0.72)
Noorbakhsh, 2011[102] Iran [Intermediate]	NR	QFT-G vs. 10 mm	NR	NR	NR

Abbreviations: 95% CI = 95 percent confidence interval; GIT = Gold In-Tube; N = number; NR = not reported; QFT = QuantiFERON-TB; TB = tuberculosis; TST = tuberculin skin test

4.3.4 Summary of children

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

The updated meta-analysis of 14 studies showed a significantly stronger association for IGRAs compared to TST in relation to a risk of LTBI/exposure level (pooled R-DOR = 1.98, 95% CI: 1.19, 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 IGRAs and TST in identifying LTBI across studies conducted in countries of high TB burden (pooled R-DOR = 1.13, 95% CI: 0.78, 1.65; I^2 = 71). In contrast, IGRA was significantly superior to TST in identifying LTBI in the settings of low TB burden (pooled R-DOR = 4.74, 95% CI: 2.15, 10.44; I^2 = 67%). In five studies both tests revealed strong associations of increasing order across 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 whether or not the BCG vaccination status influenced the odds of test positivity differentially for IGRAs and TST. Out of seven studies reporting relevant data, only three 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 6 studies were not significantly different between the BCG vaccinated vs. non-vaccinated groups. One large study showed 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, 1.33) but not for IGRA (OR = 0.99, 95% CI: 0.86, 1.12).

There was a wide variation in kappa statistic across 17 studies (five studies from CG117 and 12 more recent studies), ranging from 0.13 to 0.91. In post-2009 studies,[101, 103, 105-111] the ranges of kappa statistic

according to specific TST threshold and IGRA type were as follows: QFT-GIT vs. TST 5mm (range: 0.27-0.91), QFT-GIT vs. TST 10mm (range: 0.13-0.64), and TSPOT vs. TST 10mm (range: 0.53-0.71).

4.4 Immunocompromised people

4.4.1 Description of baseline characteristics – qualitative synthesis in text and tables

This section included 48 studies.[112-140, 147, 151, 153, 165-180] Our searches identified 32 studies[112-140, 147, 151, 153] in immunocompromised patients of which eight investigated the incidence of active TB following testing for LTBI (incidence studies)[112-117, 147, 153] and 24 investigated levels of exposure in relationship to LTBI test outcomes (exposure studies).[118-140, 151] An additional 16 studies[165-180] in immunocompromised patients were identified in CG117.

4.4.1.1 Incidence studies

Eight studies compared an IGRA test with the TST test in immunocompromised people.[112-117] Reasons for immunodeficiency (condition and procedure) varied across studies. We identified the following sub-populations: 1) HIV patients, 2) haematopoietic stem cell transplantation candidates or recipients, 3) post kidney transplantation patients, 4) haemodialysis in end stage renal disease and 5) patients with immune-mediated inflammatory disease before anti-tumour necrosis factor (TNF) alpha therapy. The studies which were included are described below according to these sub-populations. See Table 10 for further details on these studies.

One study compared the T-SPOT.TB with the TST (≥5mm) in a retrospective case study in HIV patients with a median age of 33 years and 31.1% females.[112] The study was carried out in a community setting in Switzerland with a follow up of two years. The proportion of BCG vaccinated participants was not reported.

Moon et al. (2013)[113] compared QFT-GIT with TST (≥5mm) 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 follow-up to assess for active TB was 0.8 years (0.1-2.6). BCG vaccination was high at 82%. Another study by Lee et al. 2014[147] compared QFT-GIT with TST (≥5mm or ≥10mm) in haematopoietic stem cell transplant recipient patients who were followed-up for a median of 1.3 years. The patients' mean age was 42.3 years, 47% were female, and 91% of the sample had BCG scars.[147]

Patients with post kidney transplantation were investigated by Kim et al. (2011)[114] in a prospective cohort study comparing IGRA T-SPOT.TB with TST (≥10mm). The setting was a tertiary-care hospital in South Korea. The age range reported was 40-46 years and 46% of participants were female. Patients were followed up for a median of 14 months. 79% of patients were BCG vaccinated.

Three studies investigated IGRA and TST in haemodialysis patients with end-stage renal disease.[115, 116, 153] Tests compared were QFT-GIT vs. TST (≥5mm),[115] T-SPOT.TB vs. TST (≥10mm),[153] and QFT-G, T-SPOT.TB vs. TST (two step; ≥ 10mm).[116] Anibarro et al. (2012)[115] undertook a prospective cohort study in a Spanish dialysis unit following a TB outbreak in the dialysis centre. Lee et al. (2009)[116] carried out a prospective, matched cohort study in Taiwan. The setting was unreported. The mean age and proportion of females of included patients was 62 years and 40% in Anibarro et al. (2012)[115] 44 years and 66% in Sherkat et al. (2014),[153] and 54 years and 38% in Lee et al. (2009).[116] The follow–up across the three studies ranged from 1.5[115] to two years.[116] The proportion of BCG vaccinated patients was low in Anibarro et al. (2012)[115] (13.5%), medium in Sherkat et al. 2014 (2014)[153] (27.3%), and high with 82.8% in Lee et al. (2009).[116]

Chang et al. (2011)[117] compared QFT-GIT with TST (≥10mm) in a prospective cohort study in patients with immune-mediated inflammatory diseases investigated for LTBI before the treatment with anti-TNF alpha. 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)

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
HIV							
Elzi, 2011[112] Switzerland [Low]	**Study aim:** To evaluate the sensitivity of T-SPOT.TB in comparison to TST to identify HIV-infected individuals with latent TB **Setting:** Community-based cohort **Study 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. M. Hoffmann, Janssen,	NR	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Type of tests:** IGRA (T-SPOT.TB) TST (≥ 5mm) **Cut-off values/thresholds:** IGRA: ≥ 6 spots in either of both Panel A and B; where the positive control was < 20 spots, or the negative control ≥ 10 spots, the test was scored as indeterminate TST: ≥5mm	**Mean (range or SD) age:** Median of 33 (IQR: 31-42) years **Female (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	**Total N of recruited patients:** 64 **Total N of excluded patients:** None – however, the total N 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 between test positive vs. negative groups from baseline (no

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Pfizer)				**Morbidity (n [%]):** HIV **Co-morbidity (n [%]):** NR		denominators provided)
Haematopoietic stem cell transplantation candidates							
Moon, 2013[113] South Korea [High]	**Study aim:** To compare the QFT-GIT with the TST in Hematopoietic stem cell transplant (HCT) candidates for detecting latent TB infection **Setting:** Asan Medical Center **Study design:** Prospective cohort study **Follow up:** Median 0.8 years (IQR: 0.1–2.6) **Funding source:** Basic Science Research Program through the National Research Foundation	NR	**Inclusion criteria:** All adult patients admitted for HCT **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥ 5mm) **Cut-off values/thresholds:** IGRA: According to manufacturer TST: ≥5mm	**Mean (range or SD) age:** 47 (35-55) **Female (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**	**Total N of recruited patients:** NR **Total N of excluded patients:** 52 patients died and 2 were lost to follow up during 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 lab technicians did not know the results of TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	(NRF) funded by the Ministry of Education, Science and Technology (MEST) (grant 2010-0005898)				**(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 [%]):		

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Cyclosporine 71 [29], Cyclosporine-MTX 65 [27], Cyclosporine-corticosteroid 8 [3], Corticosteroid therapy 111 [46]		
Haematopoietic stem cell transplantation recipients							
Lee, 2014 [147] South Korea [High]	**Study aim:** 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 **Setting:** tertiary hospital-based **Study design:** Prospective cohort study	Chest x-ray, a sputum AFB smear and CT scan (pulmonary TB)	**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,	**Type of tests:** QFT-GIT and TST **Cut-off values/thresholds:** QFT-GIT: NR TST (≥5mm or ≥10mm)	**Mean (range or SD) age:** 42.3 (13.8) years **Female (n [%]):** 183 [46.8] **Race/ethnicity (n [%]):** Asians (409 [100]) **Geographic origin (n[%]):** NR **BCG vaccination (n [%]):** 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	**Total N of recruited patients:** 409 **Total N of excluded patients:** 18	

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Follow up: median of 1.3 (IQR: 0.6-2.3) years **Funding source:** supported by grant from the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning		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)		**Clinical examination (yes/no):** NR **Morbidity (n [%]):** HCT recipients **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)		
Post kidney transplantation							
Kim, 2011[114] South Korea [High]	**Study aim:** To assess whether an ELISPOT assay is capable of predicting active TB development in kidney transplant (KT) recipients with negative TST results and without LTBI risk factors **Setting:** Tertiary-care hospital **Study design:**	Symptoms/signs, sputum AFB smear, and a CT scan	**Inclusion criteria:** KT patients (age≥16 years) with TST – (<10mm) and without TB risk factors (history of close contact with TB case, abnormal CXR, history of untreated or inadequately treated TB,	**Type of tests:** IGRA (T-SPOT.TB) TST (≥10mm) **Cut-off values/thresholds:** IGRA: NR TST: ≥10mm induration 48–72 h after injection, and in accordance with Korea Centers for Diseases Control	**Mean (range or SD) age:** 40.4-46.0 years **Female (n [%]):** 126 [46.3] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination (n [%]):** 215 [79.0] **History of anti-TB**	**Total N of recruited patients:** 324 **Total N of excluded patients:** 52 - the total N 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 diseases specialists blind to the results of ELISPOT assays, to avoid a verification

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Prospective cohort study **Follow up:** Median 14 month (IQR: 8-19) **Funding source:** Basic Science Research Program through National Research Foundation funded by the Ministry of Education, Science and Technology grant 2008-E00136		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 contraindicatio n for KT (e.g. malignancy)	and Prevention guidelines	**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		bias
Hemodialysis in end-stage renal disease (ESRD)							
Anibarro, 2012[115] Spain [Low]	**Study aim:** To compare IGRA with TST in patients with ESRD after a	Microscopic examination of sputum and sputum culture	**Inclusion criteria:** All patients who attended	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm)	**Mean (range or SD) age:** 62 (16.8) **Female (n [%]):** 21	**Total N of recruited patients:** 58 **Total N of**	Study does not mention how soon after the result will be

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	TB outbreak at a dialysis centre **Setting:** Outbreak investigation **Study design:** Prospective cohort study **Follow up:** 18 months **Funding source:** University of Vigo and Sudoefeder (IMMUNONET-SOE1/P1/E014)		the dialysis unit while index case was on duty **Exclusion criteria:** Patients who had a previous +ve TST test	**Cut-off values/thresholds:** IGRA: 0.35 IU/mL TST: ≥ 5mm, a second test was performed five days later if the first TST-1 was <5 mm	[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]	**excluded patients:** 6	read for the second TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Lee, 2009[116] Taiwan [High]	**Study aim:** 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 **Setting:** NR **Study design:** Prospective, matched, double cohort study **Follow up:** Two-year follow-up **Funding source:**	Asymptomatic cases are diagnosed with a chest x-ray, and symptomatic cases are 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 TST (two step; ≥ 10mm) **Cut-off values/thresholds:** IGRA: (QFT-G): according to analysis software, available for download from the Cellestis Ltd website (T-SPOT.TB): NR TST: ≥ 10mm induration for ESRD patients and BCG-unvaccinated individuals, ≥ 15mm induration for BCG-vaccinated, healthy individuals	**Mean (range or SD) age:** 53.8 (34.4-77.7) **Female (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 [%]):** NR	**Total N of recruited patients:** 64 **Total N of excluded patients:** 0	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	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)						
Sherkat, 2014[153] Iran [Intermediate]	**Study aim:** 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 **Setting:** hospital-based **Study design:** Prospective cohort study **Follow up:** 21 months (follow-up included 9 months prophylactic	NR	**Inclusion criteria:** Candidates for receiving a kidney transplant **Exclusion criteria:** Active TB, history of prior TB or isoniazid prophylactic treatment, refusal to continue prophylactic treatment, symptoms of isoniazid-induced	**Type of tests:** IGRA (T-SPOT.TB) TST (≥10mm) **Cut-off values/thresholds:** T-SPOT.TB: NR TST (≥10mm)	**Mean (range or SD) age:** 44 (15.5) years **Female (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 [%]):**	**Total N of recruited patients:** NR **Total N of excluded patients:** NR	

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	treatment and 12 months post transplantation) **Funding source:** none		hepatitis or drug reaction		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])		
Immune-mediated inflammatory diseases (IMID) before anti-TNF alpha therapy							
Chang , 2011[117] South Korea [High]	**Study aim:** To evaluate usefulness of IGRA for the diagnosis of LTBI in arthritis patients who received TNF antagonists in South Korea **Setting:** Hospital-	Medical history (current symptoms, prior history of treatment for tuberculosis, and recent history of contact with a case of active TB) and TST	**Inclusion criteria:** Inflammatory arthritis including rheumatoid arthritis and ankylosing spondylitis who visited	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds:** IGRA: ≥0.35 IU/mL	**Mean (range or SD) age:** 39 (median) **Female (n [%]):** 44 [41] **Race/ethnicity (n [%]):** Asian **Geographic origin**	**Total N of recruited patients:** 108 **Total N of excluded patients:** 1	Both the TST and QFT-IT were performed on the same day as the screening examination in all patients before

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, design, follow-up duration, and funding source**	**Method(s) of diagnosis of active TB**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	based **Study design:** Prospective cohort study **Follow up:** 18 months (median) **Funding source:** IN-SUNG Foundation for Medical Research (CA98051)	(according to the recommendation of the Korea Food and Drug Administration)	our facility to evaluate LTBI before starting TNF antagonist **Exclusion criteria:** Active TB	TST: 10mm induration after 48–72 h	**(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] and ankylosing spondylitis 61 [57] **Co-morbidity (n [%]):** NR		initiating TNF antagonists

Abbreviations: TB = tuberculosis; NR = not reported; N = number; IGRA = interferon-gamma release assay; QFT-GIT = QuantiFERON-TB Gold In-Tube; TST = tuberculosis skin test; BCG = Bacille de Calmette et Guérin; LTBI = latent tuberculosis infection; SD = standard deviation; ESRD = early stage renal

disease; +ve = positive; HIV = human immunodeficiency virus; HCT = hematopoietic stem cell transplant; MTX = methotrexate; KT = kidney transplant; AFB = acid-fast bacillus; CT = computerised tomography; CXR = chest x ray; IQR = interquartile range; QFT-G = QuantiFERON-TB Gold; TNF = tumor necrosis factor

4.4.1.2 Exposure studies

Twenty-four newly identified studies compared an IGRA test with the TST test in immunocompromised people relating test outcome to prior level of exposure.[118-140, 151] All studies within this group were therefore classed as having either a retrospective cohort or cross-sectional design. Reasons for immunodeficiency (condition and procedure) varied across studies. We identified the following sub-populations: 1) HIV patients, 2) solid organ transplantation candidates, 3) post kidney transplantation patients, 4) patients on haemodialysis for end stage renal disease, 5) patients with immune-mediated inflammatory diseases before anti-TNF alpha therapy, 6) patients with hepatitis C and 7) lupus erythematosus patients. The included studies are described below according to these sub-populations. See Table 11 for further details on these studies.

Three studies assessed the test performance of different IGRA tests compared to TST tests in patients with HIV.[123, 134, 151] Chkhartishvili et al. (2013)[123] compared QFT-GIT and T-SPOT.TB with TST (≥5mm) in HIV patients recruited from a national referral centre for HIV in Georgia where the non-exposed had no household member treated for TB and the exposed group did have a household member treated for active TB. Mutsvangwa et al. (2010)[134] compared T-SPOT.TB with TST at the ≥10mm cut-off value in HIV positive household contacts of TB cases identified in a factory in Zimbabwe. The non-exposed control consisted of contacts of factory workers without TB. Souza et al. (2014)[151] compared QFT-GIT with TST (≥5mm) in adults living with HIV and/or acquired immunodeficiency syndrome (AIDS) in outpatient sexually transmitted disease public clinics in a low TB incidence urban area (11.1/100.000 inhabitants). The rate of BCG vaccination across the three studies ranged from 76%[151] to 94%.[123] The proportion of females ranged from 28%[151] to 89%.[134] The median age reported for only two studies ranged from 38[123] to 40 years.[151]

Four studies compared either QFT-GIT[118, 122, 129] or T-SPOT.TB[128] with TST at the cut-off level of ≥5mm,[122] ≥10mm[118, 129] or both[128] in solid organ transplantation candidates. All four studies were hospital based. Two studies were undertaken in South Korea,[128, 129] one in Iran[118] and one in Spain.[122] The mean age ranged from 39.9 years[118] to 47 years,[129] 56.4 years[122] or not reported.[128] The proportion of females was close to 50% in two studies[118, 129] and less than 25% in one study.[122] One study did not report gender.[128] BCG vaccination was high in studies from Korea (78%[128] and 91%[129]) as well as in the study from Iran (91%)[118] but low in the Spanish study (31.6%).[122] Exposure to TB was universally defined as a history of (close) contact with active TB. Two studies also included newly acquired TB[128] or a history of active TB as a risk factor for LTBI.[128, 129] The non-exposed group consisted of participants without contact or low risk of LTBI.

Hadaya et al. (2013)[126] and Kim et al. (2013)[130] compared one or more IGRA tests with TST in patients post kidney transplantation. Hadaya et al. (2013)[126] compared QFT-GIT, T-SPOT.TB and TST (≥5 mm) in a Swiss hospital and Kim et al. (2013)[130] compared QFT-GIT with TST (≥10mm) in South Korean kidney transplant recipients. Exposure was defined as close contact with TB patient or prior TB according to 1) chest x-ray[126] or 2) history of treated TB or abnormal chest x-ray.[130]

Four studies investigated the agreement between IGRA and TST tests in patients on haemodialysis for end-stage renal disease.[119, 120, 124, 137] Three studies compared QFT-GIT with TST (≥10mm) [119, 120, 124] and one compared QFT-G with TST (≥10mm).[137] Chung et al. (2010)[124] additionally investigated the T-SPOT.TB. Three studies reported the setting to be hospital based[119, 120, 124] while one study did not report the study setting.[137] BCG vaccination of the study participants was low in the study from Saudi Arabia (14%)[119] and medium in the two studies from Turkey (49%[120] and 72%[137]) and the study from South Korea (67%).[124] The mean age of study participants was similar across all four studies (58,[119] 52,[120] 54[124] and 56 years[137]) and the gender distribution within the studies was balanced (52% females,[119] 50% females,[120] 43% females[124] and 53% females[137]). Exposure to TB was not well defined. Three studies described exposure as (close) contact with a TB case[119, 120, 124] while one study[137] 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.[124, 137] The comparison group included people who were at low risk of LTBI.

Patients with immune-mediated inflammatory diseases before anti-TNF alpha treatment were recruited in nine studies comparing IGRA with TST tests.[121, 125, 127, 131-133, 135, 136, 140] The combination of tests investigated varied greatly among studies. Three studies compared QFT-GIT with TST (≥5mm),[121 127, 136] while one study[140] additionally included the T-SPOT.TB. One study did not provide the threshold for a positive TST test that was compared to QFT-GIT,[133] one study compared QFT-GIT with the TST test at two different thresholds (≥5mm and ≥10mm) for different sub-groups of patients,[135] one study[131] compared QFT-G with the T-SPOT.TB and TST (≥5mm), and two studies compared the T-SPOT.TB with the TST at either only the ≥5mm threshold[125] or two different thresholds (≥5mm and ≥10mm).[132] All studies were undertaken in low TB incidence countries either in Europe[121, 125, 131-133, 135, 136, 140] or the USA.[127] And all studies were hospital based. BCG vaccination was low in studies undertaken in Spain (26%[121] and 19%[136]), the USA (34%),[127] Germany (13%)[131] and the UK (22%).[133] It was higher in studies from France (78%)[125] and Greece (76%)[140] and considerable higher in studies from Switzerland (90%)[132] and Austria (100%).[135] Gender was generally well balanced in the studies with two possible exceptions: Laffitte et al. (2009)[132] recruited a population with only 30% females and Hsia et al. (2012)[127] had a

proportion of females of 66%. One study[133] investigated children with a median age of 8.9 years while the participants' mean age in the remaining studies ranged from 37 years[135] to 52 years.[140] 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.[121, 125, 131-133, 135, 136, 140] Additional risk factors reported were origin or residence in a high incidence country[127, 132, 135, 136, 140] and a history of active TB.[121, 125, 131] The non-exposed group was generally described as having no history of TB contact.

Shen et al. (2012)[138] compared a T-SPOT.TB test with the TST (≥5mm) in Hepatitis C patients in a university hospital in China. The mean age and proportion of females were 40 years and 47%. BCG vaccination was not reported in this study and exposure was loosely defined as a history of exposure versus no exposure to TB.

Takeda et al. (2011)[139] evaluated the agreement between the QFT-2G with the TST (≥10mm) in a hospital in Japan in patients with Lupus erythematosus. The mean age and proportion of females were 38 years and 82%. 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 to a group without LTBI risk factors.

Table 11. Baseline characteristics of studies in immunocompromised patients (exposure studies)

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
HIV							
Chkhartishvili, 2013[123] Georgia [High]	**Study aim:** To assess the performance of two commercially available IGRAs (QFT-GIT and T-SPOT.TB) 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 **Setting:** National referral institution for HIV diagnosis, treatment and care **Study design:** Retrospective/cross-sectional study **Funding source:** The U.S. Civilian Research and	**Non exposed:** No household member treated for TB **Exposed 1:** Household member treated for TB **Exposed 2:** NA	**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 **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) IGRA (T-SPOT.TB) TST (≥ 5 mm) **Cut-off values/thresholds Definition of test+:** IGRA (QFT-GIT): Interferon-gamma 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 had a result of > 8 IU/ml or the positive control had a result of < 0.5 IU/ml.	**Mean (range or SD) age:** Median 38.0 (range 32.8-43.8) **Female (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	**Recruited (N):** NR **Excluded (N):** NR	Blood was drawn for the IGRAs prior to the placement of the TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	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			IGRA (T-SPOT.TB): ≥ 6 spot forming cells, or twice the nil control, indeterminate if nil control spot count was > 10 spot forming cells or if the reading in the positive control was < 20 spot forming cells TST: ≥ 5 mm of induration	**Morbidity (n [%]):** HIV **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** NR		
Mutsvangwa, 2010[134] Zimbabwe [High]	**Study aim:** To test for LTBI using T-SPOT.TB and TST, correlated test results with TB exposure in household contacts of TB cases and to assess the impact of HIV co-infection on test results in these contacts **Setting:** NR **Study design:** Retrospective	**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 (household contacts of controls) living with controls (no TB); TB cases were sampled from factories in	**Type of tests:** IGRA (T-SPOT.TB) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: NR TST: ≥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 **Geographic origin (n[%]):** Sub-Saharan Africa **BCG vaccination (n [%]):** 63 [86.0] **History of anti-TB**	**Recruited (N):** NR **Excluded (N):** NR	Persons performing and reading the assays were blind to all personal identifiers and TST results

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	cohort/cross-sectional study **Funding source:** The Wellcome Trust		Harare and controls samples randomly from the same factories. **Exclusion criteria:** NR		**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		
Souza, 2014[151] Brazil [intermediate]	**Study aim:** To evaluate the added value of QFT-GIT over the TST for detecting LTBI among persons living with HIV/AIDS; also to explore the factors associated with a positive QFT-GIT	**Non exposed**: No history of contact with index case **Exposed:** History of contact with index case	**Inclusion criteria:** People with HIV/AIDS over 17 years who were not submitted to TST in the previous five weeks **Exclusion criteria:** Patients	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm) **Cut-off values/thresholds Definition of test+:** QFT-GIT: ≥0.35	**Mean (range or SD) age:** median 40 (IQR: 32–46) years **Female (n [%]):** 85 [28.3] **Race/ethnicity (n [%]):** NR **Geographic origin**	**Recruited (N):** NR **Excluded (N):** NR	

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	and with discordant QFT-GIT/TST results **Setting:** outpatient clinics **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Fundacao de Apoio a Pesquisa do Distrito Federal,		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	UI/mL TST (≥5mm)	**(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 (300 [100]) **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** NR		
Solid organ transplantation candidates							
Ahmadinejad, 2013[118] Iran	**Study aim:** To compare the QFT and TST in	**Non exposed:** No history of exposure to active	**Inclusion criteria:** SOT candidates who	**Type of tests:** IGRA (QFT-GIT)	**Mean (range or SD) age:** 39.9 (12.7)	**Recruited (N):** 187	For prevention of potential

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
[Intermediate]	diagnosis of LTBI in solid organ transplant (SOT) candidates (kidney, liver, lung) **Setting:** Tertiary care teaching hospital **Study design:** Cross sectional/retrospective cohort study **Funding source:** Tehran University of Medical Sciences and Health Services grant	TB **Exposed 1:** Exposure history to active TB **Exposed 2:** NA	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	TST (≥10mm) **Cut-off values/threshold s Definition of test+:** IGRA: NR TST: Induration ≥10 mm	**Female (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]	**Excluded (N):** 23 (dropouts)	boosting effect of TST on QFT, blood sampling and purified protein derivative injection were done simultaneously for all patients

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					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]		
Casas, 2011b[122] Spain [Low]	**Study aim:** To compare the performance of the TST and the QFT-IT test in detecting latent TB infection in patients with end-stage liver disease (ESLD) requiring liver transplant (LT) **Setting:** Hospital-based **Study design:** Retrospective/cross-sectional study **Funding source:** Grants from the	**Non exposed:** No risk factors for TB **Exposed 1:** 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)	**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	**Type of tests:** IGRA (QFT-GIT) TST (2 step; ≥5mm) **Cut-off values/thresholds Definition of test+:** IGRA: Interferon-c level ≥0.35 IU/mL (the M. tuberculosis–specific antigen tube minus the nil tube) and indeterminate	**Mean (range or SD) age:** 56.4 (7.6) **Female (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**	**Recruited (N):** 110 **Excluded (N):** 15 (previous TB infection, HIV, dropouts, anti-TNF-alpha agents, incomplete IGRA results)	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	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	**Exposed 2:** NA	with known immunosuppressive conditions	[interferon-c level < 0.5 (the mitogen tube minus the nil tube) or > 8.0 IU/mL (the nil tube)] Plasma samples with indeterminate results were retested TST: Induration ≥ 5 mm at 48 to 72 hours in accordance with the national transplant guidelines	**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		
Kim, 2010[128] South Korea [High]	**Study aim:** To compare the results of the ELISPOT	**Non exposed:** No LTBI group	**Inclusion criteria:** Kidney transplant adult	**Type of tests:** IGRA (T-SPOT.TB)	**Mean (range or SD) age:** NR	**Recruited (N):** 213	All blood samples were collected

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	assay T-SPOT.TB with those of the TST in renal transplant candidates before transplantation in a country with an intermediate TB burden **Setting:** Clinic based **Study design:** Retrospective/cross-sectional study **Funding source:** Korea Research Foundation	**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 tuberculin skin test to positive status) **Exposed 2:** NA	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	TST (≥5mm) TST (≥10mm) **Cut-off values/threshold s Definition of test+:** IGRA: As recommended by manufacturer TST: ≥10 mm induration 48-72h after injection	**Female (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**	**Excluded (N):** 4 (n = 1 refusal, n = 1 active TB, n = 2 cancer)	before TST to avoid the possible boosting effect of TST on the ELISPOT assay

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					[%]): Isoniazid for 9 months immediately after renal transplantation 5 [19]		
Kim, 2013b[129] South Korea [High]	**Study aim:** To compare the results of the TST and QFT-GIT 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 **Setting:** Clinic based **Study design:** Retrospective/cross-sectional study **Funding source:** Grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare and	**Non exposed:** No LTBI group **Exposed 1:** (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:** NA	**Inclusion criteria:** Kidney transplant adult candidates before transplantation **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: IFN-c response of TB antigen minus that of the Nil tube ≥0.35 IU/mL and ≥25 % of the negative control value TST: induration ≥10 mm after 48–72 h	**Mean (range or SD) age:** 47 (20–69) **Female (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): y**es	**Recruited (N):** NR **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Family Affairs, Republic of Korea				**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		
Patients post kidney transplantation							
Hadaya, 2013[126] Switzerland [Low]	**Study aim:** To compare the diagnostic performance of the TST and two IGRAs (T-SPOT.TB and QFT-GIT) in renal transplant recipients (RTRs) under stable immunosuppression **Setting:** Geneva University Hospital **Study design:** Retrospective cohort/cross-	**Non exposed:** No risk for LTBI **Exposed 1:** 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:** NA	**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	**Type of tests:** IGRA (QFT-GIT) IGRA (T-SPOT.TB) TST: (≥5 mm) **Cut-off values/thresholds Definition of test+:** IGRA (QFT-GIT): according to manufacturer IGRA (T-SPOT.TB):	**Mean (range or SD) age:** 59.0 (13.2) **Female (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]	**Recruited (N):** 205 **Excluded (N):** 5 (indeterminate IGRAs)	Blood samplings for determination of M. tuberculosis-specific QGIT (Cellestis) and interferon-F-secreting T cells (T-SPOT.TB (Oxford Immunotec) were performed

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	sectional study **Funding source:** Ligue Pulmonaire Genevoise a non-profit organisation		within the preceding 3 months and signs or symptoms of acute infection	according to manufacturer TST: ≥ 5 mm transverse diameter, measured 48 to 72h after injection	**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		simultaneously

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					[6.0]		
Kim, 2013c[130] South Korea [High]	**Study aim:** To compare the QFT-GIT with the tuberculin skin test (TST) for screening of LTBI in kidney transplant recipients (KTRs) **Setting:** NR **Study design:** Retrospective cohort/cross-sectional study (with prospective part) **Funding source:** Korea health care technology R & D project, ministry for health, welfare and family affair, republic of Korea	**Non exposed:** NR **Exposed 1:** History of treated tuberculosis **Exposed 2:** Abnormal chest radiograph	**Inclusion criteria:** Kidney transplant recipients **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥ 0.35 IU/mL and ≥ 25% in the presence of TB-specific antigen minus that of the Nil tude TST**:** Induration ≥10 mm at 48 to 72 h after the injection	**Mean (range or SD) age:** 44.7 ±11.5 **Female (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**	**Recruited (N):** 109 **Excluded (N):** 4 with indeterminate QFT-GIT results (excluded for analysis)	NR

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					[%]): 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		
Hemodialysis in patients with end stage renal disease							
Al Jahdali, 2013[119] Saudi Arabia [Low]	**Study aim:** 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 TB infection in a population showing an intermediate TB prevalence	**Non exposed:** No high likelihood of LTBI **Exposed 1:** High likelihood of LTBI (contact with TB case, abnormal chest X-ray, DM, immunosuppressant in the last 12 months, failed kidney transplant or BMI ≤20) **Exposed 2:** NA	**Inclusion criteria:** Hemodialysis patients **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: 0.35 IU/ml or more for the relationship ([IFN-γ in the TB antigen tube]−[IFN-γ in the negative	**Mean (range or SD) age:** 58.42 (17.65) **Female (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	**Recruited (N):** 215 **Excluded (N):** 15 (active TB)	IGRA blood was collected before the administration of the TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Setting: Outpatient hemodialysis unit hospital-based **Study design:** Retrospective cohort/cross-sectional study **Funding source:** No funding sources			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 ≥10mm for LTBI. Results with < 10mm second TST within 3—6 weeks positive if either the 1st or 2nd test showed a response of ≥10mm	**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 12months 2 [1.0]		
Ates, 2009[120] Turkey [Intermediate]	**Study aim:** To assess the efficacy of QTF-GIT test for detection of LTBI and determine the	**Non exposed:** No tuberculosis exposure **Exposed 1:**	**Inclusion criteria:** Hemodialysis patients 18 years or older	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm)	**Mean (range or SD) age:** 51.9 (16.2) **Female (n [%]):** 137 [50.0]	**Recruited (N):** 290 **Excluded (N):** 15 (rejected tests,	Observers were blinded to the results of the TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	degree of agreement between the results of TST and QTF-GIT tests in hemodialysis patients **Setting:** Outpatient hemodialysis hospital centers **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Grant from University of Dicle	Tuberculosis exposure **Exposed 2:** NA	**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	**Cut-off values/thresholds Definition of test+:** IGRA: According to the QTF-GIT analysis software TST: Induration diameter of ≥10 mm	**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	improper blood sampling, and unsuccessful phlebotomy)	

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Chung, 2010a[124] South Korea [High]	**Study aim:** To compare two IGRAs (QFT and T-SPOT.TB) simultaneously with the TST for their diagnostic efficacy for latent TB infection in Korea, an intermediate TB-burden country **Setting:** Medical Centre **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Funding from the Gil Medical Centre	**Non exposed:** Low risk **Exposed 1:** 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:** NA	**Inclusion criteria:** Haemodialysis patients with ESRD **Exclusion criteria:** Patients who had taken empirical anti-TB medications and patients taking anti-TB medication for active TB infection	**Type of tests:** IGRA (QFT-GIT) IGRA (T-SPOT.TB) TST (≥10 mm) **Cut-off values/threshold s Definition of test+:** IGRA (QFT): As previously described. IGRA (T-SPOT.TB): As previously described TST: ≥10 mm size of the mean values of two measurements	**Mean (range or SD) age:** 54.1 (14.4) **Female (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	**Recruited (N):** NR **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					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]		
Seyhan, 2010[137] Turkey [Intermediate]	**Study aim:** To compare the results of QFT-G with TST for detecting LTBI in hemodialysis patients **Setting:** NR **Study design:** Retrospective cohort/cross-sectional study	**(1) History of active TB** **Non exposed:** No prior history of active TB **Exposed 1:** Prior history of active TB **(2) Contact of the patient with TB** **Non exposed:** No	**Inclusion criteria:** Haemodialysis patients **Exclusion criteria:** Suspicion of active TB infection, use of immunosuppressive drugs, and other known	**Type of tests:** IGRA (QFT-G) TST (≥ 10mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥0.35 IU/mL of IFN-γ in the TB antigen tube minus the	**Mean (range or SD) age:** 56.2±15.3 **Female (n [%]):** 53 [53] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):** NR **BCG vaccination (n**	**Recruited (N):** NR **Excluded (N):** NR	Blood was collected before TST placement People with an initial induration of less than 10mm were administered a second TST one week

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Funding source: None	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, and elapsed time after the contact) **(3) chest radiograph changes** **Non exposed:** No chest radiograph changes consistent with old TB	immunodeficiency status (human immunodeficiency virus [HIV], malignancy	negative control tube TST: ≥ 10mm induration	**[%]):** 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		later to cause a potential booster response. Results from the two-step testing were used in all further analyses

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
		Exposed 1: Chest radiograph changes consistent with old TB					
Immune-mediated inflammatory diseases (IMID) before anti-TNF alpha therapy							
Casas, 2011a[121] Spain [Low]	**Study aim:** 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 **Setting:** Outpatient clinics **Study design:** Retrospective cohort/cross-sectional study **Funding source:** The first author received research grant from the University Barcelona (October	**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, prior prison stay, intravenous drug abuse, health care worker, abnormal chest X-ray, and history of past TB) **Exposed 2:** NA	**Inclusion criteria:** Patients with immune-mediated inflammatory diseases (IMID) before anti–TNF-α therapy **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥ 5mm) **Cut-off values/threshold s Definition of test+:** IGRA**:** According to manufacturer, indeterminate results were retested TST: Induration of ≥5 mm at 48–72 h	**Mean (range or SD) age:** 49.1 [12.9] **Female (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	**Recruited (N):** 323 **Excluded (N):** n = 9 (no IMID: n = 2 and problems with QFT-GIT plasma sample storage: n = 7)	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	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)				**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]		
Costantino, 2013[125] France	**Study aim:** To compare TST and IGRA results in	**Non exposed:** No CRF of LTBI	**Inclusion criteria:** Patients with rheumatoid	**Type of tests:** IGRA (T-SPOT.TB)	**Mean (range or SD) age:** 51.0 (39.0–59.0)	**Recruited (N):** NR	To avoid any potential boosting

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
[Low]	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 **Setting:** Rheumatology Department of Nancy University Hospital **Study design:** Retrospective cohort/cross-sectional study **Funding source:** NR	**Exposed 1:** 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:** NA	arthritis and spondyloarthritis requiring TNF antagonists **Exclusion criteria:** Patients with previous antituberculosis chemoprophylaxis	TST (≥ 5 mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥ 6 spots, indeterminate if the negative control spot count yielded more than 10 spots or if the positive control spot count yielded fewer than 20 spots TST: induration diameter of ≥5 mm	**Female (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]	**Excluded (N):** NR	effect of TST on IGRA results, all T-SPOT.TB assays were performed before initiating TST

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Co-morbidity (n [%]): NR **Type of during-study treatment (n [%]):** DMARD 277 [49.2], Corticosteroids 254 [45.1], NSAID 255 [45.4]		
Hsia, 2012[127] USA [Low]	**Study aim:** To evaluate the performance of an IGRA versus the standard TST as a screening tool for LTBI prior to the initiation of anti–tumor necrosis factor therapy in patients with autoimmune inflammatory diseases **Setting:** NR **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Johnson & Johnson,	**Non exposed:** North America **Exposed 1:** Western Europe **Exposed 2:** Asia **Exposed 3:** Eastern Europe **Exposed4:** Latin America	**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,	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm) **Cut-off values/thresholds Definition of test+:** IGRA: According to manufacturer TST: According to the local country guidelines for defining an immunosuppressed host or induration ≥5mm	**Mean (range or SD) age:** 48.58 (12.6) **Female (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]	**Recruited (N):** 2303 **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	honoraria from Genentech, Pfizer, Celgene, Corrona, Amgen, Bristol-Myers Squibb, and Janssen		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 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]		
Kleinert, 2012[131] Germany [Low]	**Study aim**: To compare the utility of IGRA and TST in LTBI screening in a large cohort of patients with rheumatic diseases	**Non exposed**: None of the compound risk factors (CRF) were present **Exposed 1:** A	**Inclusion criteria**: Patients with rheumatic diseases **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-G) IGRA (T-SPOT.TB) TST (≥5mm) **Cut-off**	**Mean (range or SD) age:** Mean age range (50.8-59.5) **Female (n [%]):** 937 [61.3]	**Recruited (N)**: NR **Excluded (N):** None	All patients received one type of IGRA, either T-SPOT.TB or QFT,

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	receiving immunosuppressive therapy **Setting**: Hospital-based **Study design:** Retrospective cohort study **Funding source:** Abbott, Pfizer, Roche and Wyeth, Chugai, Cellestis Ltd, Oxford Immunotec Ltd, Pharmore Ltd, and Roche	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:** NA		**values/threshold s Definition of test+:** IGRA (QFT-G): NR IGRA (T-SPOT.TB): ≥6 spots TST: ≥5 mm skin induration	**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]		depending on what was available in the correspondin g laboratory

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					various other rheumatologic disorders **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** Immunosuppressive therapy (not specified)		
Laffitte, 2009[132] Switzerland [Low]	**Study aim**: (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. **Setting**: Hospital-based	**Non exposed**: No probable LTBI **Exposed 1:** 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	**Inclusion criteria**: Patients with moderate to severe psoriasis qualifying for anti-TNF-a therapy **Exclusion criteria:** NR	**Type of tests:** IGRA (T-SPOT.TB) TST (≥5mm) TST (≥10mm) **Cut-off values/threshold s Definition of test+:** IGRA: NR TST: Induration diameter ≥5mm or ≥10mm	**Mean (range or SD) age:** 48 (17–74) **Female (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**	**Recruited (N)**: NR **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Study design: Retrospective cohort/cross-sectional study **Funding source:** NR	(defined as > 40 cases in 100 000 per year) **Exposed 2:** NA			**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		
Maritsi, 2011[133] UK [Low]	**Study aim**: To describe the findings of QFT-GIT test when applied to a paediatric rheumatology population and to assess the efficacy of this test versus the methods	**Non exposed**: Low-risk group **Exposed 1:** High-risk group (TB risk evaluation was performed using the questionnaire formulated by the United States	**Inclusion criteria**: Children on infliximab since 2007 **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (NR) **Cut-off values/thresholds Definition of test+:** IGRA: NR	**Mean (range or SD) age:** Median age 8.9 years (1.5 to 13 years) **Female (n [%]):** 12 [52.1] **Race/ethnicity (n [%]):** Caucasian [55], Afro-Caribbean	**Recruited (N)**: 27 **Excluded (N):** 4 (no record of the QTB test)	Authors suggested that results for the QFT-GIT are reported as positive, negative and indeterminate

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	previously used for the exclusion of TB infection prior to starting anti-TNFα treatment **Setting**: Pediatric Rheumatology Centre **Study design:** Retrospective case study **Funding source:** Authors reported that there is no source of funding	Pediatric Tuberculosis Collaborative Group, 2004) **Exposed 2:** NA		TST: NR	[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): n**o **Morbidity (n [%]):** NR **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** 5 [22] methotrexate, 23 [100[infliximab		

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Papay, 2011[135] Austria [Low]	**Study aim:** To evaluate the impact of immune-modulatory treatment on results from TST and IGRA in IBD patients before starting therapy with a biologic agent. **Setting:** Outpatient clinic **Study design:** Retrospective cohort/cross-sectional study **Funding source:** NR	**Non exposed:** NR **Exposed 1:** Origin from a high-prevalent country **Exposed 2:** History of contact with active TB **Exposed 3:** Chest x-ray indicative of LTBI	**Inclusion criteria:** IBD patients **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST **Cut-off values/thresholds Definition of test+:** IGRA: ≥0.35 IU/mL TST: People with IM induration ≥5mm People with IBD >10 mm	**Mean (range or SD) age:** Age at screening 36.6 ± 11.3 **Female (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): y**es **Clinical examination (yes/no):** NR	**Recruited (N):** 208 **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					Morbidity (n [%]): Crohn's disease 152 [73.1]; Ulcerative colitis 56 [26.9] **Co-morbidity (n [%]):** NR **Type of during-study treatment (n [%]):** Immunotherapy		
Ramos, 2013[136] Spain [Low]	**Study aim:** 1) To evaluate the performance of QFT-GIT compared with the TST for the diagnosis of LTBI in patients with immune-mediated inflammatory disease (IMID) before TNF-a antagonist therapy, 2) to evaluate the impact of immunosuppressive therapy on QFT-GIT and TST performance in different IMID **Setting:** Outpatient infectious diseases clinic of a	**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 adults (age C 15 years) candidates for anti-TNF-a therapy who attended the clinic **Exclusion criteria:** NR	**Type of tests:** IGRA (QFT-GIT) TST (≥5mm) **Cut-off values/thresholds Definition of test+:** IGRA: ≥0.35 IU/ml; indeterminate if (1) the negative control was ≥8.0 IU/ml or (2) the positive control was <0.5 IU/ml or if IFN-c level was ≥0.10 IU/ml but <0.35 IU/ml	**Mean (range or SD) age:** Median 52 (16–82) **Female (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 [%]):**	**Recruited (N):** NR **Excluded (N):** NR	QFG and TST were performed simultaneously in a blinded fashion

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	university hospital **Study design:** Retrospective cohort/cross-sectional study **Funding source:** Grants from Conselleria de Sanidad (051/2007), and FIS (PI08/90778)			TST: Induration diameter > 5 mm	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 [%]):**		

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					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])		
Vassilopoulos, 2011[140] Greece [Low]	**Study aim:** To compare the latest IGRAs (QFT-GIT and T-SPOT.TB assays) and TST for LTBI diagnosis in rheumatic patients starting anti –TNF treatment **Setting:** Outpatient Rheumatology Clinic of Hippokration General Hospital **Study design:** Retrospective cohort study/cross-sectional study **Funding source:** Supported in part by research grants from the Hellenic	**(1) History of TB contact** **Non exposed:** No history of previous TB contact **Exposed 1:** History of previous TB contact **(2) Chest x-ray** **Non exposed:** Chest x-ray without signs suggestive of old TB **Exposed 1:** Chest x-ray suggestive of old TB **(3) Risk factor for TB**	**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	**Type of tests:** IGRA (QFT-GIT) IGRA (T-SPOT.TB) TST (≥ 5mm) **Cut-off values/thresholds Definition of test+:** IGRA: NR TST: Induration ≥5mm	**Mean (range or SD) age:** 52 ±16 **Female (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	**Recruited (N):** 157 **Excluded (N):** 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 in order to avoid potential interference with the IGRA results

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Society for Rheumatology and the Special Account for Research Grants, National and Kapodistrian University of Athens, Athens, Greece	**Non exposed:** No risk factor for TB (≥ 1) **Exposed 1:** 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)	treatment with anti-TB agents, including isoniazid for LTBI, or a history of previous treatment with anti-TNF agents or other biologics		**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])		
Hepatitis C							
Shen, 2012[138] China [High]	**Study aim:** To evaluated the diagnostic value of ELISPOT measuring interferon-Y in hepatitis C patients with LTBI **Setting:** University hospital **Study design:**	**Non exposed:** No history of TB exposure and no clinical symptoms (n = 39) **Exposed 1:** History of exposure to tuberculosis (suspected having TB, but no	**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	**Type of tests:** IGRA (T-SPOT.TB): ELISPOT TST (≥5 mm) **Cut-off values/thresholds Definition of test+:** IGRA: NR	**Mean (range or SD) age:** TB exposure group (n = 40) 42.9± 18.6); no TB exposure group (n = 39) 37.8 ±17.6 **Female (n [%]):** TB exposure 37 [47]; no TB exposure 17 [45] **Race/ethnicity (n [%]):** NR	**Recruited (N):** NR **Excluded (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
	Retrospective study **Funding source:** None	symptoms of TB, n = 31) **Exposed 2:** NA	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) **Exclusion criteria:** NR	TST: Induration ≥5 mm	**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		
Lupus erythematosus							
Takeda, 2011[139]	**Study aim:** To evaluate whether	**Non exposed**: Without risk of	**Inclusion criteria:** SLE	**Type of tests:** IGRA (QFT-2G)	**Mean (range or SD) age:** 38.3 (15.2)	**Recruited (N):** NR	NA

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
Japan [Low]	QFT-2G is useful in detecting LTBI in systemic lupus erythematosus (SLE) patients **Setting:** Hospital based **Study design:** Retrospective cohort/cross-sectional study **Funding source:** NR	LTBI **Exposed 1:** 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:** NA	patients; non-SLE connective tissue disease **Exclusion criteria:** NR	TST (≥10 mm) **Cut-off values/threshold s Definition of test+:** IGRA: ≥ 0.35 IU/mL TST: ≥10 mm, according to the usual criterion of the TST in Japan	**Female (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-**	**Excluded (N):** NR	

Subgroup of interest – immunocompromised people (specified by main condition/procedure)							
Study ID (Author name, year, and country)	**Study aim, setting, and design**	**Definition of construct validity (i.e., LTBI exposure-based proxy)**	**Study participants' inclusion/ exclusion criteria**	**Type and positivity threshold(s) of tests compared**	**Characteristics of study participants at baseline**	**N of recruited and excluded study participants**	**Comments**
					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]		

Abbreviations: TB = tuberculosis; NR = not reported; N = number; IGRA = Interferon-Gamma Release Assay; QFT-GIT = QuantiFERON-TB Gold In-Tube; TST = Tuberculosis Skin Test; BCG = Bacille de Calmette et Guérin; LTBI = latent tuberculosis infection; SD = standard deviation; ESRD = early stage renal disease; +ve = positive; HIV = human immunodeficiency virus; HCT = hematopoietic stem cell transplant; KTR = kidney transplant recipients; CXR = chest x ray; QFT-G = QuantiFERON-TB Gold; TNF = tumor necrosis factor; SOR = solid organ transplant; LT = liver transplant; ESLD = end-stage liver disease; RTR = renal transplant recipient; IFN = interferon; IMID = immune-mediated inflammatory disease; CRF = compound risk factor; IBD = inflammatory bowel disease; DMARD = disease-modifying anti-rheumatic drug; AIDS=acquired immunodeficiency syndrome

4.4.2 Study quality

4.4.2.1 Incidence of active TB

Of the eight included incidence studies[112-117] concerning immunocompromised patients identified since CG117,[10] one [114] had a low risk of bias (ROB) rating, three studies[113, 115, 147] had a moderate ROB rating, and four studies[112, 116, 117, 153] had high ROB rating. Potential ROB due to confounding was noted in five included studies.[112, 115-117 153] Overall, most of the studies had appropriate study designs, study attrition and statistical analysis and reporting. See Table 12 for further details.

Table 12. Summary assessment of risk of bias (ROB) for the included immunocompromised incidence studies (adapted from Hayden et al., 2013)[88]

First author, Year, Study ID	**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** *risk of bias in misclassification of individuals in relation to construct validity groups*	**Study Confounding** *risk of bias due to confounding*	**Statistical Analysis and Reporting** *risk of bias due to analysis and selective reporting*	**Total ROB** *high, moderate, low*
Anibarro, 2012[115] [Low]	Low	Low	Low	Moderate	Moderate	High	Low	Moderate ROB
Chang, 2011[117] [High]	Low	Moderate	Low	Moderate	High	High	Low	High ROB
Elzi, 2011[112] [Low]	High	High	Low	Low	Moderate	High	Low	High ROB
Kim, 2011[114] [High]	Low	Low	Low	Low	Low	Moderate	Low	Low ROB
Lee, 2009[116] [High]	Low	High	Low	Low	Moderate	High	Low	High ROB
Lee, 2014[147] [High]	Low	High	Moderate	Moderate	Moderate	Low	Low	Moderate ROB
Moon, 2013[113] [High]	Low	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate ROB
Sherkat, 2014[153] [Intermediate]	Low	High	High	Moderate	High	High	Moderate	High ROB

4.4.2.2 Exposure levels

Of the 24 included exposure studies[118-140, 151] concerning immunocompromised patients identified since CG117, 19 studies[118, 120-124, 126-134,138-140, 151] were identified as low quality and the remaining 5 studies[119, 125, 135-137] were rated as moderate quality. However, all studies failed to identify blinding of the test results

from exposure and only two studies[124, 137] provided adequate description of exposure. See Table 13 for further details.

Table 13. Summary of quality assessment for the included immunocompromised exposure studies (adapted from Dinnes et al., 2007)[43]

First author, Year, Study ID	**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]#, inadequate or unreported [no]*	**Overall quality score of satisfactory features** [£]
Ahmadinejad, 2013[118] [Intermediate]	Yes	No	No	No	No	Low quality
Al Jahdali, 2013[119] [Low]	Yes	No	Yes	No	Yes	Moderate quality
Ates, 2009[120] [Intermediate]	No	No	No	No	No	Low quality
Casas, 2011a[121] [Low]	No	No	No	No	Yes	Low quality
Casas, 2011b[122] [Low]	Yes	No	Yes	No	No	Low quality
Chkhartishvili, 2013[123] [High]	No	No	Yes	No	Yes	Low quality
Chung, 2010a[124] [High]	No	No	No	Yes	Yes	Low quality
Costantino, 2013[125] [Low]	Yes	No	Yes	No	Yes	Moderate quality
Hadaya, 2013[126] [Low]	No	No	No	No	Yes	Low quality
Hsia, 2012[127] [Low]	No	No	No	No	Yes	Low quality
Kim, 2010[128] [High]	Yes	No	No	No	Yes	Low quality
Kim, 2013b[129] [High]	No	No	Yes	No	Yes	Low quality
Kim, 2013c[130] [High]	No	No	Yes	No	No	Low quality
Kleinert, 2012[131] [Low]	No	No	No	No	Yes	Low quality
Laffitte, 2009[132] [Low]	Yes	No	No	No	Yes	Low quality
Maritsi, 2011[133] [Low]	Yes	No	No	No	No	Low quality
Mutsvangwa, 2010[134] [High]	No	No	No	No	Yes	Low quality
Papay, 2011[135] [Low]	Yes	No	Yes	No	Yes	Moderate quality

First author, Year, Study ID	**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]#, inadequate or unreported [no]*	**Overall quality score of satisfactory features** [£]
Ramos, 2013[136] [Low]	Yes	No	Yes	No	Yes	Moderate quality
Seyhan, 2010[137] [Intermediate]	No	No	Yes	Yes	Yes	Moderate quality
Shen, 2012[138] [High]	No	No	Yes	No	Yes	Low quality
Souza, 2014[151] [intermediate]	Yes	Yes	No	No	No	Low quality
Takeda, 2011[139] [Low]	No	No	Yes	No	Yes	Low quality
Vassilopoulos, 2011[140] [Low]	Yes	No	No	No	Yes	Low quality

[#] ≥ 90% of participants were included in the follow-up analysis [yes response] and < 90% were classified as "no response"

[£] Studies with 1 or 2 "yes" ratings = Low quality; studies with 3 "yes" ratings = Moderate quality; studies with 4 or 5 "yes" ratings = High quality

Please note the following item has been removed from the original Dinnes et al., (2007)[43]checklist: "study design" (as all studies were considered are retrospective), this item has been removed. Furthermore, the following item has been added: "sample attrition"

4.4.3 Comparative performance of tests (diagnostic accuracy indices for identifying LTBI)

4.4.3.1 Incidence of active TB

4.4.3.1.1 Ratios of cumulative incidence ratios (R-CIRs):

This section included eight newly identified studies.[112-117 147, 153] For six of the eight studies,[112, 114, 115, 117, 147, 153] R-CIRs were not available due to zero events and/or unreported incidence data for either or both compared tests. Therefore, MA of R-CIRs could not be performed. Only two studies (in stem cell transplant candidates and haemodialysis/end stage renal disease) reported sufficient data for calculating R-CIRs and these were not combined because of different clinical conditions and TST thresholds.[113, 116] (see Table 14). In both of these studies the reported R-CIRs comparing IGRAs (QFT-G/GIT or T-SPOT.TB) with TST were not statistically significant (with 95% CIs), rendering these results as inconclusive. Only one study,[147] showed that QFT-GIT performed better than TST (at 5mm or 10mm threshold) in identifying people with LTBI (incidence of active TB in QFT-GIT positives vs. TST positives: 11.54% vs. 0.0%).

Table 14. Comparison of the test performance - diagnostic accuracy indices for identifying LTBI (incidence studies)

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
Anibarro, 2012[115] Spain [Low]	**N test results** QFT-GIT: 52 TST: 52 **Test (+/-)** QFT-GIT (18/34) TST≥ 5 mm (11/41) **N indeterminate** QFT-GIT: 0 TST: 0 **N lost to follow-up** 4	**QFT (GIT)** SN: NA SP: NA PPV: NA NPV: 100 (89.28, 100)	**TST ≥ 5 mm** SN: NA SP: NA PPV: NA NPV: 100 (89.28, 100)	**QFT (GIT)** CI (+): NA CI (-): 0/32 (0.00) CIR: NA IDR (+): NR IDR (-): NR IDRR: NA	**TST ≥ 5 mm** CI (+):NA CI (-): 0/32 (0.00) CIR: NA IDR (+): NR IDR (-): NR IDRR: NA	**R-CIR [QFT (GIT)] vs. TST ≥ 5 mm** NA **R-IDRR [QFT (GIT)] vs. TST ≥ 5 mm** NA
Chang, 2011[117] South Korea [High]	**N test results** QFT-GIT: 100 TST: 107 **Test (+/-)** QFT-GIT (36/64) TST≥10 mm (36/71) **N indeterminate** QFT-GIT: 7	**QFT (GIT)** SN: NA SP: 100 (94.8, 100) PPV: NA NPV: 100 (94.8, 100)	**TST ≥ 10 mm** SN: NA SP: 77.14 (66.05, 85.41) PPV: 0/16 (0.0) NPV: 100 (93.4, 100)	**QFT (GIT)** CI (+): NA CI (-): 0/64 (0.00) CIR: NA IDR (+): NR IDR (-): NR IDRR: NR	**TST ≥ 10 mm** CI (+): 0/16 (0.00) CI (-): 0/54 (0.00) CIR: NA IDR (+): NR IDR (-): NR IDRR: NR	**R-CIR [QFT (GIT)] vs. TST ≥ 10 mm** NA **R-IDRR [QFT (GIT)] vs. TST ≥ 10 mm** NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	TST: 0 **N lost to follow-up** 0					
Elzi, 2011[112] Switzerland [Low]	**N test results** T-SPOT: 43 TST: 44 **Test (+/-)** T-SPOT (25/18) TST≥ 5 mm (22/22) **N indeterminate** T-SPOT: 21 TST: 0 **N lost to follow-up** NR	**T-SPOT** SN: 58.14 (43.33, 71.62) SP: NA PPV: NA NPV: NA **T-SPOT and TST ≥ 5 mm** SN: 65.91 (51.14, 78.12) SP: NA PPV: NA NPV: NA	**TST ≥ 5 mm** SN: 50.00 (35.83, 64.17) SP: NA PPV: NA NPV: NA	**T-SPOT** CI (+): NA CI (-): NA CIR: NA IDR (+): NA IDR (-): NA IDRR: NA **T-SPOT and TST ≥ 5 mm** CI (+): NA CI (-): NA CIR: NA IDR (+): NA IDR (-): NA IDRR: NA	**TST ≥ 5 mm** CI (+): NA CI (-): NA CIR: NA IDR (+): NA IDR (-): NA IDRR: NA	**R-CIR (T-SPOT) vs. TST ≥ 5 mm** NA **R-IDRR (T-SPOT) vs. TST ≥ 5 mm** NA **R-CIR (T-SPOT and TST) vs. TST ≥ 5 mm** NA **R-IDRR (T-SPOT and TST) vs. TST ≥ 5 mm** NA
Kim, 2011[114] South Korea [High]	**N test results** T-SPOT: 242 TST: 272 **Test (+/-)** T-SPOT (71/171) TST≥ 10 mm (0/272)	**T-SPOT** SN: 100 (51.01, 100.00) SP: 71.84 (65.82, 77.18) PPV: 5.63 (2.21, 13.61) NPV: 100 (97.80, 100)	**TST ≥ 10 mm** SN: NA SP: NA PPV: NA NPV: 98.53 (96.28, 99.43)	**T-SPOT** CI (+): 5.63 (2.21, 13.61) CI (-): 0/171 (0.0) CIR: NA IDR (+):3.28/100 p-y (0.89, 8.39) IDR (-): 0.00/100 p-y	**TST ≥ 10 mm** CI (+): NA CI (-): 1.47 (0.43, 3.85) CIR: NA IDR (+): NA IDR (-): 0.83/100 p-y (0.23, 2.12) IDRR: NA	**R-CIR (T-SPOT) vs. TST ≥ 10 mm** NA **R-IDRR (T-SPOT) vs. TST ≥ 10 mm** NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	N indeterminate T-SPOT: 30 TST: 0 **N lost to follow-up** 2			(NR) IDR difference: 3.3/100 p-y (1.3, 5.3)		
Lee, 2009[116] Taiwan [High]	**N test results** QFT-G: 30 T-SPOT: 32 TST: 32 **Test (+/-)** QFT-G (12/18) T-SPOT (15/17) TST≥ 10 mm (20/12) **N indeterminate** QFT-G: 2 T-SPOT: 0 TST: 0 **N lost to follow-up** 0	**QFT (G)** SN: 100 (20.65, 100) SP: 60.00 (44.00, 77.31) PPV: 8.33 (1.49, 35.39) NPV: 100 (82.41, 100) **T-SPOT** SN: 0.00 (0.00, 65.76) SP: 50.00 (33.15, 66.85) PPV: 0.00 (0.00, 20.39) NPV: 88.24 (65.66, 96.71)	**TST ≥ 10 mm (two-step)** SN: 50.00 (9.45, 90.55) SP: 36.67 (21.87, 54.49) PPV: 5.00 (0.89, 23.61) NPV: 100 (74.12, 100)	**QFT (G)** CI (+): 8.33 (1.49, 35.39) CI (-): 5.56 (5.40, 27.29) CIR: 1.55 (0.02, 124.2) IDR (+): 3.40 per 100/p-y (NR) IDR (-): NR IDRR: NA **T-SPOT** CI (+): 6.67 (0.17, 31.9) CI (-): 11.76 (2.03, 35.59) CIR: 0.57 (0.01, 12.1) IDR (+): NR IDR (-): NR IDRR: NA	**TST ≥ 10 mm (two-step)** CI (+): 5.00 (0.89, 23.61) CI (-): 9.09 (0.23, 41.3) CIR: 0.55 (0.01, 47.06) IDR (+): NR IDR (-): NR IDRR: NA	**R-CIR [QFT (G)] vs. TST ≥ 10 mm (two-step)** 2.82 (95% CI: 0.13, 62.64) **R-IDRR [QFT (G)] vs. TST ≥ 10 mm (two-step)** NA **R-CIR (T-SPOT) vs. TST ≥ 10 mm (two-step)** 1.04 (95% CI: 0.06, 17.34) **R-IDRR (T-SPOT) vs. TST ≥ 10 mm (two-step)** NA
Lee, 2014[147]	**N test results**	**QFT (GIT)**	**TST ≥ 5 mm**	**QFT (GIT)**	**TST ≥ 5 mm**	**R-CIR [QFT**

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
South Korea [High]	QFT-GIT: 159 TST: 169 **Test (+/-)** QFT-GIT (26/133) TST≥ 5 mm (19/150) TST≥10 mm (12/157) **N indeterminate** QFT-GIT: 10 TST: 0 **N lost to follow-up:** 0	SN: 60.00 (23.07, 88.24) SP: 85.06 (78.59, 89.84) PPV: 11.54 (4.00, 28.98) NPV: 98.5 (94.68, 99.59)	SN: 0.0 (0.0, 43.45) SP: 88.41 (82.61, 92.46) PPV: 0.0 (0.0, 16.82) NPV: 96.67 (92.43, 98.57) **TST ≥ 10 mm** SN: 0.0 (95% CI: 0.0, 43.45) SP: 92.68 (87.65, 95.77) PPV: 0.0% (0.0, 24.25) NPV: 96.82 (92.76, 98.63)	CI (+): 11.54 (3.17, 29.80) CI (-):1.50 (0.07, 5.66) CIR: 7.67 (1.34, 43.67) IDR (+): 5.43 per 100 p-y (1.12, 15.88) IDR (-): 0.80 per 100 p-y (0.10, 2.88) IDRR: 6.78 per 100 p-y (NR)	CI (+): 0.0 (0.0, 19.79) CI (-): 3.33 (1.22, 7.77) CIR: 0.0 IDR (+): 0 per 100 p-y (0.00, 8.41) IDR (-): 1.79 per 100 p-y (0.58, 4.18) IDRR: 0 per 100 p-y (NR) **TST ≥ 10 mm** CI (+): 0.0 (0.0, 28.20) CI (-): 3.18 (1.16, 7.43) CIR: 0.0 IDR (+): 0.0 per 100 p-y (0.0, 14.93) IDR (-): NR IDRR: NA	**(GIT)] vs. TST ≥ 5 mm** NA **R-IDRR [QFT (GIT)] vs. TST ≥ 5 mm** NA **R-CIR [QFT (GIT)] vs. TST ≥ 10 mm** NA **R-IDRR [QFT (GIT)] vs. TST ≥ 10 mm** NA
Moon, 2013[113] South Korea [High]	**N test results** QFT-GIT: 210 TST: 244 **Test (+/-)** QFT-GIT (40/170) TST≥ 5 mm (39/205)	**QFT (GIT)** SN: 50.00 (9.45, 90.55) SP: 81.25 (75.4, 85.97) PPV: 2.50 (0.44, 12.88) NPV: 99.41 (96.74, 99.9)	**TST ≥ 5 mm** SN: 0.00 (0.00, 65.76) SP: 83.88 (78.73, 87.98) PPV: 0.00 (0.00, 8.96) NPV: 99.02 (96.51, 99.73)	**QFT (GIT)** CI (+): 2.50 (0.44, 12.88) CI (-): 0.58 (0.00, 3.59) CIR: 4.25 (0.27, 66.49) IDR (+): 2.80/100 p-y (0.07, 15.81) IDR (-): NR	**TST ≥ 5 mm** CI (+): 2.56 (0.06, 13.5) CI (-): 0.97 (0.03, 3.71) CIR: 2.63 (0.04, 51.4) IDR (+): 0/100 p-y (0.00, 8.00) IDR (-): NR	**R-CIR [QFT (GIT)] vs. TST ≥ 5 mm** 1.62 (0.16, 16.18) **R-IDRR [QFT (GIT)] vs. TST ≥ 5 mm** 1.62 (0.16, 16.18)

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	N indeterminate QFT-GIT: 34 TST: 0 **N lost to follow-up** 2			IDRR: NA	IDRR: NA	
Sherkat, 2014 [153] Iran [Intermediate]	**N test results** T-SPOT: 44 TST: 44 **Test (+/-)** T-SPOT (6/38) TST≥ 10 mm (8/36) **N indeterminate** T-SPOT: NR TST: NR **N lost to follow-up:** 1	**T-SPOT** SN: 100 (20.65, 100) SP: 88.37 (75.52, 94.93) PPV: 16.67 (3.00, 56.35) NPV: 100 (90.82, 100)	**TST ≥ 10 mm** SN: 100 (20.65, 100) SP: 83.72 (70.03, 91.88) PPV: 12.5 (2.24, 47.09) NPV: 100 (90.36, 100)	**T-SPOT** CI (+): 16.67 (3.00, 56.35) CI (-): 0.0 (0.00, 10.93) CIR: NA	**TST ≥ 10 mm** CI (+): 12.5 (0.11, 47.09) CI (-): 0.0 (0.00, 11.47) CIR: NA	**R-CIR (T-SPOT) vs. TST ≥ 10 mm** NA

Abbreviations: N = number; SN = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; CI = cumulative incidence; CIR = cumulative incidence ratio; IDR = incidence density rate; IDRR = incidence density rate ratio; TB = tuberculosis; R-CIR = ratio of cumulative incidence ratio; R-IDRR = ratio of incidence density rate ratio; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test; P-Y = person-year(s); 95% CI = 95 percent confidence interval

4.4.3.1.2 Sensitivity and specificity:

This section included eight newly identified studies.[112-117, 147, 153] The study by Anibarro and colleagues did not report test performance parameters of sensitivity and specificity.[115] Across the remaining seven studies, there was a wide variability and the absence of clear pattern in the estimates of sensitivity (IGRA/TST range: 0%-100%) (Figure 25 & Figure 26) and specificity (IGRAs range: 50%-88%; TST range: 37%-93%) (see Figure 27, Figure 28). Some or all of this variation was due to zero count events (unstable estimates), underlying differences in study populations/conditions, and TST thresholds. No meta-analysis was performed given the observed heterogeneity.

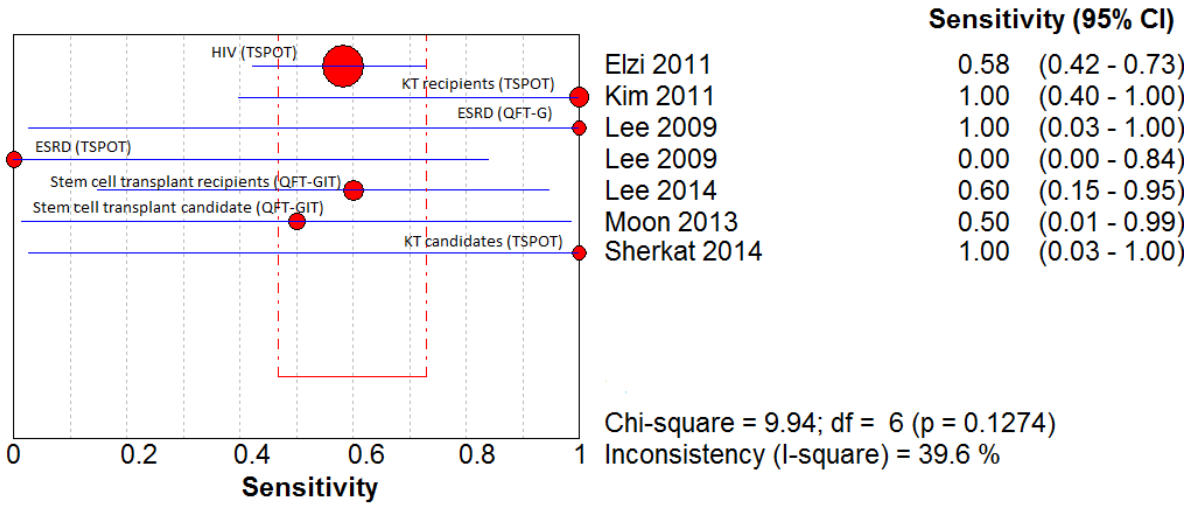


Figure 25. Forest plot of sensitivity based on incidence of active TB (IGRA) in immunocompromised patients

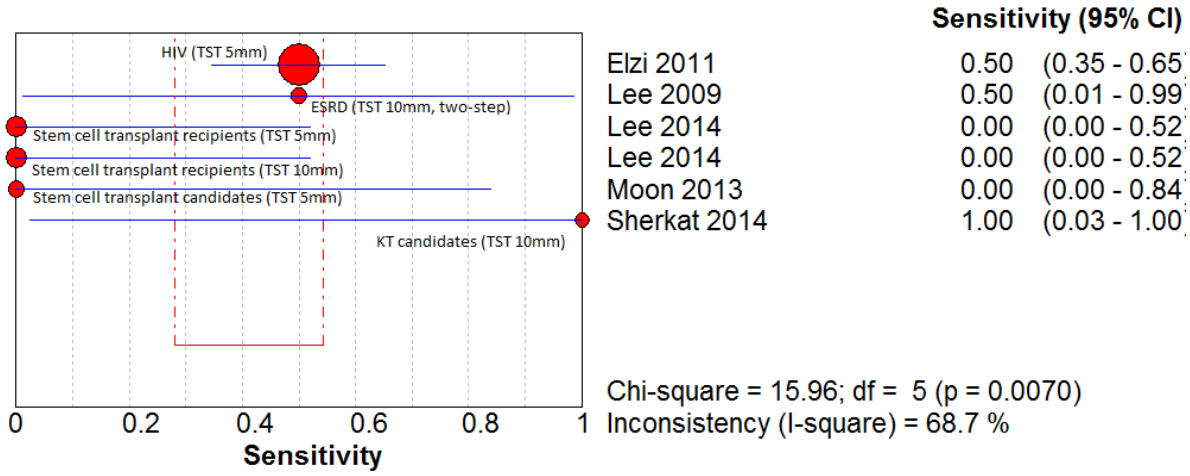


Figure 26. Forest plot of sensitivity based on incidence of active TB (TST) in immunocompromised patients

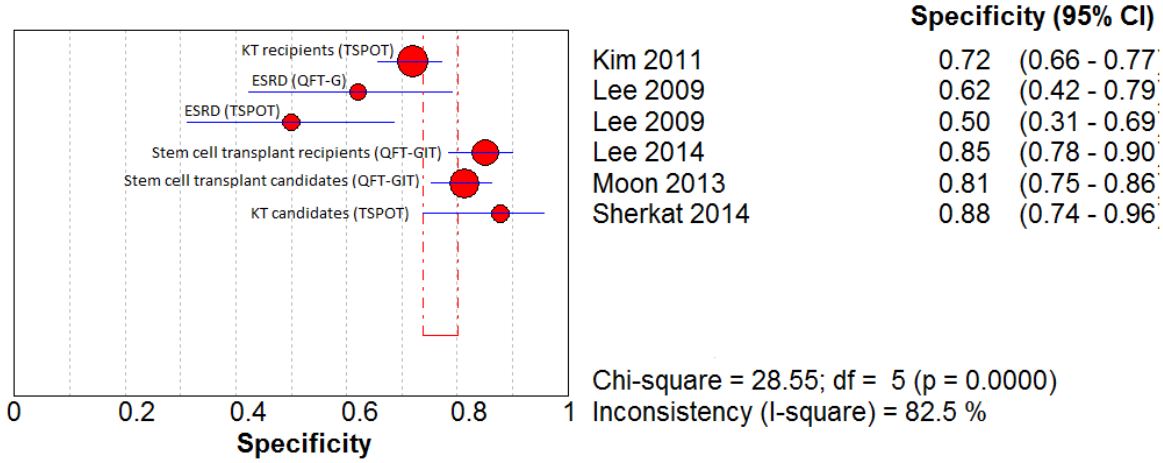


Figure 27. Forest plot of specificity based on incidence of active TB (IGRA) in immunocompromised patients

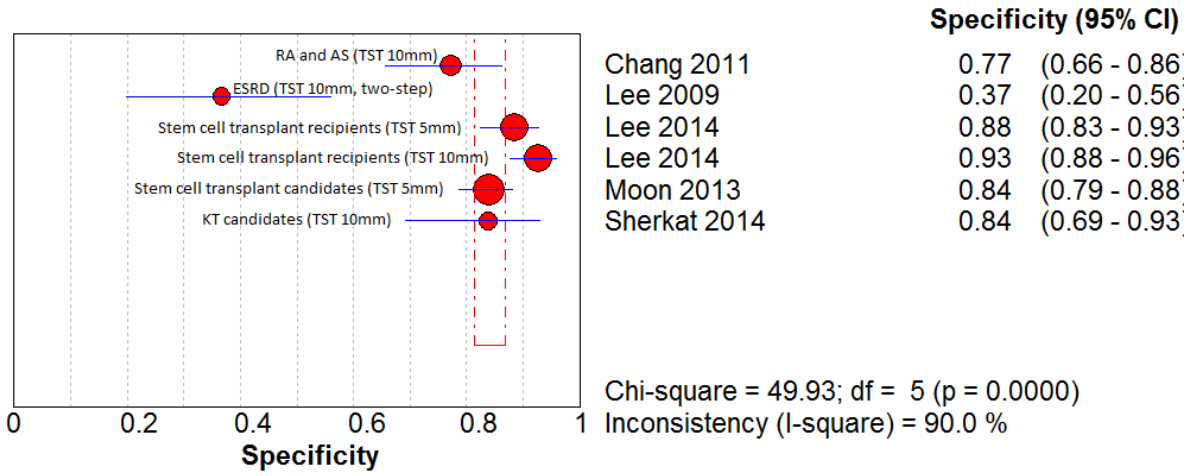


Figure 28. Forest plot of specificity based on incidence of active TB (TST) in immunocompromised patients

4.4.3.2 Exposure levels

4.4.3.2.1 Ratios of diagnostic odds ratios (R-DORs):

This section included 26 studies: two studies from CG117[172, 178] and 24 more recent studies[118-140, 151] (see Table 15). The association between the screening test results and the risk of LTBI/exposure measured using the ratio of diagnostic odds ratios (R-DOR; IGRA vs. TST) in individual studies ranged from 0.07[129] to 8.45.[138] R-DORs for three studies could not be estimated due to missing data.[118, 130, 133]

Table 15. Comparison of the test performance – diagnostic accuracy indices for identifying LTBI (exposure studies)

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
Ahmadinejad, 2013[118] Iran [Intermediate]	**N test results** QFT-GIT: 159 TST: 164 **Test (+/-)** QFT-GIT (33/126) TST≥10 mm (26/138) **N indeterminate** QFT-GIT: 5 TST: 0	**QFT (GIT)** Exposure history to active TB vs. no such history SN: 0.00 SP: 78.57 (71.44, 84.32) PPV: 0.00 NPV: 96.03 (91.05, 98.29)	**TST ≥ 10 mm** Exposure history to active TB vs. no such history SN: 0.00 SP: 83.65 (77.12, 88.59) PPV: 0.00 NPV: 96.38 (91.8, 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: NA R-DORa: NA
Al Jahdali, 2013[119] Saudi Arabia [Low]	**N test results** QFT-GIT: 200 TST: 200 **Test (+/-)** QFT-GIT (65/135) TST≥ 10 mm (26/174) **N indeterminate** QFT-GIT: NR TST: NR	**QFT (GIT)** High likelihood of LTBI vs. no high likelihood of LTBI SN: 33.12 (26.00, 41.00) SP: 69.57 (55.19, 80.92) PPV: 78.46 (67.03, 86.71) NPV: 23.70 (17.32, 31.54)	**TST ≥ 10 mm (two-step)** High likelihood of LTBI vs. no high likelihood of LTBI SN: 12.34 (8.04, 18.47) SP: 84.78 (71.78, 92.43) PPV: 73.08 (53.92, 86.3) NPV: 22.41 (16.85, 29.17)	**QFT (GIT)** High likelihood of LTBI vs. no high likelihood of LTBI DOR: 1.13 (0.55, 2.31) DORa: NR	**TST ≥ 10 mm (two-step)** High likelihood of LTBI vs. no high likelihood of LTBI DOR: 0.78 (0.31, 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, 2.64) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
Ates, 2009[120] Turkey [Intermediate]	**N test results** QFT-GIT: 246 TST: 259 **Test (+/-)** QFT-GIT (115/131) TST≥ 10 mm (92/167) **N indeterminate** QFT-GIT: 29 TST: 16	**QFT (GIT)** TB exposure vs. No TB exposure SN: 58.82 (36.01, 78.39) SP: 54.15 (47.68, 60.48) PPV: 8.69 (4.79, 15.27) NPV: 94.66 (89.38, 97.39)	**TST ≥ 10 mm** TB exposure vs. No TB exposure SN: 29.41 (13.28, 53.13) SP: 64.05 (57.83, 69.83) PPV: 5.43 (2.34, 12.10) NPV: 92.81 (87.86, 95.84)	**QFT (GIT)** TB exposure vs. No TB exposure DOR: 1.68 (0.62, 4.58) DORa: 1.30 (0.43, 3.91)	**TST ≥ 10 mm** TB exposure vs. No TB exposure DOR: 0.74 (0.25, 2.17) DORa: 0.49 (0.17, 1.45)	**QFT-GIT vs. TST ≥ 10 mm** TB exposure vs. No TB exposure R-DOR: 2.27 (1.07, 4.81) R-DORa: 2.65 (1.21, 5.82)
Casas, 2011a[121] Spain [Low]	**N test results** QFT-GIT: 214 TST: 214 **Test (+/-)** QFT-GIT (45/157) TST≥ 5 mm (52/162) **N indeterminate** 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, 5.10) DORa: 2.90 (1.30, 6.30)	**TST ≥ 5 mm** Risk factors for TB infection vs. No Risk factors for TB infection DOR: 2.80 (1.40, 5.50) DORa: 2.90 (1.40, 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, 1.48) R-ORa: 1.00 (0.58, 1.73)
Casas, 2011b[122] Spain [Low]	**N test results** QFT-GIT: 95 TST: 95	**QFT (GIT)** Risk factors for TB infection vs. No Risk	**TST ≥ 5 mm (two-step)** Risk factors for TB infection vs. No Risk	**QFT (GIT)** Risk factors for TB infection vs. No	**TST ≥ 5 mm (two-step)** Risk factors for TB infection vs. No Risk	**QFT-GIT vs. TST ≥ 5 mm (two-step)** Risk factors for TB infection vs. No Risk

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	Test (+/-) QFT-GIT (42/51) TST≥ 5 mm (44/51) **N indeterminate** QFT-GIT: 2 TST: 0	factors for TB infection SN: 45.00 (33.09, 57.51) SP: 57.14 (40.86, 72.02) PPV: 64.29 (49.17, 77.01) NPV: 37.74 (25.94, 51.19)	factors for TB infection SN: 50.00 (37.73, 62.27) SP: 60.00 (43.57, 74.45) PPV: 68.18 (53.44, 80.00) NPV: 41.18 (28.75, 54.83)	Risk factors for TB infection DOR: 1.66 (0.66, 3.33) DORa: 1.50 (0.50, 4.10)	factors for TB infection DOR: 1.25 (0.50, 2.50) DORa: 1.80 (0.60, 5.10)	factors for TB infection R-DOR: 1.33 (0.74, 2.38) R-DORa: 0.83 (0.39, 1.79)
Chkhartishvili, 2013[123] Georgia [High]	**N test results** QFT-GIT: 237 T-SPOT: 218 TST: 236 **Test (+/-)** QFT-GIT (70/167) T-SPOT (56/162) TST≥ 5 mm (41/195) **N indeterminate** QFT-GIT: 3 T-SPOT: 22 TST: 4	**QFT (GIT)** Household member treated for TB vs. No household member treated for TB SN: NR SP: NR PPV: NR NPV: NR **T-SPOT** 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, 1.97) DORa: NR **T-SPOT** Household member treated for TB vs. No household member treated for TB DOR: 1.48 (0.44, 5.00) DORa: NR	**TST ≥5 mm** Household member treated for TB vs. No household member treated for TB DOR: 1.48 (0.39, 5.62) DORa: NR	**QFT-GIT vs. TST ≥ 5 mm** Household member treated for TB vs. No household member treated for TB R-OR: 0.29 (0.10, 0.82) R-ORa: NA **T-SPOT vs. TST ≥ 5 mm** Household member treated for TB vs. No household member treated for TB R-OR: 1.00 (0.40, 2.51) R-ORa: NA
Chung,	**N test results**	**QFT (GIT)**	**TST ≥ 10 mm**	**QFT (GIT)**	**TST ≥ 10 mm**	**QFT-G vs. TST ≥**

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
2010a[124] South Korea [High]	QFT-G: 146 T-SPOT: 146 TST: 146 **Test (+/-)** QFT-G (56/90) T-SPOT (83/63) TST≥ 10 mm (32/114) **N indeterminate** QFT-G: NR T-SPOT: NR TST: NR	High-risk for LTBI vs. low-risk for LTBI SN: 52.94 (30.96, 73.84) SP: 63.57 (54.98, 71.37) PPV: 16.07 (8.69, 27.81) NPV: 91.11 (83.43, 95.43) **T-SPOT** High-risk for LTBI vs. low-risk for LTBI SN: 47.06 (26.16, 69.04) SP: 41.86 (33.70, 50.49) PPV: 9.64 (4.96, 17.88) NPV: 85.71 (75.03, 92.30)	High-risk for LTBI vs. low-risk for LTBI SN: 11.76 (3.28, 34.34) SP: 76.74 (68.75, 83.20) PPV: 6.25 (1.73, 20.15) NPV: 86.84 (79.42, 91.86)	High-risk for LTBI vs. low-risk for LTBI DOR: 1.96 (0.71, 5.43) DORa: NR **T-SPOT** High-risk for LTBI vs. low-risk for LTBI DOR: 0.64 (0.23, 1.76) DORa: NR	High-risk for LTBI vs. low-risk for LTBI DOR: 0.44 (0.09, 2.03) DORa: NR	**10 mm** High-risk for LTBI vs. low-risk for LTBI R-OR: 4.45 (1.72, 11.51) R-DORa: NA **T-SPOT vs. TST ≥ 10 mm** High-risk for LTBI vs. low-risk for LTBI R-DOR: 1.45 (0.56, 3.76) R-DORa: NA
Costantino, 2013[125] France [Low]	**N test results** T-SPOT: 475 TST: 514 **Test (+/-)** T-SPOT (122/353) TST≥ 5 mm (196/318)	**T-SPOT** Conventional risk factors for LTBI vs. no risk factors for LTBI SN: 47.92 (34.47, 61.67) SP: 76.81 (72.58, 80.57)	**TST ≥ 5 mm** Conventional risk factors for LTBI vs. no risk factors for LTBI SN: 63.27 (49.27, 75.34) SP: 64.52 (60.06, 68.73)	**T-SPOT** Conventional risk factors for LTBI vs. no risk factors for LTBI DOR: 3.05 (1.65, 5.60) DORa: 2.70 (1.49,	**TST ≥ 5 mm** Conventional risk factors for LTBI vs. no risk factors for LTBI DOR: 3.13 (1.70, 5.77) DORa: 1.95 (1.13,	**T-SPOT vs. TST ≥ 5 mm** Conventional risk factors for LTBI vs. no risk factors for LTBI R-DOR: 0.97 (0.63, 1.51) R-DORa: 1.38 (0.92,

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	N indeterminate T-SPOT: 88 TST: 49	PPV: 18.85 (12.9, 26.70) NPV: 92.92 (89.75, 95.16)	PPV: 15.82 (11.37, 21.58) NPV: 94.34 (91.23, 96.39)	4.89)	3.36)	2.09)
Hadaya, 2013[126] Switzerland [Low]	**N test results** QFT-GIT: 202 T-SPOT: 203 TST: 200 **Test (+/-)** QFT-GIT (47/155) T-SPOT (41/162) TST≥ 5 mm (9/191) **N indeterminate** QFT-GIT: 3 T-SPOT: 2 TST: 0	**QFT (GIT)** Risk for LTBI vs. No risk for LTBI SN: 33.30 (19.60, 49.50) SP: 80.10 (72.90, 86.20) PPV: NR NPV: 81.10 (73.80, 87.00) **T-SPOT** SN: 33.30 (19.60, 49.50) SP: 85.50 (78.90, 90.70) PPV: NR NPV: 81.90 (75.00, 87.60)	**TST ≥5 mm** Risk for LTBI vs. No risk for LTBI SN: 7.10 (1.50, 19.50) SP: 95.50 (90.80, 98.20) PPV: NR NPV: 78.40 (71.70, 84.20)	**QFT (GIT)** Risk for LTBI vs. No risk for LTBI DOR: 2.01 (1.25, 2.76) DORa: NR **T-SPOT** Risk for LTBI vs. No risk for LTBI DOR: 3.02 (1.36, 6.71) DORa: NR	**TST ≥ 5 mm** Risk for LTBI vs. No risk for LTBI DOR: 1.73 (0.41, 7.24) DORa: NR	**QFT-GIT vs. TST ≥ 5 mm** Risk for LTBI vs. No risk for LTBI R-DOR: 1.16 (0.51, 2.66) R-DORa: NA **T-SPOT vs. TST ≥ 5 mm** Risk for LTBI vs. No risk for LTBI R-DOR: 1.75 (0.76, 4.04) R-DORa: NA
Hsia, 2012[127] USA [Low]	**N test results** QFT-GIT: 2241 TST: 2282 **Test (+/-)** QFT-GIT (160/2081)	**QFT (GIT)** Geographic study location SN: NR SP: NR PPV: NR NPV: NR	**TST ≥ 5 mm** Geographic study location SN: NR SP: NR PPV: NR NPV: NR	**QFT (GIT)** Western Europe vs. North America DOR: NR DORa: 3.41 (1.99, 5.83)	**TST ≥ 5 mm** Western Europe vs. North America DOR: NR DORa: 2.10 (1.30, 3.38)	**QFT-GIT vs. TST ≥5 mm** Western Europe vs. North America R-DOR: NA R-DORa:1.62 (1.13, 2.34)

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	TST≥ 5 mm (215/2067) **N indeterminate** QFT-GIT: 41 TST: 0			Latin America vs. North America DOR: NR DORa: 3.43 (1.64, 7.19) Eastern Europe vs. North America DOR: NR DORa: 3.58 (1.93, 6.63) Asia vs. North America DOR: NR DORa: 8.48 (4.78, 15.03)	Latin America vs. North America DOR: NR DORa: 1.56 (0.80, 3.05) Eastern Europe vs. North America DOR: NR DORa: 0.95 (0.53, 1.70) Asia vs. North America DOR: NR DORa: 7.47 (4.61, 12.08)	Latin America vs. North America R-DOR: NA R-DORa: 2.20 (1.32, 3.66) Eastern Europe vs. North America R-DOR: NA R-DORa: 3.77 (2.44, 5.81) Asia vs. North America R-DOR: NA R-DORa: 1.14 (0.77, 1.66)
Kim, 2010[128] South Korea [Low]	**N test results** T-SPOT: 184 TST≥5mm: 209 TST≥10mm:209 **Test (+/-)** T-SPOT (65/119) TST≥ 5mm (47/162) TST ≥ 10mm (21/188) **N indeterminate** T-SPOT: 25	**T-SPOT** Risk group for LTBI vs. No risk group for LTBI SN: 52.63 (31.71, 72.67) SP: 66.67 (59.17, 73.41) PPV: 15.38 (8.57, 26.06) NPV: 92.44 (86.25, 95.97)	**TST ≥ 5 mm** Risk group for LTBI vs. No risk group for LTBI SN: 36.36 (19.73, 57.05) SP: 79.14 (72.76, 84.35) PPV: 17.02 (8.88, 30.14) NPV: 91.36 (86.02, 94.78)	**T-SPOT** Risk group for LTBI vs. No risk group for LTBI DOR: 2.35 (0.90, 6.12) DORa: 2.38 (0.87, 6.52)	**TST ≥ 5 mm** Risk group for LTBI vs. No risk group for LTBI DOR: 2.17 (0.85, 5.54) DORa: 2.11 (0.82, 5.46) **TST ≥ 10 mm** Risk group for LTBI vs. No risk group for LTBI	**T-SPOT vs. TST ≥ 5 mm** Risk group for LTBI vs. No risk group for LTBI R-DOR: 1.02 (0.52, 2.03) R-DORa: 1.08 (0.55, 2.15) **T-SPOT vs. TST ≥ 10 mm** Risk group for LTBI vs. No risk group for

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	TST≥5mm: 0 TST≥10mm: 0		**TST ≥10 mm** Risk group for LTBI vs. No risk group for LTBI SN: 18.18 (7.31, 38.52) SP: 90.91 (85.92, 94.25) PPV: 19.05 (7.66, 40.00) NPV: 90.43 (85.37, 93.86)		DOR: 2.22 (0.67, 7.32) DORa: 2.12 (0.60, 7.49)	LTBI R-DOR: 1.00 (0.46, 2.19) R-DORa: 1.06 (0.48, 2.31)
Kim, 2013b[129] South Korea [High]	**N test results** QFT-GIT: 120 TST: 119 **Test (+/-)** QFT-GIT (53/67) TST≥10 mm (35/91) **N indeterminate** QFT-GIT: 6 TST: 7	**QFT (GIT)** Risk group for LTBI vs. No risk group for LTBI SN: 73.33 (48.05, 89.1) SP: 60.00 (50.44, 68.86) PPV: 20.75 (12.00, 33.46) NPV: 94.03 (85.63, 97.65)	**TST ≥ 10 mm** Risk group for LTBI vs. No risk group for LTBI SN: 86.67 (62.12, 96.26) SP: 90.38 (83.2, 94.69) PPV: 56.52 (36.81, 74.37) NPV: 97.92 (92.72, 99.43)	**QFT (GIT)** Risk group for LTBI vs. No risk group for LTBI DOR: 4.13 (1.23, 13.82) DORa: 4.62 (1.15, 18.64)	**TST ≥ 10 mm** Risk group for LTBI vs. No risk group for LTBI DOR: 61.1 (12.03, 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, 0.19) R-DORa: NA
Kim, 2013c[130] South Korea [High]	**N test results** QFT-GIT: 102 TST: 93 **Test (+/-)** QFT-GIT (21/81)	**QFT (GIT)** History of treated tuberculosis vs. no such history SN: 100 (34.24, 100)	**TST ≥ 10 mm** History of treated tuberculosis vs. no such history SN: NR	**QFT (GIT)** History of treated tuberculosis vs. no such history DOR: NR	**TST ≥ 10 mm** History of treated tuberculosis vs. no such history DOR: NR	**QFT-GIT vs. TST ≥ 10 mm** History of treated tuberculosis vs. no such history R-DOR: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	TST≥ 10 mm (12/81) **N indeterminate** QFT-GIT: 4 TST: 0	SP: 81.32 (72.10, 88.00) PPV: 10.53 (2.93, 31.39) NPV: 100 (95.06, 100) Abnormal chest radiograph vs. No abnormal chest radiograph SN: 75.00 (30.06, 95.44) SP: 82.02 (72.77, 88.62) PPV: 15.79 (5.52, 37.57) NPV: 98.65 (92.73, 99.76)	SP: NR PPV: NR NPV: NR Abnormal chest radiograph vs. No abnormal chest radiograph SN: NR SP: NR PPV: NR NPV: NR	DORa: 9.21 (NR) Abnormal chest radiograph vs. No abnormal chest radiograph DOR: 13.69 (1.33, 140.30) DORa: 27.95 (1.22, 636.62)	DORa: NR (NS) Abnormal chest radiograph vs. No abnormal chest radiograph DOR: NR DORa: NR (NS)	R-DORa: NA Abnormal chest radiograph vs. No abnormal chest radiograph R-DOR: NA R-DORa: NA
Kleinert, 2012[131] Germany [Low]	**N test results** QFT-G: 685 T-SPOT: 844 TST: 1529 **Test (+/-)** QFT-G (50/635) T-SPOT (70/774) TST≥ 5 mm (173/1356) **N indeterminate** QFT-G + T-	**QFT (G)** Presence of compound risk factor vs. Absence of compound risk factor SN: 16.67 (9.02, 28.74) SP: 93.5 (91.3, 95.17) PPV: 18.00 (9.77, 30.8) NPV: 92.91 (90.65, 94.66)	**TST ≥ 5 mm** Presence of compound risk factor vs. Absence of compound risk factor SN: 39.34 (31.13, 48.21) SP: 91.12 (89.52, 92.49) PPV: 27.75 (21.61, 34.85) NPV: 94.54 (93.2,	**QFT (G)** Presence of compound risk factor vs. Absence of compound risk factor DOR: 2.88 (1.31, 6.29) DORa: 2.63 (1.15, 5.98)	**TST ≥ 5 mm** Presence of compound risk factor vs. Absence of compound risk factor DOR: 6.65 (4.42, 9.99) DORa: 6.20 (4.08, 9.44)	**QFT-G vs. TST ≥ 10 mm** Presence of compound risk factor vs. Absence of compound risk factor R-DOR: 0.43 (0.28, 0.68) R-DORa: 0.42 (0.26, 0.68)

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	SPOT: 80 TST: NR	**T-SPOT** Presence of compound risk factor vs. Absence of compound risk factor SN: 35.29 (25.00, 47.16) SP: 94.07 (92.18, 95.53) PPV: 34.29 (24.25, 45.96) NPV: 94.32 (92.45, 95.74)	95.63)	**T-SPOT** Presence of compound risk factor vs. Absence of compound risk factor DOR: 8.65 (4.84, 15.46) DORa: 8.74 (4.83, 15.82)		**T-SPOT vs. TST ≥ 10 mm** Presence of compound risk factor vs. Absence of compound risk factor R-DOR: 1.30 (0.91, 1.87) R-DORa: 1.41 (0.97, 2.04)
Laffitte, 2009[132] Switzerland [Low]	**N test results** T-SPOT: 50 TST≥ 5 mm: 50 TST≥ 10 mm:50 **Test (+/-)** T-SPOT (10/40) TST≥ 5 mm (20/30) TST ≥ 10 mm (18/32) **N indeterminate** T-SPOT: NR TST≥ 5 mm: NR TST≥ 10 mm: NR	**T-SPOT** Probable LTBI vs. No probable LTBI SN: 36.36 (19.73, 57.05) SP: 92.86 (77.35, 98.02) PPV: 80.00 (49.02, 94.33) NPV: 65.00 (49.51, 77.87)	**TST ≥ 5 mm** Probable LTBI vs. No probable LTBI SN: 50.00 (30.72, 69.28) SP: 67.86 (49.34, 82.07) PPV: 55.00 (34.21, 74.18) NPV: 63.33 (45.51, 78.13) **TST ≥ 10 mm** Probable LTBI vs. No probable LTBI SN: 54.55 (34.66, 73.08)	**T-SPOT** Probable LTBI vs. No probable LTBI DOR: 7.43 (1.38, 39.90) DORa: NR	**TST ≥ 5 mm** Probable LTBI vs. No probable LTBI DOR: 3.00 (0.93, 9.70) DORa: NR **TST ≥10 mm** Probable LTBI vs. No probable LTBI DOR: 2.08 (0.64, 6.73) DORa: NR	**T-SPOT vs. TST ≥ 5 mm** Probable LTBI vs. No probable LTBI R-DOR: 3.52 (1.25, 9.96) R-DORa: NA **T-SPOT vs. TST ≥ 10 mm** Probable LTBI vs. No probable LTBI R-DOR: 1.69 (0.58, 4.89) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
			SP: 78.57 (60.46, 89.79) PPV: 66.67 (43.75, 83.72) NPV: 68.75 (51.43, 82.05)			
Maritsi, 2011[133] UK [Low]	**N test results** QFT-GIT: 23 TST: 14 **Test (+/-)** QFT-GIT (1/20) TST≥ NR mm (0/14) **N indeterminate** QFT-GIT: 2 TST: 0	**QFT (GIT)** High-risk group vs. Low risk group SN: 33.33 (6.15, 79.23) SP: 100 (82.41, 100) PPV: 100 (20.65, 100) NPV: 90.00 (69.9, 97.21)	**TST ≥ NR mm** High-risk group vs. Low risk group SN: 0.00 (0.00, 56.15) SP: 100 (74.12, 100) PPV: NA NPV: 78.57 (52.41, 92.43)	**QFT (GIT)** High-risk group vs. Low risk group DOR: NA DORa: NA	**TST ≥ NR mm** High-risk group vs. Low risk group DOR: NA DORa: NA	**QFT-GIT vs. TST≥NR mm** High-risk group vs. Low risk group R-DOR: NA R-DORa: NA
Mutsvangwa, 2010[134] Zimbabwe [High]	**N test results** T-SPOT: 73 TST: 73 **Test (+/-)** T-SPOT (22/51) TST≥ 10 mm (33/40) **N indeterminate** T-SPOT: NR TST: NR	**T-SPOT** Contact of index TB case vs. contact of index control SN: 34.55 (23.36, 47.75) SP: 83.33 (60.78, 94.16) PPV: 86.36 (66.66, 95.25) NPV: 29.41 (18.71,	**TST ≥10 mm (two-step)** Contact of index TB case vs. contact of index control SN: 49.09 (36.38, 61.92) SP: 66.67 (43.75, 83.72) PPV: 81.82 (65.61, 91.39) NPV: 30.00 (18.07,	**T-SPOT** Contact of index TB case vs. contact of index control DOR: 2.64 (0.67, 10.27) DORa: NR	**TST ≥ 10 mm (two-step)** Contact of index TB case vs. contact of index control DOR: 1.93 (0.63, 5.87) DORa: NR	**T-SPOT vs. TST ≥ 10 mm (two-step)** Contact of index TB case vs. contact of index R-DOR: 1.37 (0.56, 3.36) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
		43.0) Smear status of index case (Smear-, culture + vs. Smear-, culture -) SN: NR SP: NR PPV: NR NPV: NR Smear status of index case (Smear +, culture + vs. Smear-, culture -) SN: NR SP: NR PPV: NR NPV: NR	45.43) Smear status of index case (Smear-, culture + vs. Smear-, culture -) SN: NR SP: NR PPV: NR NPV: NR Smear status of index case (Smear +, culture + vs. Smear-, culture -) SN: NR SP: NR PPV: NR NPV: NR	Smear status of index case (Smear-, culture + vs. Smear-, culture -) DOR: 1.60 (0.20, 12.69) DORa: 1.87 (0.22, 16.16) Smear status of index case (Smear +, culture + vs. Smear-, culture -) DOR: 4.80 (1.05, 21.91) DORa: 5.36 (1.11, 25.93)	Smear status of index case (Smear-, culture + vs. Smear-, culture -) DOR: 1.50 (0.24, 9.46) DORa: 1.09 (0.13, 9.42) Smear status of index case (Smear +, culture + vs. Smear-, culture -) DOR: 3.50 (0.88, 13.93) DORa: 3.43 (0.76 to 15.52)	Smear status of index case (Smear-, culture + vs. Smear-, culture -) R-DOR: 1.07 (0.26, 4.39) R-DORa: 1.72 (0.36, 8.06) Smear status of index case (Smear +, culture + vs. Smear-, culture -) R-DOR: 1.37 (0.48, 3.91) R-DORa: 1.56 (0.51, 4.76)
Papay, 2011[135] Austria [Low]	**N test results** QFT-GIT: 192 TST: 192 **Test (+/-)** QFT-GIT/G (15/177) TST≥ 5 mm (26/166) **N indeterminate**	**QFT (GIT)** Presence of risk factors vs absence of risk factors SN: 13.85 (7.45, 24.27) SP: 95.28 (90.08, 97.82) PPV: 60.00 (35.75, 80.18)	**TST ≥ 5 mm** Presence of risk factors vs absence of risk factors SN: 21.74 (13.64, 32.82) SP: 92.09 (86.38, 95.52) PPV: 57.69 (38.95, 74.46)	**QFT (GIT)** Presence of risk factors vs absence of risk factors DOR: 3.24 (1.10, 9.54) DORa: NR	**TST ≥ 5 mm** Presence of risk factors vs absence of risk factors DOR: 3.23 (1.39, 7.49) DORa: NR	**QFT-GIT vs. TST ≥ 5 mm** Presence of risk factors vs absence of risk factors R-DOR: 1.00 (0.50, 2.02) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	QFT-GIT/G: 0 TST: 0	NPV: 68.36 (61.18, 74.76) Origin from a high-incidence country vs origin from a low-incidence country SN: 14.29 (5.69, 31.49) SP: 93.29 (88.39, 96.21) PPV: 26.67 (10.9, 51.95) NPV: 86.44 (80.62, 90.72) History of contact with index case vs no history of contact SN: 20.00 (5.668, 50.98) SP: 92.86 (88.16, 95.78) PPV: 13.33 (3.736, 37.88) NPV: 95.48 (91.34, 97.69)	NPV: 70.33 (63.33, 76.49) Origin from a high-incidence country vs origin from a low-incidence country SN: 37.93 (22.69, 56) SP: 91.62 (86.64, 94.86) PPV: 42.31 (25.54, 61.05) NPV: 90.11 (84.91, 93.65) History of contact with index case vs no history of contact SN: 36.36 (15.17, 64.62) SP: 88.83 (83.67, 92.51) PPV: 15.38 (6.15, 33.53) NPV: 96.15 (92.27, 98.12)	Origin from a high-incidence country vs origin from a low-incidence country DOR: 2.32 (0.68, 7.87) DORa: NR History of contact with index case vs no history of contact DOR: 3.25 (0.62, 16.91) DORa: NR	Origin from a high-incidence country vs origin from a low-incidence country DOR: 6.68 (2.67, 16.73) DORa: NR History of contact with index case vs no history of contact DOR: 4.54 (1.23, 16.78) DORa: NR	Origin from a high-incidence country vs origin from a low-incidence country R-DOR: 0.35 (0.16, 0.76) R-DORa: NA History of contact with index case vs no history of contact R-DOR: 0.72 (0.24, 2.10) R-DORa: NA
Ramos, 2013[136] Spain [Low]	**N test results** QFT-GIT: 153 TST: 153	**QFT (GIT)** Contact of index TB case vs. contact of	**TST ≥ 5 mm** Contact of index TB case vs. contact of	**QFT (GIT)** Contact of index TB case vs. contact	**TST ≥ 5 mm** Contact of index TB case vs. contact of	**QFT-GIT vs. TST ≥ 5 mm** Contact of index TB case vs. contact of

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	Test (+/-) QFT-GIT (15/137) TST≥ 5 mm (43/110) **N indeterminate** QFT-GIT: 1 T-SPOT: 0 TST: 0	index control SN: 42.86 (15.82, 74.95) SP: 91.72 (86.09, 95.20) PPV: 20.00 (7.04, 45.19) NPV: 97.08 (92.73, 98.86) Born in an endemic country vs not born in an endemic country SN: 50.00 (21.52, 78.48) SP: 92.36 (86.84, 95.68) PPV: 26.67 (10.90, 51.95) NPV: 97.08 (92.73, 98.86)	index control SN: 57.14 (25.05, 84.18) SP: 73.29 (65.58, 79.8) PPV: 9.30 (3.67, 21.6) NPV: 97.27 (92.29, 99.07) Born in an endemic country vs not born in an endemic country SN: 50.00 (21.52, 78.48) SP: 73.1 (65.36, 79.66) PPV: 9.30 (3.67, 21.60) NPV: 96.36 (91.02, 98.58)	of index control DOR: 8.31 (1.66, 41.56) DORa: NR Born in an endemic country vs not born in an endemic country DOR: 12.09 (2.65, 55.07) DORa: NR	index control DOR: 3.66 (0.78, 17.08) DORa: NR Born in an endemic country vs not born in an endemic country DOR: 2.72 (0.65, 11.40) DORa: NR	index control R-DOR: 2.27 (0.73, 7.08) R-DORa: NA Born in an endemic country vs not born in an endemic country R-DOR: 4.44 (1.53, 12.89) R-DORa: NA
Seyhan, 2010[137] Turkey [Intermediate]	**N test results** QFT-GIT: 100 TST: 100 **Test (+/-)** QFT-GIT: (43/57) TST≥ 10 mm (34/66) **N indeterminate**	**QFT (GIT)** Previous contact with an index case vs no contact SN: 76.92 (49.74, 91.82) SP: 62.07 (51.57, 71.55) PPV: 23.26 (13.15,	**TST ≥ 10 mm** Previous contact with an index case vs no contact SN: 46.15 (23.21, 70.86) SP: 67.82 (57.43, 76.7) PPV: 17.65 (8.349,	**QFT (GIT)** Previous contact with an index case vs no contact DOR: 5.45 (1.40, 21.27) DORa: NA	**TST ≥ 10 mm** Previous contact with an index case vs no contact DOR: 1.81(0.55, 5.87) DORa: NA	**QFT-GIT vs. TST ≥ 10 mm** Previous contact with an index case vs no contact R-DOR: 3.01 (1.20, 7.56) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	QFT-GIT: NA TST: 0	37.74) NPV: 94.74 CI (85.63, 98.19) Previous TB disease vs no previous disease SN: 75.0 (40.93, 92.85) SP: 59.78 (49.57, 69.22) PPV: 13.95 (6.556, 27.26) NPV: 96.49 (88.08, 99.03)	33.51) NPV: 89.39 (79.69, 94.77) Previous TB disease vs no previous disease SN: 37.5 (13.68, 69.43) SP: 66.3 (56.17, 75.14) PPV: 8.824 (3.047, 22.96) NPV: 92.42 (83.46, 96.72)	Previous TB disease vs no previous disease DOR: 4.46 (0.85, 23.31) DORa: NA	Previous TB disease vs no previous disease DOR: 1.18, (0.26, 5.26) DORa: NA	Previous TB disease vs no previous disease R-DOR: 3.78 (1.21, 11.83) R-DORa: NA
Shen, 2012[138] China [High]	**N test results** T-SPOT: 70 TST: 70 **Test (+/-)** T-SPOT (26/44) TST≥ 5 mm (34/36) **N indeterminate** T-SPOT: 0 TST: 0	**T-SPOT** Suspected TB disease vs no suspected TB SN: 70.97 (53.41, 83.90) SP: 89.74 (76.42, 95.94) PPV: 84.62 (66.47, 93.85) NPV: 79.55 (65.5, 88.85)	**TST ≥ 5 mm** Suspected TB disease vs no suspected TB SN: 61.29 (43.82, 76.27) SP: 61.54 (45.9, 75.11) PPV: 55.88 (39.45, 71.12) NPV: 66.67 (50.33, 79.79)	**T-SPOT** Suspected TB disease vs no suspected TB DOR: 21.39 (5.87, 77.93) DORa: NA	**TST ≥ 5 mm** Suspected TB disease vs no suspected TB DOR: 2.53 (0.96, 6.67) DORa: NA	**T-SPOT vs. TST ≥ 5 mm** Suspected TB disease vs no suspected TB R-DOR: 8.45 (3.71, 19.28) R-DORa: NA
Souza, 2014[151] Brazil [intermediate]	**N test results** QFT-GIT: 299 TST: 300 **Test (+/-)**	**QFT-GIT** History of contact with index case vs. no history of contact with index case	**TST ≥ 5 mm** History of contact with index case vs. no history of contact with index case	**QFT-GIT** History of contact with index case vs. no history of contact with index	**TST ≥ 5 mm** History of contact with index case vs. no history of contact with index case	**QFT-GIT vs. TST ≥ 5 mm** History of contact with index case vs. no history of contact

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	QFT-GIT (14/285) TST≥ 5 mm (10/290) **N indeterminate** QFT-GIT: 1 TST: 0	SN: 0.0 (0.00, 9.89) SP: 94.96 (91.57, 97.03) PPV: 0.0 (0.00, 22.81) NPV: 87.5 (83.11, 90.87)	SN: 2.86 (0.50, 14.53) SP: 96.91 (94.02, 98.43) PPV: 11.11 (1.99, 43.5) NPV: 88.07 (83.79, 91.34)	case DOR: 0.50 (0.06, 4.24) DORa: NR	DOR: 0.93 (0.11, 7.61) DORa: 1.21 (0.13, 11.16)	with index case R-DOR: 0.54 (0.12, 2.49) R-DORa: NA
Takeda, 2011[139] Japan [Low]	**N test results** QFT-GIT: 71 TST: 43 **Test (+/-)** QFT-GIT: (2/46) TST≥ 10 mm (3/40) **N indeterminate** QFT-GIT: 23 T-SPOT: NA TST: 0	**QFT (GIT)** Risk of LTBI vs no risk of LTBI SN: 11.11 (10, 32.80) SP:100.00 (88.65, 100.00) PPV: 100.00 (34.24, 100.00) NPV: 65.22 (53.45, 75.38)	**TST ≥ 10 mm** Risk of LTBI vs no risk of LTBI SN: 7.14 (1.27, 31.47) SP: 93.10 (78.04, 98.09) PPV: 33.33(6.15, 79.23) NPV: 67.50 CI (52.02, 79.92)	**QFT (GIT)** Risk of LTBI vs no risk of LTBI DOR: 3.75 (0.31, 44.6) DORa: NA	**TST ≥ 10 mm** Risk of LTBI vs no risk of LTBI DOR: 1.04 (0.08, 12.53) DORa: NA	**QFT-GIT vs. TST ≥ 10 mm** Risk of LTBI vs no risk of LTBI R-DOR: 3.61 (0.59, 21.99) R-DORa: NA
Vassilopoulos, 2011[140] Greece [Low]	**N test results** QFT-GIT: 157 T-SPOT: 157 TST: 157 **Test (+/-)** QFT-GIT (32/123) T-SPOT (39/116) TST≥ 5 mm	**T-SPOT** TB exposure vs no exposure SN: 25.00 (11.19, 46.87) SP: 74.81 (66.88, 81.38) PPV: 12.82(5.60,	**TST ≥ 5 mm** TB exposure vs no exposure SN: 50.00 (29.93, 70.07) SP: 64.44, (56.07, 72.02 PPV: 17.24 (9.64,	**T-SPOT** TB exposure vs no exposure DOR: 0.99, (0.33, 2.92) DORa: NA	**TST ≥ 5 mm** TB exposure vs no exposure DOR: 1.81 (0.70, 4.66) DORa: NA	**T-SPOT vs. TST ≥ 5 mm** TB exposure vs no exposure R-DOR: 0.55 (0.26, 1.14) R-DORa: NA

Subgroup of interest – immunocompromised people (specify main condition/procedure)						
Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	(58/97) **N indeterminate** QFT-GIT: 2 T-SPOT: 2 TST: 2	26.71) NPV: 87.07 (79.76, 92.00) **QFT (GIT)** TB exposure vs no exposure SN: 15.00 (5.23, 36.04) SP: 78.52 (70.85, 84.61) PPV: 9.37 (3.24, 24.22) NPV: 86.18 (78.98, 91.19)	28.91) NPV: 89.69 (82.05, 94.3)	**QFT (GIT)** TB exposure vs no exposure DOR: 0.64 (0.17, 2.35) DORa: NA		**QFT-GIT vs. TST ≥ 5 mm** TB exposure vs no exposure R-DOR: 0.35 (0.15, 0.81) R-DORa: NA

Abbreviations: N = number; SN = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; DOR = diagnostic odds ratio; DORa = adjusted diagnostic odds ratio; R-DOR = ratio of diagnostic odds ratio; R-DORa = adjusted ratio of diagnostic odds ratio; TB = tuberculosis; 95% CI = 95 percent confidence interval; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test

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

Within-subgroup heterogeneity by IGRA type (QFT-GIT, TSPOT) and TST threshold (5mm, 10mm, 15mm) could not be examined for most subgroups due to 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 (see Figure 30, Figure 31, Figure 32, Figure 33). For example, for participants with immune-mediated inflammatory diseases before anti-TNF-α therapy, the non-uniformity persisted even after accounting for the type of IGRA (QFT-GIT) and TST threshold (5mm) (pooled R-DOR = 0.90, 95% CI: 0.52, 1.54; I^2 = 80%) (see Figure 30). However, the stratification by IGRA type and TST threshold revealed that, TST 5mm was better than IGRA (QFT-GIT) in detecting LTBI in participants with HIV (Pooled R-DOR=0.35, 95% CI: 0.15, 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[128] and QFT-GIT[122]) and TST (5mm) in relation to the identification of LTBI (see Figure 30, Figure 32, and Figure 33). In contrast, in another study of solid organ transplantation candidates, TST 10mm outperformed QFT-GIT (R-DOR=0.07, 95% CI: 0.02, 0.19) (see Figure 30).[129] In two studies, the performance of QFT-GIT did not significantly differ from that of TST among participants with lupus erythematosus (QFT-GIT vs. TST 10mm; R-DOR=3.60, 95% CI: 0.59, 21.96)[139] and kidney transplant recipients (QFT-GIT vs. TST 5mm; R-DOR=1.16, 95% CI: 0.51, 2.66)[126] (see Figure 30, Figure 31).

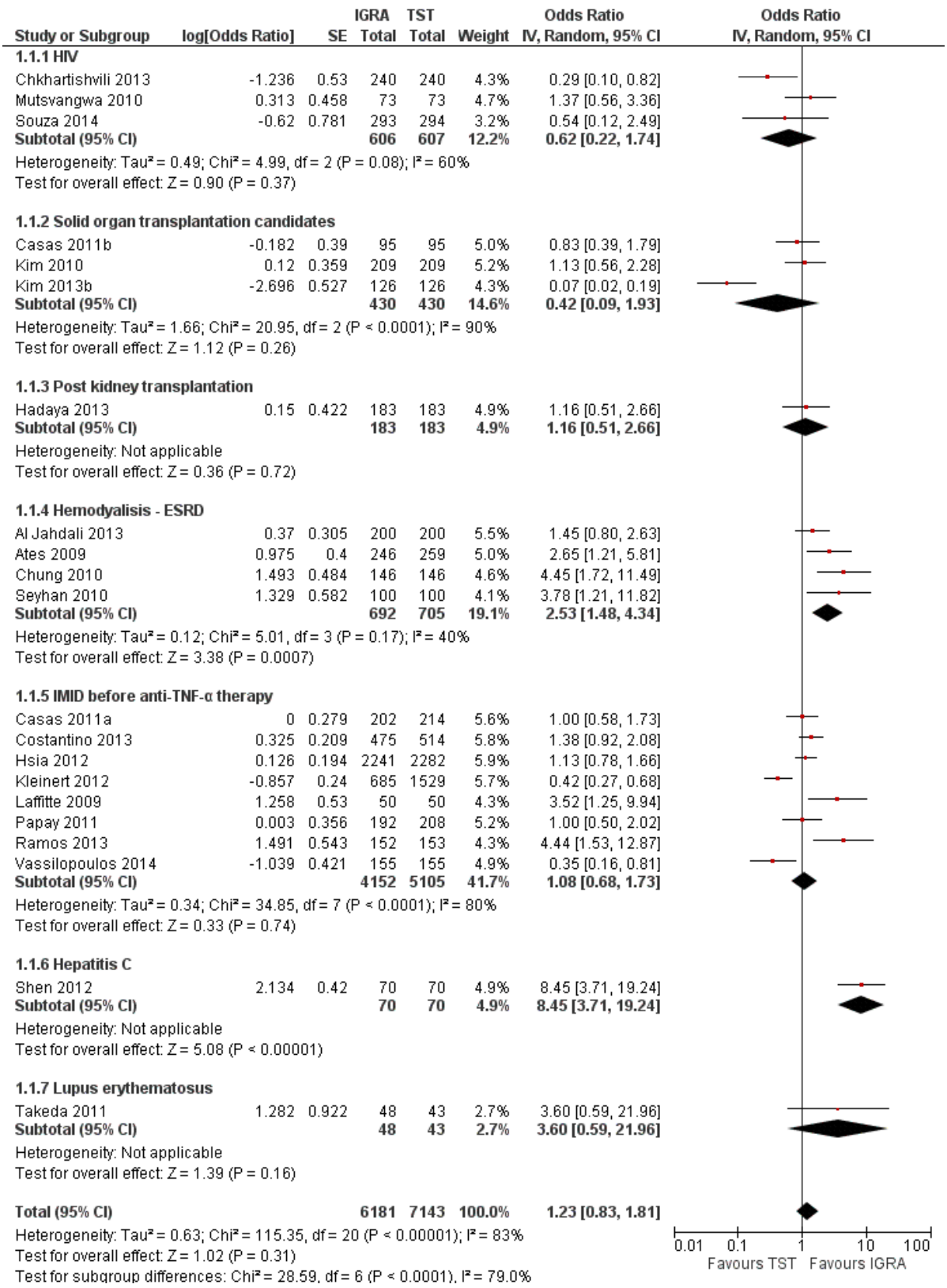


Figure 29. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRAs vs. TST in all studies based on high risk and low risk exposure in immunocompromised patients

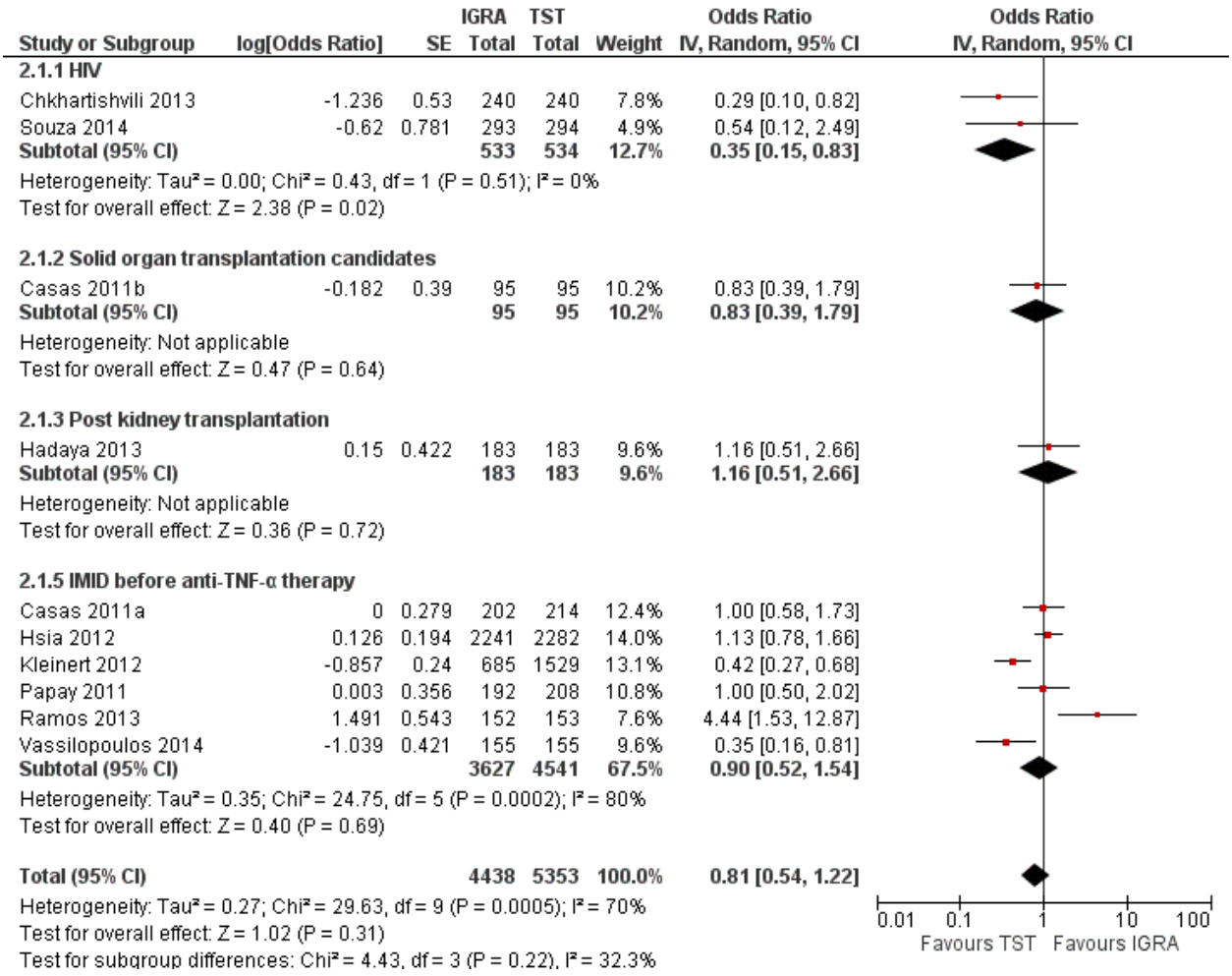


Figure 30. Pooled ratio of diagnostic odds ratio (R-DOR) of QFT-GIT/G vs. TST 5mm based on high risk and low risk exposure in immunocompromised patients

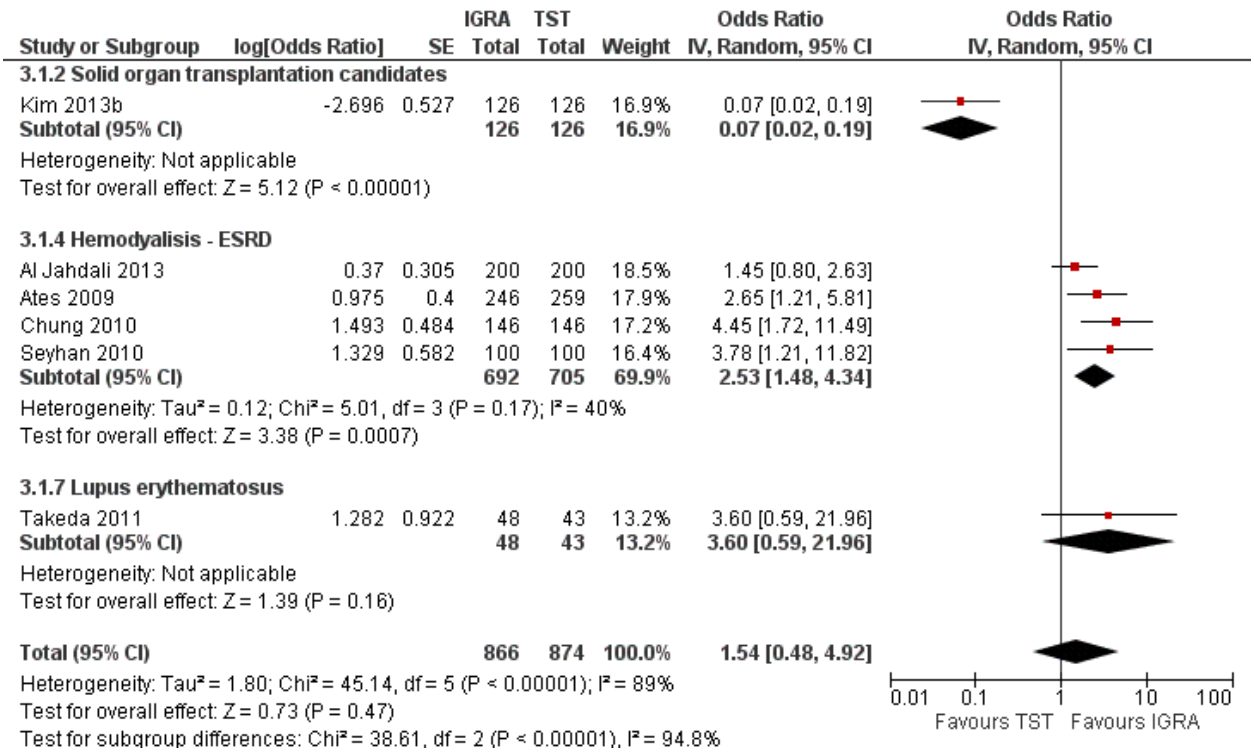


Figure 31. Pooled ratio of diagnostic odds ratio (R-DOR) of QFT-GIT/G vs. TST 10mm based on high risk and low risk exposure in immunocompromised patients

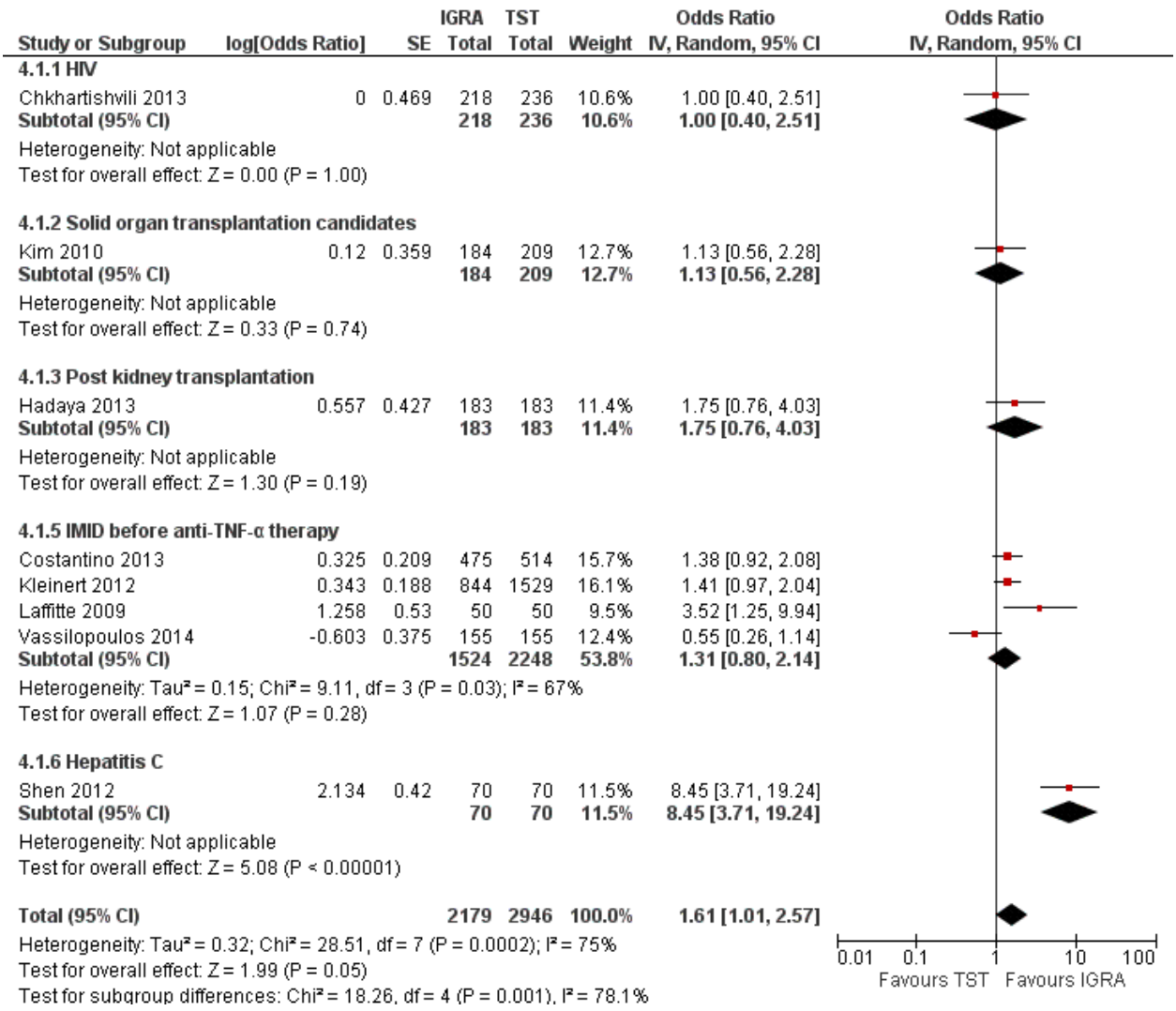


Figure 32. Pooled ratio of diagnostic odds ratio (R-DOR) of TSPOT vs. TST 5mm based on high risk and low risk exposure in immunocompromised patients

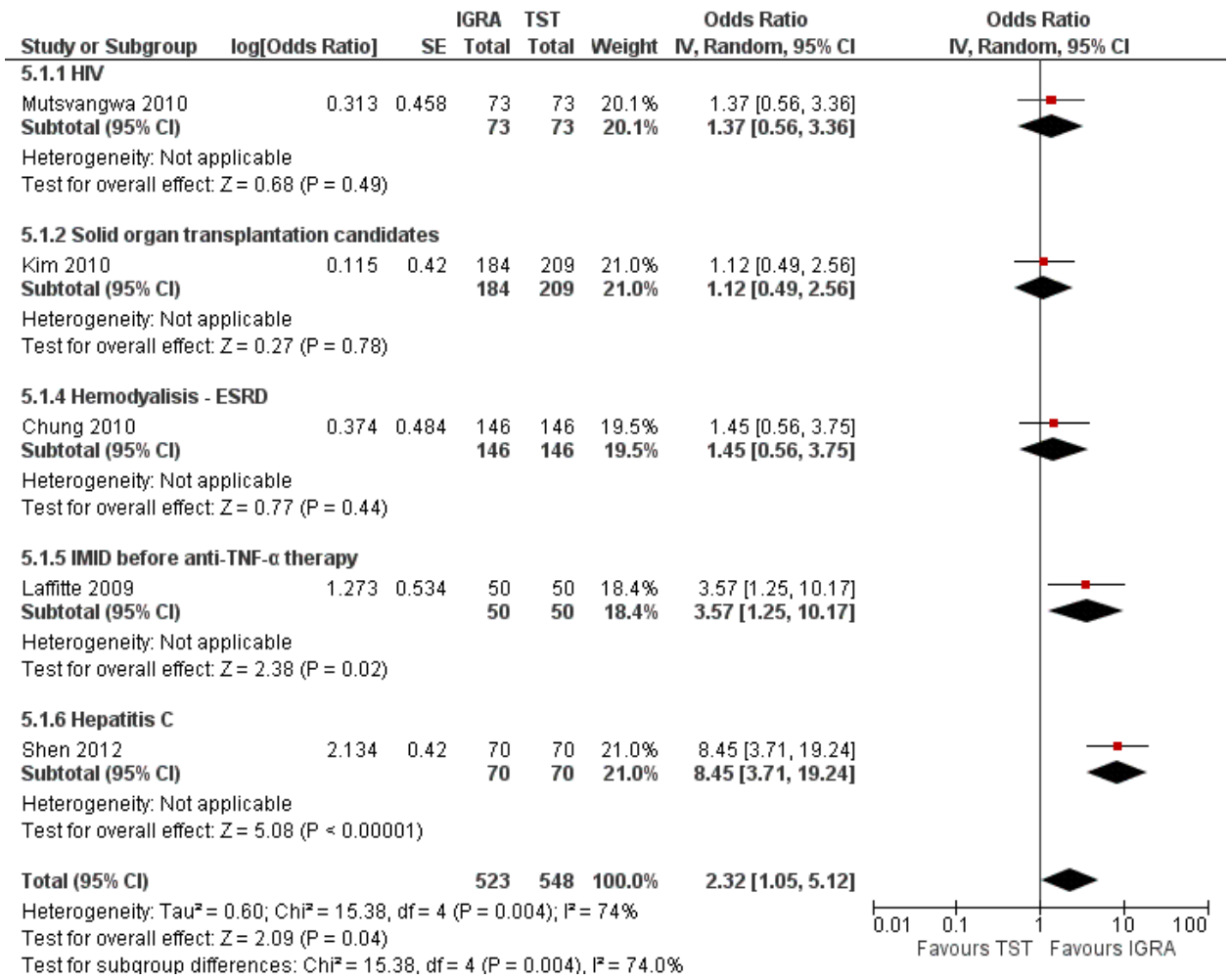


Figure 33. Pooled ratio of diagnostic odds ratio (R-DOR) of TSPOT vs. TST 10mm based on high risk and low risk exposure in immunocompromised patients

Sensitivity and specificity

This section incorporates 24 newly identified recent studies[118-140, 151] (Table 15). Three studies did not report sensitivity and specificity parameters for both IGRA and TST[121, 123, 127] and one study[130] reported them for only TST. The forest plots for the remaining 21 studies displayed a wide variability in sensitivity (IGRAs range: 0%-75%; TST-5mm range: 0%-61%; TST-10mm range: 0%-87%) and specificity (IGRAs range: 57%-100%; TST-5mm range: 62%-96%; TST-10mm range: 64%-93%). The heterogeneity persisted even after stratifying the estimates by the type of IGRA (QFT-GIT, TSPOT) and TST threshold (5mm, 10mm). Of the two IGRAs, QFT-GIT/G demonstrated markedly wider variation in the estimates of specificity and sensitivity than TSPOT. In general, for both IGRA and TST, specificity tended to be greater than sensitivity (see Figure 34, Figure 35, Figure 36, Figure 37, Figure 38, Figure 39, Figure 40, Figure 41). The absence of any clear pattern in the distribution of sensitivity and specificity values reflect

underlying between-study differences in study populations/conditions, settings, and variation in exposure definitions and measurement. In light of the observed heterogeneity, no meta-analysis was undertaken.

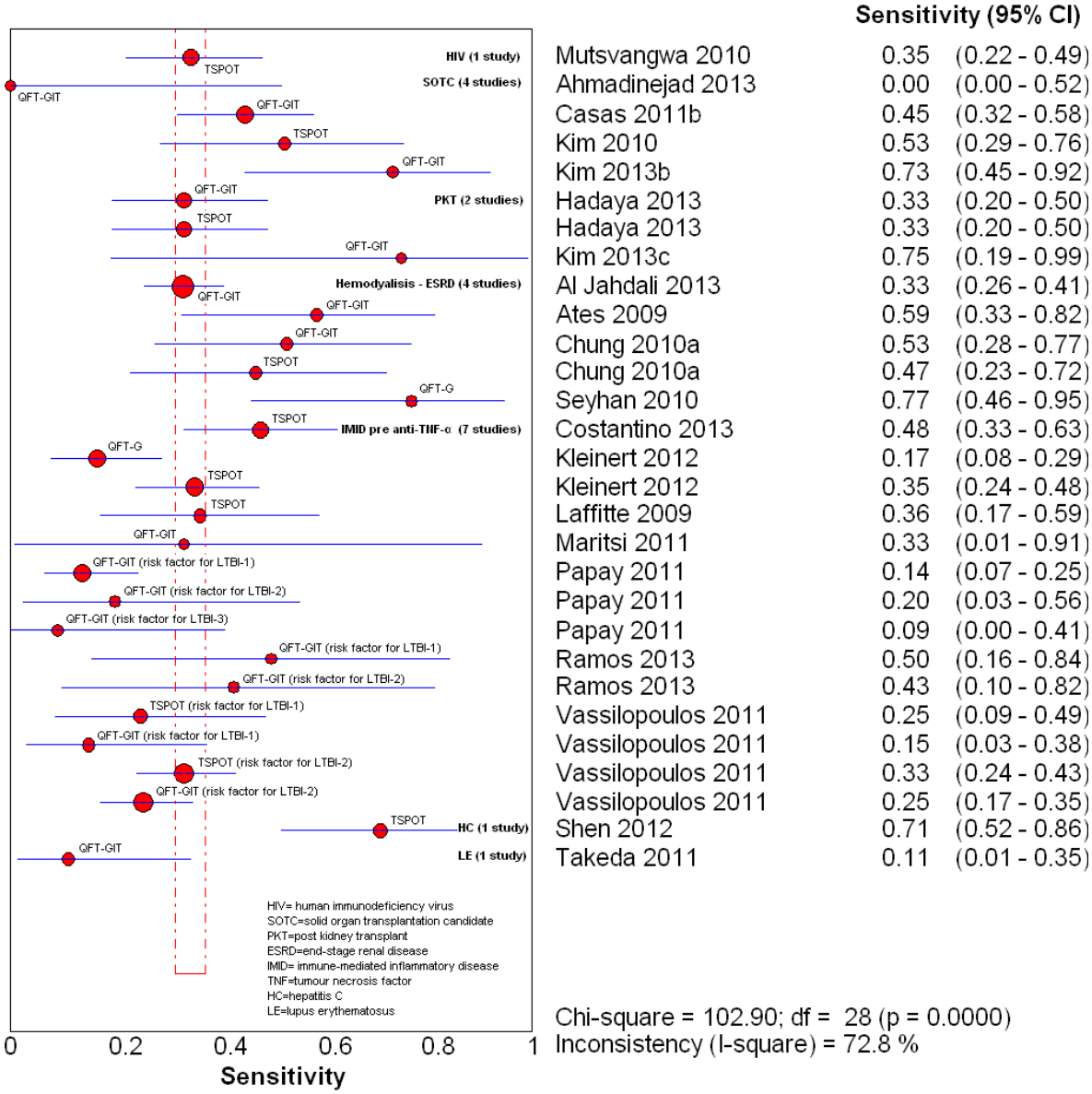
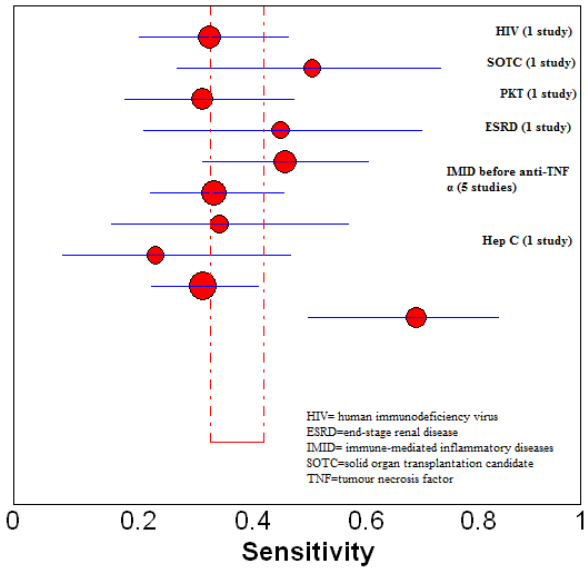


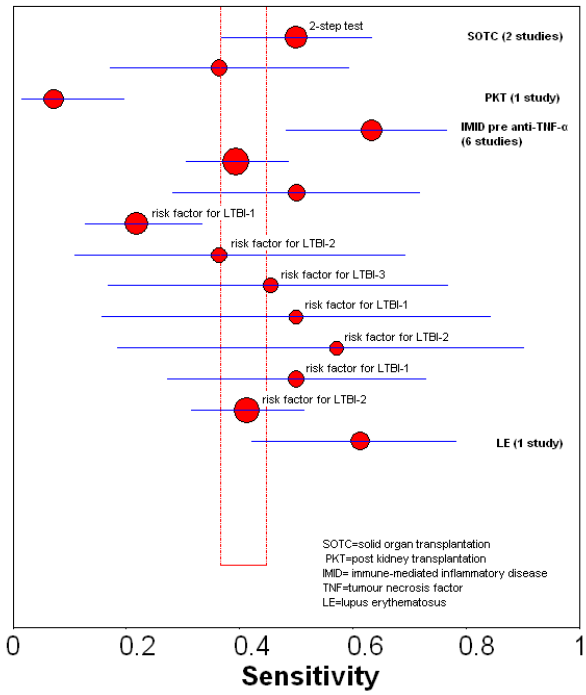
Figure 34. Forest plot of sensitivity based on exposure groups (IGRA) in immunocompromised patients



	Sensitivity (95% CI)	
Mutsvangwa 2010	0.35	(0.22 - 0.49)
Kim 2010	0.53	(0.29 - 0.76)
Hadaya 2013	0.33	(0.20 - 0.50)
Chung 2010a	0.47	(0.23 - 0.72)
Costantino 2013	0.48	(0.33 - 0.63)
Kleinert 2012	0.35	(0.24 - 0.48)
Laffitte 2009	0.36	(0.17 - 0.59)
Vassilopoulos 2011	0.25	(0.09 - 0.49)
Vassilopoulos 2011	0.33	(0.24 - 0.43)
Shen 2012	0.71	(0.52 - 0.86)

Chi-square = 21.08; df = 9 (p = 0.0123)
Inconsistency (I-square) = 57.3 %

Figure 35. Forest plot of sensitivity based on exposure groups (TSPOT) in immunocompromised patients



	Sensitivity (95% CI)	
Casas 2011b	0.50	(0.37 - 0.63)
Kim 2010	0.36	(0.17 - 0.59)
Hadaya 2013	0.07	(0.01 - 0.19)
Costantino 2013	0.63	(0.48 - 0.77)
Kleinert 2012	0.39	(0.31 - 0.49)
Laffitte 2009	0.50	(0.28 - 0.72)
Papay 2011	0.22	(0.13 - 0.33)
Papay 2011	0.36	(0.11 - 0.69)
Papay 2011	0.45	(0.17 - 0.77)
Ramos 2013	0.50	(0.16 - 0.84)
Ramos 2013	0.57	(0.18 - 0.90)
Vassilopoulos 2011	0.50	(0.27 - 0.73)
Vassilopoulos 2011	0.41	(0.32 - 0.51)
Shen 2012	0.61	(0.42 - 0.78)

Chi-square = 56.22; df = 13 (p = 0.0000)
Inconsistency (I-square) = 76.9 %

Figure 36. Forest plot of sensitivity based on exposure groups (TST 5mm) in immunocompromised patients

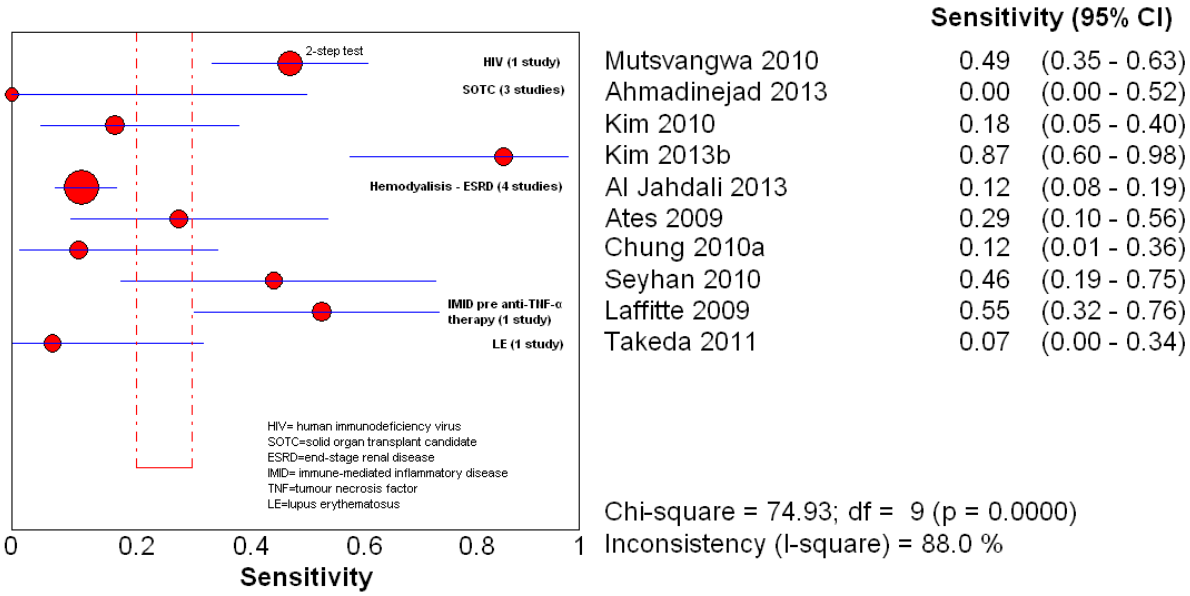


Figure 37. Forest plot of sensitivity based on exposure groups (TST 10mm) in immunocompromised patients

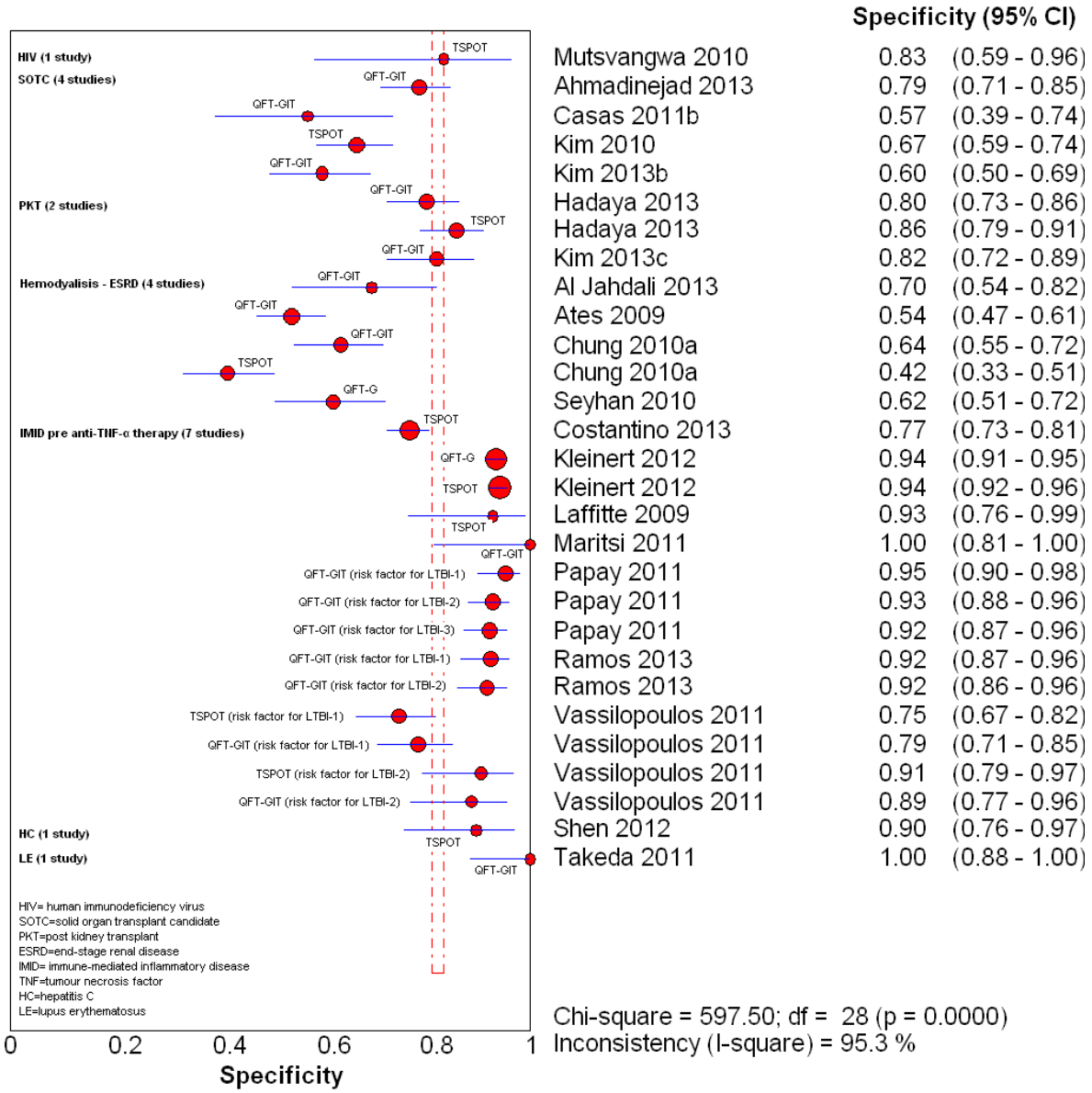


Figure 38. Forest plot of specificity based on exposure groups (IGRA) in immunocompromised patients

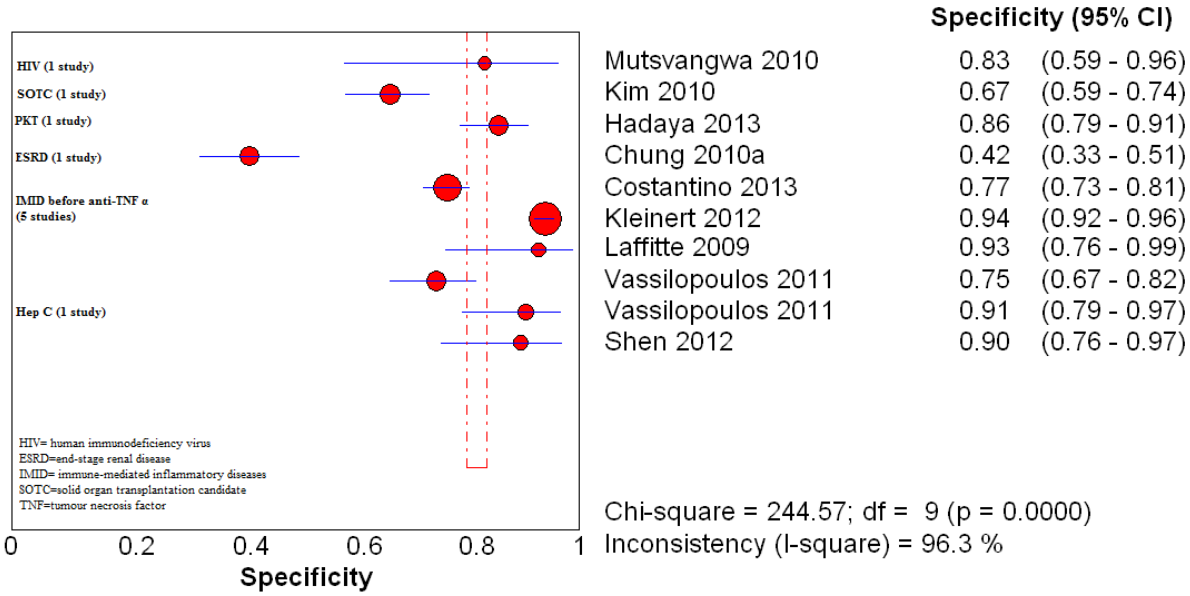


Figure 39. Forest plot of specificity based on exposure groups (TSPOT) in immunocompromised patients

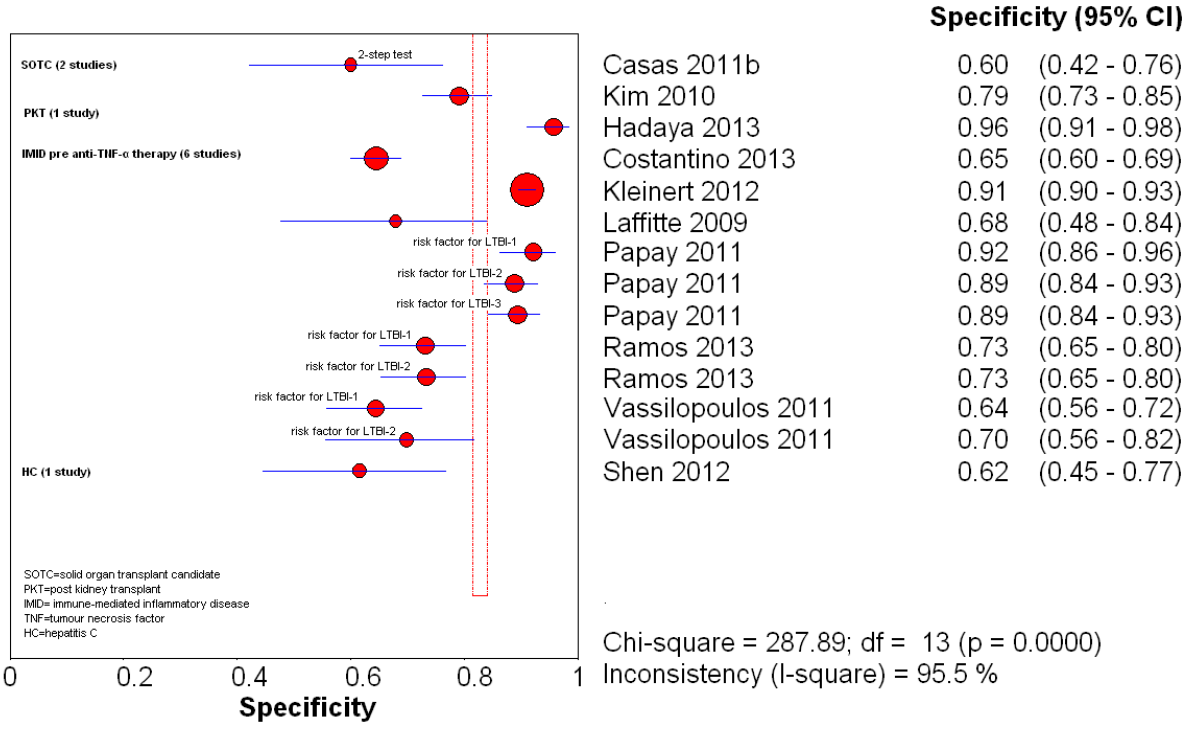


Figure 40. Forest plot of specificity based on exposure groups (TST 5mm) in immunocompromised patients

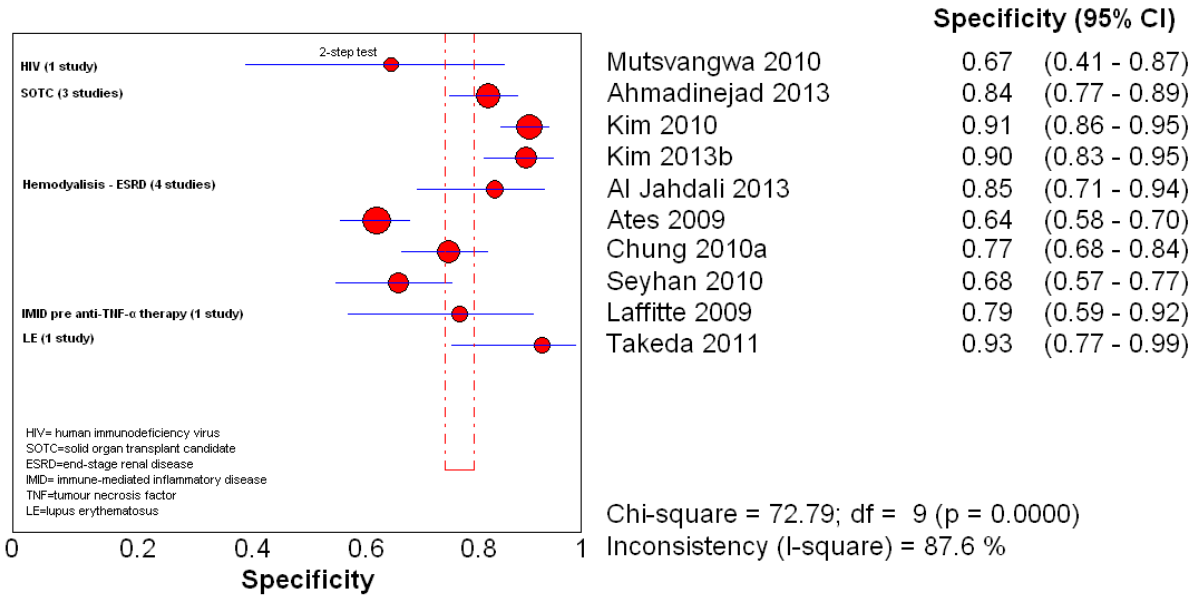


Figure 41. Forest plot of specificity based on exposure groups (TST 10mm) in immunocompromised patients

4.4.3.2.2 Influence of BCG vaccination status on test positivity:

Of the 24 newly identified studies included in this section,[118-140, 151] only 14[118, 120-123, 125, 127-129, 131, 132, 136, 137, 140] reported on the association between test positivity and BCG vaccination status. Overall, there was no evidence indicating differential effect of BCG vaccination status on IGRA and TST positivity.[118, 120-123, 128, 129, 131, 132, 135-140] In other words, the odds of test positivity for IGRA and TST were not significantly different between the BCG vaccinated vs. non-vaccinated groups (Table 16). Only one study demonstrated significantly increased OR for TST-10mm positivity (OR = 4.28, 95% CI: 1.35, 13.64) as opposed to a non-significant OR for IGRA (OR = 1.89, 95% CI: 0.75, 4.73) in relation to BCG vaccination status.[137]

Table 16. Association between test positivity and BCG vaccination (exposure studies)

Subgroup of interest – immunocompromised people (specify main condition/procedure)				
Study ID (Author name, year, and 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[118] Iran [Intermediate]	159	QFT-GIT	0.38 (95% CI: 0.11, 1.24)	NR
	164	TST-10mm	0.60 (95% CI: 0.15, 2.34)	NR
Al Jahdali, 2013[119] Saudi Arabia [Low]	NA	QFT-GIT	NR	NR
	NA	TST-10mm (two-step)	NR	NR
Ates, 2009[120] Turkey [Intermediate]	246	QFT-GIT	1.13 (95% CI: 0.68, 1.86)	1.14 (95% CI: 0.68, 1.92)
	259	TST-10mm	0.85 (95% CI: 0.51, 1.43)	0.87 (95% CI: 0.50, 1.51)
Casas, 2011a[121] Spain [Low]	214	QFT-GIT	1.20 (95% CI: 0.50, 3.20)	NR
	214	TST-5mm	1.70 (95% CI: 0.90, 3.40)	1.50 (95% CI: 0.70, 3.40)
Casas, 2011b[122] Spain [Low]	95	QFT-GIT	0.62 (95% CI: 0.26, 1.42)	NR
	95	TST-5mm (two-step)	0.83 (95% CI: 0.35, 2.00)	NR
Chkhartishvili, 2013[123] Georgia [High]	240	QFT-GIT	1.41 (95% CI: 0.38, 5.29)	NR
	240	T-SPOT	1.78 (95% CI: 0.38, 8.28)	NR
	240	TST-5mm	2.55 (95% CI: 0.32, 20.18)	NR
Chung, 2010a[124] South Korea [High]	146	QFT-GIT	NR	NR
	146	T-SPOT	NR	NR
	146	TST-10mm	NR	NR
Costantino, 2013[125] France [Low]	563	T-SPOT	NR	0.39 (95% CI: 0.24, 0.62)
	563	TST-5mm	NR	NR (p = 0.11, NS)
Hadaya, 2013[126] Switzerland [Low]	183	QFT-GIT	NR	NR
	183	T-SPOT	NR	NR
	183	TST-5mm	NR	NR
Hsia, 2012[127] USA [Low]	2029	QFT-GIT	NR	1.00 (95% CI: 0.66, 1.51) adjusted
	2029	TST-5mm	NR	2.47 (95% CI: 1.71, 3.55) adjusted
Kim, 2010[128] South Korea [High]	184	T-SPOT	0.69 (95% CI: 0.36, 1.34)	NR
	209	TST-5mm	1.25 (95% CI: 0.55, 2.82)	NR
	209	TST-10mm	0.89 (95% CI: 0.31, 2.58)	NR
Kim, 2013b[129] South Korea [High]	120	QFT-GIT	1.94 (95% CI: 0.48, 7.91)	2.32 (95% CI: 0.50, 10.66)
	119	TST-10mm	2.56 (95% CI: 0.31, 21.06)	3.32 (95% CI: 0.38, 28.97)
Kim, 2013c[130] South Korea [High]	93	QFT-GIT	NR	NR
	93	TST-10mm	NR	NR
Kleinert, 2012[131] Germany [Low]	685	QFT-G	NR	0.43 (95% CI: 0.17, 1.10)
	844	T-SPOT	NR	1.07 (95% CI: 0.47, 2.43)

Subgroup of interest – immunocompromised people (specify main condition/procedure)				
Study ID (Author name, year, and 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**
	1529	TST-5mm	3.17 (95% CI: 2.19, 4.58)	2.95 (95% CI: 2.00, 4.35)
Laffitte, 2009[132] Switzerland [Low]	50	T-SPOT	1.00 (95% CI: 0.01, 10.07)	NR
	50	TST-5mm	2.92 (95% CI: 0.30, 28.29)	NR
	50	TST-10mm	2.43 (95% CI: 0.25, 23.57)	NR
Maritsi, 2011[133] UK [Low]	NR	QFT-GIT	NR	NR
	NR	TST-NR mm	NR	NR
Mutsvangwa, 2010[134] Zimbabwe [High]	NR	T-SPOT	NR	NR
	NR	TST-10mm (two-step)	NR	NR
Papay, 2011[135] Austria [Low]	192	QFT-GIT	NR	NR
	192	TST-5mm	NR	NR
Ramos, 2013[136] Spain [Low]	153	QFT-GIT	NR	5.10 (95% CI: 1.50, 17.50)
	153	TST-5mm	NR	2.40 (95% CI: 1.01, 5.80)
Seyhan, 2010[137] Turkey [Intermediate]	100	QFT-G	NR	NR
	100	TST-10mm	NR	4.10 (95% CI: 1.30, 13.90)
Shen, 2012[138] China [High]	70	T-SPOT	NR	NR
	70	TST-5mm	NR	NR
Souza, 2014[151] Brazil [Intermediate]	299	QFT-GIT	NR	NR
	300	TST-5mm	NR	NR
Takeda, 2011[139] Japan [Low]	71	QFT-2G	NR	NR
	43	TST-10mm	NR	NR
Vassilopoulos, 2011[140] Greece [Low]	157	T-SPOT	0.75, 95% CI (NR; p = 0.45)	0.51, 95% CI (NR; p = 0.17)
	157	TST	1.36, 95% CI (NR; p = 0.39)	1.43, 95% CI (NR; p = 0.34)
	157	QFT-GIT	1.14, 95% CI (NR; p = 0.76)	1.05, 95% CI (NR; p = 0.90)

Abbreviations: TB = tuberculosis; NR = not reported; N = number; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test; 95% CI = 95 percent confidence interval

4.4.3.3 Between-test concordance, discordance, and agreement

This section included 16 studies reviewed in CG117[165-180] (see Appendix 6) and 32 more recent studies[112-140 147, 151, 153] reviewed in this update (see Appendix 9). Overall (in CG117 and its update), there were nine studies conducted in people with HIV,[112, 123, 134, 151, 165, 168-170, 179] three studies in people with hematologic disorders,[113, 147, 173] four studies in solid organ transplantation candidates,[118, 122, 128, 129] three studies in people who underwent kidney transplantation,[114, 126, 130] seven studies in people with end-stage renal disease/haemodialysis,[115, 116, 119, 120, 124, 137, 153] one study in hepatitis C,[138] one study in lupus erythematosus,[139] and 18 studies in patients with immune-mediated inflammatory diseases before anti-TNF-α therapy (rheumatoid arthritis, rheumatic or inflammatory diseases).[117, 121, 125, 127, 131-133, 135, 136, 140, 166, 167, 172, 174, 176-178, 180] The remaining two studies looked at patients with chronic liver[171] and mixed conditions (HIV with liver transplantation).[175]

The data on between-test concordance, discordance, and agreement from 32 more recent studies are presented in Table 17. Six[114, 124, 131, 133, 138, 139] of the 32 studies did not report this data (Table 17). Overall percent 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), hematologic 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), end-stage renal disease/haemodialysis (concordance: 60%-86.4%; kappa: 0.21-0.49), and immune-mediated inflammatory diseases before anti-TNF-α therapy (concordance: 60%-93%; kappa: 0.08-0.56) (see Table 17).

Table 17. Between-test concordance and discordance (exposure + incidence studies – 32 more recent studies)

Subgroup of interest – immunocompromised people (specify main condition/procedure)					
Study ID (Author name, year, and country) [burden]	**Sample size (N) total or by subgroup**	**Type of IGRA vs. TST induration threshold**	**Concordance (%) 95% CI**	**Discordance (%) 95% CI**	**Agreement kappa 95% CI**
HIV					
Chkhartishvili, 2013[123] Georgia [High]	233	QFT-GIT vs. 5mm	74.25 (68.27, 79.44)	25.75 (20.56, 31.73)	0.29 (0.16, 0.42)
	217	TSPOT vs. 5mm	75.12 (68.96, 80.4)	24.88 (19.6, 31.04)	0.22 (0.07, 0.29)
Elzi, 2011[112] Switzerland [Low]	32	TSPOT vs. 5mm	56.25 (39.33, 71.83)	43.75 (28.17, 60.67)	0.12 (-0.22, -0.46)
Mutsvangwa, 2010[134] Zimbabwe [High]	Total	TSPOT vs. 10mm (two-step)	NR	NR	NR
	55 TB index case contacts	TSPOT vs. 10mm (two-step)	70.91 (57.86, 81.23)	29.09 (18.77, 42.14)	0.41 (0.16, 0.66)
	18 Control index contacts	TSPOT vs. 10mm (two-step)	72.22 (49.13, 87.5)	27.78 (12.5, 50.87)	0.28 (-0.13, 0.70)
Souza, 2014 [151] Brazil [Intermediate]	299	QFT-GIT vs. 5mm	96.00 (93.12, 97.69)	4.01 (2.31, 6.88)	0.48 (0.37, 0.59)
hematopoietic stem cell transplantation candidates					
Moon, 2013[113] South Korea [High]	210	QFT-GIT vs. 5mm	73.81 (67.47, 79.29)	26.19 (20.71, 32.53)	0.09 (-0.04, -0.22)
	210	QFT-GIT vs. 10mm	78.57 (72.53, 83.58)	21.43 (16.42, 27.47)	0.15 (0.02, 0.27)
	176 with BCG history	QFT-GIT vs. 5mm	74.43 (67.51, 80.31)	25.57 (19.69, 32.49)	0.13, (-0.02, 0.27)
	34 no BCG history	QFT-GIT vs. 5mm	70.59 (53.83, 83.17)	29.41 (16.83, 46.17)	-0.10 (-0.35, 0.14)
hematopoietic stem cell transplantation recipients					
Lee, 2014[147] South Korea [High]	159	QFT-GIT vs. 5mm	79.87 (72.97, 85.37)	20.13 (14.63, 27.03)	0.16 (0.01, 0.31)
	159	QFT-GIT vs. 10mm	NR	NR	NR
Solid organ transplantation candidates					
Ahmadinejad, 2013[118] Iran [Intermediate]	159	QFT-GIT vs. 10mm	79.87 (72.97, 85.37)	20.13 (14.63, 27.03)	0.32 (0.17, 0.47)
Casas, 2011b[122] Spain [Low]	95	QFT-GIT vs. 5mm (two-step)	78.95 (69.71, 85.94)	36.36 (24.93, 49.58)	0.57 (0.37, 0.77)
Kim, 2010[128] South Korea [High]	184 total	TSPOT vs. 10mm	71.2 (64.27, 77.25)	28.8 (22.75, 35.73)	0.23 (0.12, 0.34)
	145 BCG vaccinated	TSPOT vs. 10mm	70.34 (62.46, 77.18)	29.66 (22.82, 37.54)	0.19 (0.06, 0.31)
Kim, 2013b[129] South Korea [High]	119	QFT-G vs. 10mm	65.49 (56.34, 73.61)	34.51 (26.39, 43.66)	0.26 (0.10, 0.41)

Post kidney transplantation					
Kim, 2011[114] South Korea [High]	NR	NR	NR	NR	NR
Hadaya, 2013[126] Switzerland [Low]	200	QFT-GIT vs. 5mm	NR	NR	0.11 (P = 0.010)
	200	TSPOT vs. 5mm	NR	NR	0.09 (P = 0.034)
Kim, 2013c[130] South Korea [High]	93	QFT-G vs. 10mm	79.57 (70.28, 86.51)	20.43 (13.49, 29.72)	0.27 (0.07, 0.46)
Haemodialysis - ESRD					
Anibarro, 2012[115] Spain [Low]	52	QFT-GIT vs. 5mm	71.15 (57.73, 81.67)	28.85 (18.33, 42.27)	0.21 (0.04, 0.37)
	52	QFT-GIT vs. 5mm (two step TST)	78.85 (65.97, 87.76)	21.15 (12.24, 34.03)	0.49 (0.22, 0.74)
Lee, 2009[116] Taiwan [High]	32	QFT-G vs. 10mm (two step TST)	60.00 (NR)	40.00 (NR)	0.25 (-0.06, -0.56)
	32	TSPOT vs. 10mm (two step TST)	65.60 (NR)	34.40 (NR)	0.32 (-0.01, -0.65)
Al Jahdali, 2013[119] Saudi Arabia [Low]	200	QFT-GIT vs. 10mm (two-step)	75.50 (69.10, 80.94)	24.50 (19.06, 30.90)	0.34 (0.22, 0.45)
Ates, 2009[120] Turkey [Indeterminate]	230	QFT-GIT vs.10mm	67.83 (61.54, 73.53)	32.17 (26.47, 38.46)	0.34 (0.21, 0.47)
Chung, 2010a[124] South Korea [High]	146	QFT-G vs. 10mm	NR	NR	NR
	146	TSPOT vs. 10mm	NR	NR	NR
Seyhan, 2010[137] Turkey [Indeterminate]	100	QFT-GIT vs.10mm	65.00 (55.25, 73.64)	35.00 (26.36, 44.75)	0.27 (0.07, 0.46)
Sherkat, 2014[153] Iran [intermediate]	44	TSPOT vs. 10mm	86.36 (73.29, 93.6)	13.64 (6.40, 26.71)	0.49 (0.20, 0.78)
IMID before anti-TNF-α therapy					
Casas, 2011a[121] Spain [Low]	202	QFT-GIT vs.5mm	84.16 (78.49, 88.55)	15.84 (11.45, 21.51)	0.56 (0.42, 0.70)
Chang, 2011[117] South Korea [High]	100	QFT-GIT vs. 10mm	67.0 (57.31, 75.44)	33.0 (24.56, 42.69)	0.26 (0.07, 0.45)
	42 RA sample	QFT-GIT vs. 10mm	76.20 (61.47, 86.52)	23.80 (13.48, 38.53)	0.46 (0.21, 0.72)
	58 AS sample	QFT-GIT vs. 10mm	60.34 (47.49, 71.91)	39.66 (28.09, 52.51)	0.14 (-0.10, 0.39)
Costantino, 2013[125] France [Low]	444 total	TSPOT vs. 5mm	62.84 (58.25, 67.2)	37.16 (32.8, 41.75)	0.16 (0.07, 0.25)
	NR BCG vaccinated	TSPOT vs. 5mm	NR	NR	0.15 (NR)
	NR BCG non-vaccinated	TSPOT vs. 5mm	NR	NR	0.22 (NR)
Hsia, 2012[127] USA [Low]	2282 total	QFT-GIT vs. 5mm	NR	NR	0.22 (0.15, 0.27)
	781 BCG vaccinated	QFT-GIT vs. 5mm	82.84 (80.04, 85.32)	17.16 (14.68, 19.96)	0.20 (0.13, 0.27)
	1248 BCG non-vaccinated	QFT-GIT vs. 5mm	93.11 (91.57, 94.39)	6.89 (5.61, 8.43)	0.32 (0.26, 0.37)

Kleinert, 2012[131] Germany [Low]	685	QFT-G vs. 5mm	NR	NR	NR
	844	TSPOT vs. 5mm	NR	NR	NR
Laffitte, 2009[132] Switzerland [Low]	50	TSPOT vs. 5mm	72.00 (58.33, 82.53)	28.00 (17.47, 41.67)	0.36 (0.12, 0.61)
Maritsi, 2011[133] South Africa [High]	NR	QFT-G vs. NR mm	NR	NR	NR
Papay, 2011[135] Austria [Low]	192	QFT-GIT vs. 5mm	84.90 (79.15, 89.27)	15.10 (10.73, 20.85)	0.21 (0.07, 0.34)
Ramos, 2013[136] Spain [Low]	90	QFT-GIT vs. 5mm	75.56 (65.75, 83.27)	24.44 (16.73, 34.25)	0.08 (-0.05, 0.22)
Vassilopolous, 2014[140] Greece [Low]	155	QFT-GIT vs. 5mm	63.87 (56.06, 71.01)	36.13 (28.99, 43.94)	0.15 (0.01, 0.29)
	155	TSPOT vs. 5mm	71.0 (63.38, 77.54)	29.03 (22.46, 36.62)	0.34 (0.17, 0.50)
Hepatitis C					
Shen, 2012[138] China [High]	70	TSPOT vs. 5mm	NR	NR	NR
Lupus erythematosus					
Takeda, 2011a[139] Japan [Low]	NR	QFT-GIT vs. 10mm	NR	NR	NR

Abbreviations: 95% CI = 95 percent confidence interval; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test

Four studies reported between-test agreement parameters by BCG vaccination status,[113, 125, 127, 128] three of which showed lower percent concordance and kappa values for BCG vaccinated vs. non-vaccinated participants[125, 127, 128] (see Table 17).

4.4.3.4 Indeterminate test results

This section included three studies reviewed in CG117 (see Appendix 6) and 31 more recent studies (see above the previous section) (see Appendix 9). Of the recent studies, six did not report this outcome.[119, 124, 131, 132, 134, 153]

The proportion of indeterminate results according to each condition and type of IGRA test ranged as follows: HIV (QFT-GIT: 0.30%-17.87%; TSPOT: 32.80%),[112, 123, 151, 168, 169, 179] hematologic disorders (QFT-GIT: 6.00%-13.93%),[113, 147] solid organ transplantation candidates (QFT-GIT: 2.11%-4.76%; TSPOT: 11.96%)[118, 122, 128, 129] post kidney transplantation (QFT-GIT: 1.64%- 4.30%; TSPOT: 11%),[114, 126, 130] end-stage renal disease/haemodialysis (QFT-GIT: 0%-10.55%; TSPOT: 0%),[115, 116, 120, 137] immune-mediated inflammatory diseases before anti-TNF-α therapy (QFT-GIT: 0%-7.69%; TSPOT: 0%-15.63%),[117, 121, 125, 127, 135, 136, 140] hepatitis C (TSPOT: 0%),[138] and lupus erythematosus (QFT-GIT: 32.39%).[139]

4.4.4 Summary of Immunocompromised studies

This section included 48 studies: 16 studies reviewed in CG117 (see Appendix 6) and 32 more recent studies published in 2009 or onwards (see Appendix 9). The studies were stratified and analysed according to the following subgroups: HIV, solid organ transplantation candidates, post kidney transplantation, haemodialysis – end stage renal disease, immune-mediated inflammatory diseases before anti-TNF-α therapy, Hepatitis C, and lupus erythematosus. The majority of the more recent studies were rated as being at moderate/high risk of bias (incidence studies) or being of moderate/low methodological quality (exposure studies).

Only two of eight studies reported sufficient data for calculating R-CIRs to compare the performance of IGRA and TST in predicting the incidence of active TB. The R-CIR estimates in both studies were non-significant with very wide 95% CIs, thereby rendering their interpretation inconclusive. These studies were not combined because TST was used with different thresholds and one study used two-step TST.

Across the 32 newly identified studies, there was a wide variability and the absence of clear pattern in the estimates of sensitivity and specificity. In general, for both IGRA and TST, specificity tended to be

greater than sensitivity. Some or all of the observed variation was due to zero count events (unstable estimates), underlying differences in study populations/conditions, settings, variation in exposure definitions and measurement, and TST thresholds. The heterogeneity persisted even after stratifying the estimates by the type of IGRA (QFT-GIT, TSPOT) and TST threshold (5mm, 10mm). 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 measured with ratio of diagnostic odds ratios (R-DOR; IGRA vs. TST) in individual studies ranged from 0.07 to 8.45. The forest plot analysis of R-DORs included 21 studies and revealed significant amount of heterogeneity across all subgroups of participants except for haemodialysis in whom IGRA (QFT-GIT) was more strongly associated with exposure groups than TST 10mm (Pooled R-DOR = 2.53, 95% CI: 1.48, 4.34). Similarly, in participants with hepatitis C, IGRA (TSPOT) outperformed TST 5mm in detecting LTBI (R-DOR = 8.45, 95% CI: 3.71, 19.24). For most subgroups the within-subgroup heterogeneity by IGRA type (QFT-GIT, TSPOT) and TST threshold (5mm, 10mm, 15mm) could not be examined due to sparse data. In people with HIV/AIDS, TST 10 mm performed significantly better than QFT-GIT (Pooled R-DOR = 0.35, 95% CI: 0.15, 0.83). For the remaining subgroups (e.g., lupus erythematosus, solid organ transplantation candidates, kidney transplant recipients), the performance of QFT-GIT did not significantly differ from that of TST (wide 95% CIs and inconclusive results).

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 significantly increased OR for TST-10mm positivity (OR = 4.28, 95% CI: 1.35, 13.64) as opposed to the non-significant OR for IGRA (OR = 1.89, 95% CI: 0.75, 4.73) in relation to BCG vaccination status.

Overall percent 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), hematologic 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), end-stage renal disease/haemodialysis (concordance: 60%-86.4%; kappa: 0.21-0.49), and immune-mediated inflammatory diseases before anti-TNF-α therapy (concordance: 60%-93%; kappa: 0.08-0.56). Three studies reported between-test agreement parameters by BCG vaccination status, which showed lower percent concordance and kappa values for BCG vaccinated vs. non-vaccinated participants.

4.5 Recent arrivals from countries with a high incidence of TB

4.5.1 Description of baseline characteristics

This section included 15 studies in total.[141-145, 164, 181-189] Our searches identified five studies[141-145] in individuals that had recently arrived from mainly high TB incidence countries: two investigated the incidence of active TB following testing for LTBI (incidence studies)[141, 142] and three investigated levels of exposure in relationship to LTBI test outcomes (exposure studies).[143-145] An additional 10 studies[164, 181-189] in recently arrived immigrants were identified in CG117. Details of the additional studies included from CG117 can be found in Appendix 6.

4.5.1.1 Incidence studies

Two studies[141, 142] investigated the agreement of a QFT test with the TST in individuals recently arrived from high TB incidence countries, one from Norway[141] and the second one from the Netherlands.[142] Both studies were prospective cohorts in design and were community based. Follow-up ranged from 23 to 32 months in Harstadt et al. (2010).[141] Kik et al. (2010)[142] followed up participants for 24 months.

Type of tests compared were QFT-GIT and TST with cut-off values of ≥6mm and ≥15mm[141] and QFT-GIT, T-SPOT.TB and TST (≥ 10mm and ≥ 15mm).[142] Around 25%[141] and 44%[142] of patients in the studies were female. The mean age ranged from 16 to 45 years[142] and 18 to >50 years. [141] In Kik et al (2010)[142] about 8% of the study population originated from Europe/North America, another 8% from South America, 36% from Asia, approximately 29% from African countries other than sub-Saharan countries and 17% from sub-Saharan Africa. 1.5% of participants were of unknown geographic origin. In this study the proportion of patients who had received BCG vaccination was high at 81%.[142] In Harstadt et al. (2010)[141] 13% of participants tested were from Europe, 42% from Africa, a further 42% from Asia, and 3% from other countries. BCG vaccination was not reported in this study. See Table 18 for further details on these studies.

Table 18. Baseline characteristics of studies on recent arrivals from countries with a high incidence of TB (incidence studies)

Study ID (Author name, year, and country) [burden]	Study aim, setting, design, follow-up duration, and funding source	Method(s) of diagnosis of active TB	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
Harstad, 2010[141] Norway [Low]	**Study aim:** To compare PPV and NPV between QFT-GIT and the TST in asylum seekers in Norway **Setting:** Community-based **Study design:** Prospective cohort study **Follow up:** 23-32 months **Funding source:** Norwegian Health Association; The 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: ≥6mm and ≥15mm	**Mean (range or SD) age:** 18–34 years (n = 587), 35–49 years (n = 201), and ≥50 years (n = 35) **Female (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	**Total N or recruited patients:** NR **Total N of excluded patients:** NR	NA

Study ID (Author name, year, and country) [burden]	Study aim, setting, design, follow-up duration, and funding source	Method(s) of diagnosis of active TB	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
					Clinical examination (yes/no): NR **Morbidity (n [%]):** NA **Co-morbidity (n [%]):** NA		
Kik, 2010[142] Netherlands [Low]	**Study aim:** To assess the 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 **Study design:** Prospective cohort study **Follow up:** 24 months	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	**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 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	**Type of tests:** IGRA (QFT-GIT), IGRA (T-SPOT.TB), TST **Cut-off values/thresholds:** IGRA: Two-tube format positive test was defined as ≥ 0.35 IU/mL-1 IGRA (T-SPOT.TB): According to the manufacturer TST: ≥ 10mm and ≥ 15mm	**Mean (range or SD) age:** Range: 16–24 (n = 53 [15.6%]), range: 25–34 (n = 80 [23.6%]), range: 35–44 (n = 115 [33.9%]), and range: ≥45 (n = 91 [26.8%]) **Female (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	**Total N or recruited patients:** 433 **Total N of excluded patients:** 91(furthermore, five contacts were excluded in the secondary analysis, since their follow-up started12 months before August 1, 2008)	NA

Study ID (Author name, year, and country) [burden]	Study aim, setting, design, follow-up duration, and funding source	Method(s) of diagnosis of active TB	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
	Funding source: Unrestricted grants from the Netherlands Organization for Health Research and Development	TB disease was based on chest radiography, symptoms, smear and/or culture results	were given preventive treatment		[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		

Abbreviations: TB = tuberculosis; NR = not reported; N = number; IGRA = Interferon-gamma release assay; QFT-GIT = QuantiFERON-TB Gold In-Tube; TST = tuberculosis skin test; BCG = Bacille de Calmette et Guérin; LTBI = latent tuberculosis infection; SD = standard deviation; HIV = human immunodeficiency virus; PPV = positive predictive value; NPV = negative predictive value

4.5.1.2 Exposure studies

Three studies compared an IGRA test with the TST test in recent arrivals from countries with a high incidence of TB relating test outcome to prior level of exposure.[143-145] All studies within this group were therefore classed as having either a retrospective cohort or cross-sectional design. The tests compared were QFT-GIT and TST (≥10mm),[143-145] while Lucas et al. (2010)[143] also tested the T-SPOT.TB. The studies were undertaken in community settings in Australia [143] and Italy.[144, 145] Lucas et al. (2010)[143] studied children with a mean age of 7.5 years from Africa (78%) and Asia (22%) where the exposed group had definite or suspected household TB contact and the unexposed did not. BCG vaccination in this cohort was 69%. Participants in the Italian studies were young adults of whom 55% were females in Orlando et al. (2010)[144] but only 4% were females in Saracino et al. (2009)[145] Immigrants arrived from Latin America (50%), Eastern Europe (27%), Africa (16%) and Asia (7%) in one study[144] and from Africa (48%), Eastern Mediterranean countries (47%), Europe (3%) and South-East Asia (2%) in the other.[145] While the former study reported an overall very low rate of BCG vaccination (6%),[144] the latter study did not report BCG vaccination of participants.[145] Both studies defined exposure groups by geographical area of origin and the level of TB burden[145] or TB prevalence[144] in the country of origin. In addition, Orlando et al. (2010)[144] specified a third exposed group as contacts of TB cases and compared with an unexposed group without TB contact. See Table 19 for further details on these studies.

Table 19. Baseline characteristics of studies on recent arrivals from countries with a high incidence of TB (exposure studies)

Study ID (Author name, year, and country) [burden]	Study aim, setting, and design	Definition of construct validity (i.e., LTBI exposure-based proxy)	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
Lucas, 2010[143] Australia [Low]	**Study aim:** To compare IGRAs and TST for the diagnosis of LTBI in recently resettled refugee children **Setting:** Community based **Study design:** Retrospective cohort/cross sectional study **Funding source:** Oxford Immunotech	**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:** Not reported	**Type of tests:** IGRA (T-SPOT.TB) IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA (T-SPOT.TB): NR IGRA (QFT-GIT): NR TST: ≥10 mm given that all children originated from high prevalence countries ≥15 mm if children were <5 years old and had received BCG, 5mm was subtracted from these cut-off values for children at increased risk	**Mean (range or SD) age:** 7.5 (2.8-11.9) **Female (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	**Recruited (N):** 524 **Excluded (N):** NR	NA

Study ID (Author name, year, and country) [burden]	Study aim, setting, and design	Definition of construct validity (i.e., LTBI exposure-based proxy)	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
				for TB infection (such as household contacts) and for those >1 year of age	**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		
Orlando, 2010[144] Italy [Low]	**Study aim:** To compare the efficiency and efficacy of TST and QFT-GIT for the detection of LTBI in recent immigrants from highly endemic countries **Setting:** Community-	**(1) Continent** **Non exposed:** Africa (reference group) **Exposed 1:** Asia **Exposed 2:** East Europe **Exposed 3:** Latin America **(2) TB prevalence** **Non exposed:** <50 (reference	**Inclusion criteria:** NR **Exclusion criteria:** Active TB	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds** **Definition of test+:** IGRA: Positive if the INF-c value after stimulation with TB-antigen minus the value in the Nil control	**Mean (range or SD) age:** Median 35.3 years (IQR: 27.7–44.5) **Female (n [%]):** 630 [55.7] **Race/ethnicity (n [%]):** NR **Geographic origin (n[%]):**	**Recruited (N):** NR **Excluded (N):** NR	NA

Study ID (Author name, year, and country) [burden]	Study aim, setting, and design	Definition of construct validity (i.e., LTBI exposure-based proxy)	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
	based (outpatient ward) **Study design:** Retrospective cohort/cross-sectional study **Funding source:** The Provincia di Milano, Assessorato alle Politiche Sociali	group) **Exposed 1:** 50-200 **Exposed 2:** >200 **(3) Contact with TB patient** **Non exposed:** No (reference group) **Exposed 1:** Yes		was ≥0.35 UI/ml TST: ≥ 10 mm of induration in persons recently arrived from highly endemic areas	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		

Study ID (Author name, year, and country) [burden]	Study aim, setting, and design	Definition of construct validity (i.e., LTBI exposure-based proxy)	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
					Type of during-study treatment (n [%]): treatment for LTBI was offered to 57 of the 79 eligible patients according to standard guidelines		
Saracino, 2009[145] Italy [Low]	**Study aim:** 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 **Setting:** Community-based **Study design:** Retrospective cohort/cross-sectional study **Funding**	**(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	**Inclusion criteria:** Recent (less than two months) immigrants to Italy **Exclusion criteria:** Active TB, HIV	**Type of tests:** IGRA (QFT-GIT) TST (≥10mm) **Cut-off values/thresholds Definition of test+:** IGRA: Positive if the IFN-γ level was above the cut-off test value (≥0.35 IU/mL) TST: After 72 hours if ≥10mm (≥5mm and ≥15mm were used for comparison)	**Mean (range or SD) age:** 27.1 (6.2) **Female (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	**Recruited (N):** NR **Excluded (N):** NR	NA

Study ID (Author name, year, and country) [burden]	Study aim, setting, and design	Definition of construct validity (i.e., LTBI exposure-based proxy)	Study participants' inclusion/ exclusion criteria	Type and positivity threshold(s) of tests compared	Characteristics of study participants at baseline	N of recruited and excluded study participants	Comments
	source: NR	**Exposed 2:** Eastern Mediterranean **Exposed 3:** European **Exposed 4:** South-East Asian			**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		

Abbreviations: TB = tuberculosis; NR = not reported; N = number; IGRA = interferon-gamma release assay; QFT-GIT = QuantiFERON-TB Gold In-Tube; TST = tuberculosis skin test; BCG = Bacille de Calmette et Guérin; LTBI = latent tuberculosis infection; SD = standard deviation; HIV = human immunodeficiency virus; IFN = interferon

4.5.2 Study quality

4.5.2.1 Incidence of active TB (n = 2)

Only one study provided adequate description about study design, study participants, study attrition, statistical analysis and reporting therefore, this study was judged to have low risk of bias.[142] Another study was judged as being at high risk of bias due to selection, confounding and partial selecting reporting of results[141] (see Table 20 for further details).

Table 20. Summary assessment of risk of bias (ROB) for the included studies on recent arrivals from countries with a high incidence of TB (adapted from Hayden et al., 2013)[88]

First author, Year, Study ID	**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** *risk of bias in misclassification of individuals in relation to construct validity groups*	**Study Confounding** *risk of bias due to confounding*	**Statistical Analysis and Reporting** *risk of bias due to analysis and selective reporting*	**Total ROB** *high, moderate, low*
Harstad, 2010[141] [Low]	Low	High	Low	High	Moderate	High	High	High ROB
Kik, 2010[142] [Low]	Low	Low	Low	Low	Low	Low	Low	Low ROB

4.5.2.2 Exposure levels (n = 3)

All of the three exposure studies[143-145] identified since CG117 concerning recent arrivals from countries with a high incidence of TB were rated as low quality.[143-145] There was a lack of blinding of test result from exposure, inadequate description of exposure and in all three studies, there was inadequate reporting of sample attrition (see Table 21 for further details).

Table 21. Summary of quality assessment for the studies on recent arrivals from countries with a high incidence of TB (adapted from Dinnes et al., 2007)[43]

First author, Year, Study ID	**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]#, inadequate or unreported [no]*	**Overall quality score of satisfactory features** [£]
Lucas, 2010[143] [Low]	Yes	No	No	No	No	Low quality
Orlando, 2010[144] [Low]	Yes	No	Yes	No	No	Low quality
Saracino, 2009[145] [Low]	No	No	Yes	No	No	Low quality

[#] ≥ 90% of participants were included in the follow-up analysis [yes response] and < 90% were classified as "no response"

[£] Studies with 1 or 2 "yes" ratings = Low quality; studies with 3 "yes" ratings = Moderate quality; studies with 4 or 5 "yes" ratings = High quality

Please note the following item has been removed from the original Dinnes et al., (2007)[43] checklist: "study design" (as all studies were considered are retrospective), this item has been removed. Furthermore, the following item has been added: "sample attrition"

4.5.3 Comparative performance of tests (diagnostic accuracy indices for identifying LTBI)

4.5.3.1 Incidence of active TB (new studies n = 2)

4.5.3.1.1 Ratios of cumulative incidence ratios (R-CIRs):

This section included 2 studies which followed-up participants for the development of active TB.[141, 142] Both studies correlated IGRA (QFT-GIT[140] QFT-G and TSPOT[141]) and TST results with cumulative incidence of active TB. The resulting CIRs for QFT-GIT were not significantly different from that for TST-5mm (R-CIR = 2.55, 95% CI: 0.57, 11.40)[141] and TST-10mm (R-CIR = 0.87, 95% CI: 0.17, 4.56).[142] See Table 22. Similarly, in the latter study,[141] the CIR for TSPOT vs. TST-15mm was not significant (R-CIR=0.37, 95% CI: 0.10, 1.41).

Table 22. Incidence of active TB for studies on recent arrivals from countries with a high incidence of TB

Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
Harstad, 2010[141] Norway [Low]	**N test results** QFT-GIT/G: 823 T-SPOT: 823 TST: 823 **Test (+/-)** QFT-GIT/G (246/577) TST ≥ 6 mm (426/395) TST ≥15 mm (128/693) **N indeterminate** QFT-GIT/G: NR TST: NR **N lost to follow-up:** NR	**QFT (GIT/G)** SN: 88.89 (56.5,98.01) SP: 71.46 (68.25,74.47) PPV: 3.36 NPV: 99.83 (99.02, 99.97)	**TST ≥ 6 mm** SN: 88.89 (56.5, 98.01) SP: 49.19 (45.74, 52.65) PPV: 1.92 (0.98, 3.75) NPV: 99.75 (98.58, 99.96) **TST ≥ 15 mm** SN: 33.33 (12.06, 64.58) SP: 85.32 (82.71, 87.60) PPV: 2.48 (0.84, 7.03) NPV: 99.13 (98.12, 99.6)	**QFT (GIT/G)** CI (+): 3.36 (1.71, 6.49) CI (-):0.17 (0.00, 1.08) CIR: 19.39 (2.43, 154.2) IDR (+): NR IDR (-): NR IDRR: NR	**TST ≥ 6 mm** CI (+):1.92 (0.98, 3.75) CI (-):0.25 (0.00, 1.57) CIR: 7.61 (0.95, 60.59) IDR (+): NR IDR (-):NR IDRR: NR **TST ≥ 15 mm** CI (+):2.48 (0.84, 7.03) CI (-):0.86 (0.35, 1.92) CIR: 2.86 (0.725, 11.28) IDR (+): NR IDR (-):NR IDRR: NR	**R-CIR [QFT (GIT/G)] vs. TST ≥ 6 mm** 2.55(95% CI: 0.57, 11.40) **R-IDRR [QFT (GIT/G)] vs. TST ≥ 6 mm** NR **R-CIR [QFT(GIT/G)] vs. TST ≥ 15 mm** 0.38(95% CI: 0.11, 1.34) **R-IDRR [QFT(GIT/G)] vs. TST ≥ 15mm** NR
Kik, 2010[142] The Netherlands [Low]	**N test results** QFT-GIT/G: 339 T-SPOT: 339 TST: 339 **Test (+/-)** QFT-GIT/G	**QFT (GIT/G)** SN: 62.50 (30.57, 86.32) SP: 45.77 (40.38, 51.25) PPV: 2.80 (1.20, 6.40) NPV: 98.0 (94.20, 99.31)	**TST ≥ 10 mm** SN: 100.00 (70.08, 100.00) SP: 15.45 (11.95, 19.75) PPV: 3.12 (1.65, 5.83) NPV: 100.00 (93.00, 100.00)	**QFT (GIT/G)** CI (+): 2.80 (1.20, 6.40) CI (-): 2.00 (0.42, 6.02) CIR: 1.39 (0.34, 5.74) IDR (+): NR IDR (-): NR IDRR: NR	**TST ≥ 10 mm** CI (+): 3.12 (1.65, 5.83) CI (-):1.96 (0.05, 10.4) CIR: 1.59 (0.21, 71.2) IDR (+): NR IDR (-): NR IDRR: NR	**R-CIR [QFT (GIT/G)] vs. TST ≥ 10 mm** 0.87 (95% CI: 0.17, 4.56) **R-IDRR [QFT (GIT/G)] vs.**

Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Development of active TB**		
				CI in %, CIR IDR in per P-Y, IDRR (95% CI)		**R-CIR R-IDRR (95% CI)**
		IGRA QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA vs. TST (by threshold)**
	(178/149) T-SPOT (181/118) TST ≥10 mm (288/51) TST ≥ 15 mm (184/138) **N indeterminate** QFT-GIT/G: 12 T-SPOT: 40 TST ≥10 mm: 0 TST ≥15mm: 0 **N lost to follow-up**	**T-SPOT** SN: 5.00 (40.93, 92.85) SP: 39.86 (34.4, 45.58) PPV: 3.31 (1.52, 7.04) NPV: 98.31 (94.03, 99.53)	**TST ≥ 15mm** SN: 87.5 (52.91, 97.76) SP: 43.63 (38.25, 49.16) PPV: 3.80 (1.85, 7.64) NPV: 99.28 (96.01, 99.87)	**T-SPOT** CI (+):3.31 (1.52, 7.04) CI (-):1.69 (0.08, 6.35) CIR: 1.95 (0.40, 9.52) IDR (+): NR IDR (-): NR IDRR: NR	**TST ≥ 15 mm** CI (+):3.80 (1.85, 7.64) CI (-):0.72 (0.00, 4.39) CIR: 5.25 (0.65, 42.17) IDR (+): NR IDR (-): NR IDRR: NR	**TST ≥ 10 mm** NR **R-CIR (T-SPOT) vs. TST ≥ 15 mm** 0.37(0.10, 1.41) **R-IDRR (T-SPOT) vs. TST ≥ 15 mm** NR

Abbreviations: N = number; SN = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; CI = cumulative incidence; CIR = cumulative incidence ratio; IDR = incidence density rate; IDRR = incidence density rate ratio; TB = tuberculosis; R-CIR = ratio of cumulative incidence ratio; R-IDRR = ratio of incidence density rate ratio; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test; P-Y = person-year(s); 95% CI = 95 percent confidence interval

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

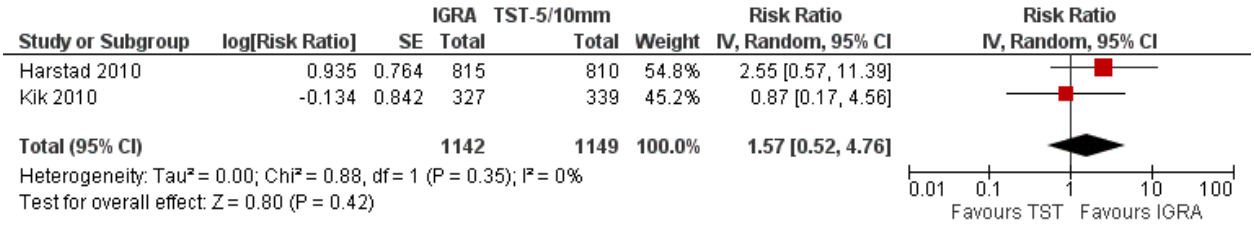


Figure 42. Pooled ratio of diagnostic odds ratio (R-DOR) of QFT-GIT vs. TST (5mm or 10mm) based on high risk and low risk exposure in recent arrivals from countries with a high incidence of TB

4.5.4 Sensitivity and specificity

This section incorporates two newly identified recent studies.[141, 142] There was a homogeneity in sensitivity of both QFT-GIT (pooled sensitivity: 76%, 95% CI: 50, 93; I^2 = 30.8%) and TST 5mm/10mm (pooled sensitivity: 94%, 95% CI: 73, 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 (Figure 43, Figure 44, Figure 45, Figure 46). In summary, QFT-GIT demonstrated greater specificity values (range: 46%-71%) compared to TST (range: 15%-49%), but lower sensitivity (pooled estimate: 76%) compared to TST (pooled estimate: 94%). One study showed TST-15mm to have performed better than TSPOT both in terms of sensitivity (87% vs. 75%) and specificity (44% vs. 40%).[142]

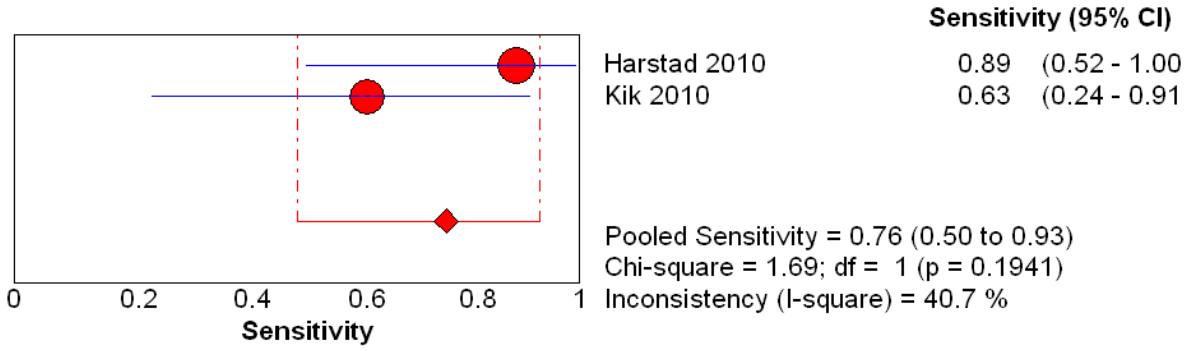


Figure 43. Forest plot of sensitivity based on incidence of active TB (QFT-GIT) in recent arrivals from countries with a high incidence of TB

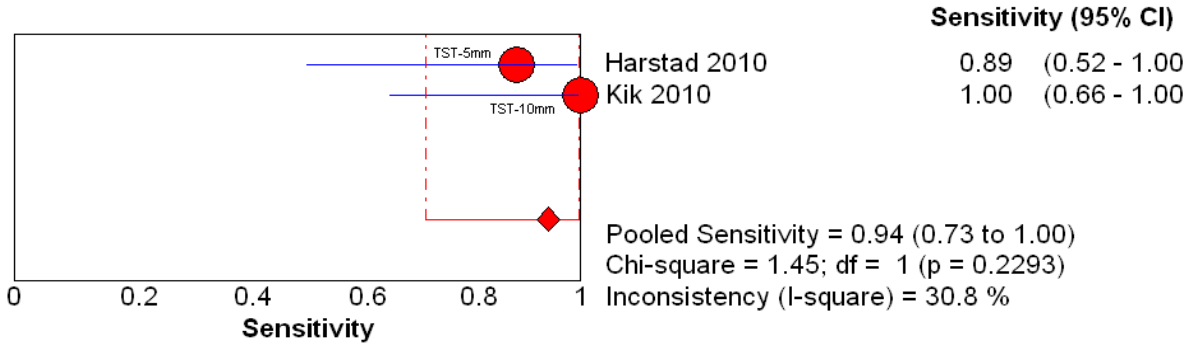


Figure 44. Forest plot of sensitivity based on incidence of active TB (TST) in recent arrivals from countries with a high incidence of TB

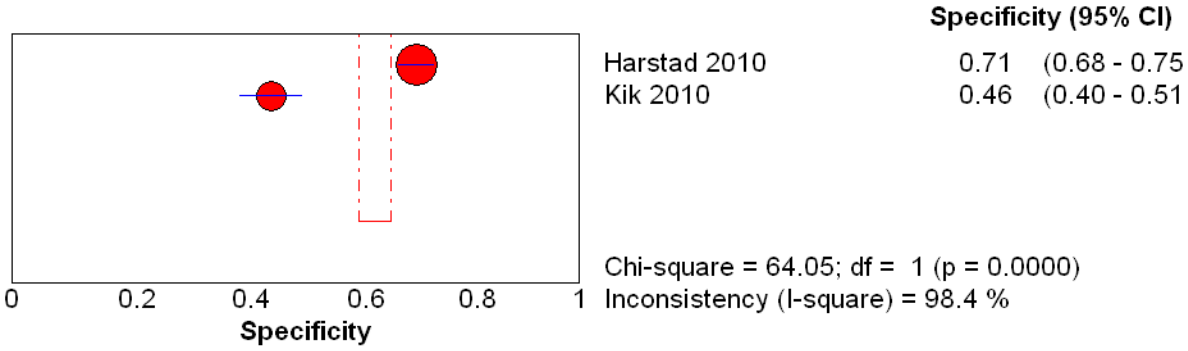


Figure 45. Forest plot of specificity based on incidence of active TB (QFT-GIT) in recent arrivals from countries with a high incidence of TB

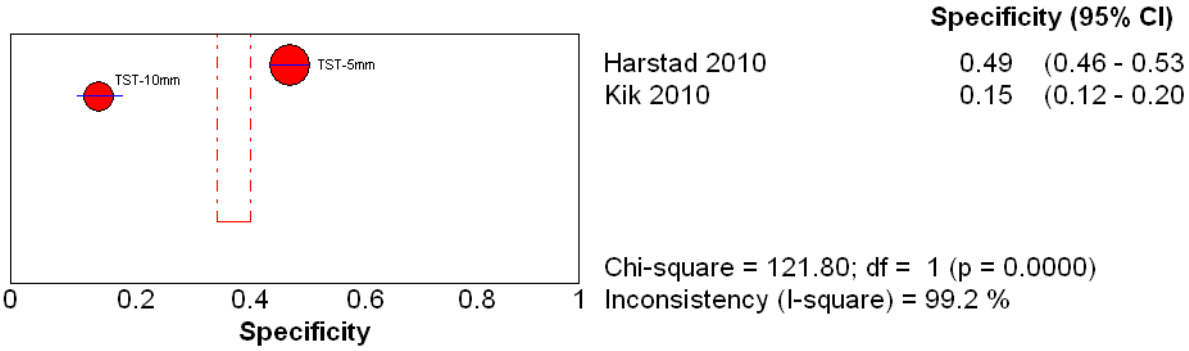


Figure 46. Forest plot of specificity based on incidence of active TB (TST) in recent arrivals from countries with a high incidence of TB

4.5.4.1 Exposure levels

4.5.4.1.1 Ratios of diagnostic odds ratios (R-DORs):

Seven of the 10 studies reviewed in CG117 (see Appendix 6) found significant strong associations presented as DORs for both IGRA and TST (5mm, 10mm, 15mm) across exposure gradient groups defined as place of birth, racial group, country prevalence.[164, 183, 184, 186-189] The estimates of R-DORs comparing IGRA to TST across these studies ranged from 0.14[189] to 0.98.[186] Since the CG117 report did not provide the 95% confidence intervals around these estimates, it is not clear what the predictive performance of IGRA relative to TST is in terms of identifying LTBI. As for the studies identified in the present review, one study showed that IGRA compared to TST was more strongly correlated with the exposure groups of geographic 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, 1.49).[144] In two other studies,[143, 145] the comparisons of IGRA and TST in relation to exposure to TB (R-DOR = 0.60, 95% CI: 0.32, 1.12) and birth in TB burden country (R-DOR = 1.00, 95% CI: 0.60, 1.66), were not statistically significant (see Table 23).

Table 23. Comparison of the test performance – diagnostic accuracy indices for identifying LTBI (exposure studies) in recent arrivals from countries with a high incidence of TB

Study ID (Author name, year, and country) [burden]	Test results	Test diagnostic accuracy in % (95% CI)		Construct validity (i.e., LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		R-DOR (95% CI)
		IGRA QFT (GIT/G) and/or TSPOT	TST (by threshold)	IGRA QFT (GIT/G) and/or T-SPOT	TST (by threshold)	IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)
Lucas, 2010[143] Australia [Low]	**N test results** QFT-GIT: 460 T-SPOT: 420 TST: 304 **Test (+/-)** QFT-GIT (45/345) T-SPOT (38/374) TST≥ 10 mm (54/250) **N indeterminate** QFT-GIT/G: 70 T-SPOT: 8 TST: 0 **N lost to follow-up**	**QFT (GIT)** High exposure level vs low exposure level SN: NR SP: NR PPV: NR NPV: NR **T-SPOT** 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** SN: NR SP: NR PPV: NR NPV: NR	**QFT (GIT)** High exposure level vs low exposure level <u>Low</u> DOR: 2.40 (95% CI: 1.00, 5.80) DORa: NA <u>Low</u> DOR: 2.50 (95% CI: 0.90, 6.50) DORa: NA	**TST ≥ 10 mm** High exposure level vs low exposure level <u>Low</u> DOR: 4.00 (95% CI: 1.70, 9.50) DORa: NA <u>Low</u> DOR: 4.00 (95% CI: 1.70, 9.50) DORa: NA	**QFT-GIT vs. TST ≥ 10 mm** High exposure level vs low exposure level <u>Low</u> R-DOR: 0.60 (95%CI: 0.32, 1.12) R-DORa: NA <u>Low</u> R-DOR: 0.63 (95% CI: 0.32, 1.22) R-DORa: NA
Orlando, 2010[144] Italy [Low]	**N test results** QFT-GIT: 1130 T-SPOT: TST: 1129 **Test (+/-)** QFT-GIT/G (337/778) TST≥ 10 mm	**QFT (GIT)** Asian continent vs African continent SN: NR SP: NR PPV: NR NPV: NR	**TST ≥ 10 mm** Asian continent vs African continent SN: NR SP: NR PPV: NR	**QFT (GIT)** Asian continent vs African continent DOR: 1.61 (0.90, 2.88) DORa: 1.07 (0.52, 2.23)	**TST ≥ 10 mm** Asian continent vs African continent DOR: 0.91 (0.50, 1.64) DORa: 0.72 (0.34, 1.53)	**QFT-GIT vs. TST ≥ 10 mm** Asian continent vs African continent R-DOR: 1.77 (1.16, 2.70) R-DORa: 1.49 (0.87, 2.53)

Study ID (Author name, year, and country) [burden]	**Test results**	**Test diagnostic accuracy in % (95% CI)**		**Construct validity (i.e., LTBI exposure-based proxy)**		
				DOR (95% CI) (vs. non-exposed; reference group)		**R-DOR (95% CI)**
		IGRA QFT (GIT/G) and/or TSPOT	**TST (by threshold)**	**IGRA** QFT (GIT/G) and/or T-SPOT	**TST (by threshold)**	**IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)**
	(407/492) **N indeterminate** QFT-GIT:15 TST: 0 **N lost to follow-up** TST: 230 (dropouts)	Latin America vs Africa SN: NR SP: NR PPV: NR NPV: NR TB prevalence Contact with TB case vs. no contact SN: NR SP: NR PPV: NR NPV: NR	NPV: NR Latin America vs Africa SN: NR SP: NR PPV: NR NPV: NR TB prevalence Contact with TB case vs. no contact SN: NR SP: NR PPV: NR NPV: NR	Latin America vs Africa DOR: 1.46 (0.99, 2.16) DORa: 0.81 (0.46, 1.42) TB prevalence Contact with TB case vs. no contact DOR: 2.54 (1.82, 3.54) DORa: 2.11 (1.47, 3.03)	Latin America vs Africa DOR: 0.86 (0.59, 1.26) DORa: 0.57 (0.33, 1.00) TB prevalence Contact with TB case vs. no contact DOR: 1.87 (1.30, 2.69) DORa: 1.87 (1.24, 2.80)	Latin America vs Africa R-DOR: 1.70 (1.29, 2.24) R-DORa: 1.42 (0.95, 2.24) TB prevalence Contact with TB case vs. no contact DOR: 1.36 (1.06, 1.75) DORa: 1.13 (0.85, 1.49)
Saracino, 2009[145] Australia [Low]	**N test results** QFT-GIT/G: 452 TST: 452 **Test (+/-)** QFT-GIT/G (107/172) TST≥ 10 mm (72/207) **N indeterminate** QFT-GIT/G: 173 TST: 173 **N lost to follow-**	**QFT (GIT/G)** 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/G)** Region of origin vs region of origin DOR:NR DORa: NA	**TST ≥ 10 mm** Region of origin vs region of origin DOR: NR DORa: NA	**QFT-GIT/G vs. TST ≥ 10 mm** Region of origin vs region of origin R-DOR: NR R-DORa: NA

Study ID (Author name, year, and country) [burden]	Test results	Test diagnostic accuracy in % (95% CI)		Construct validity (i.e., LTBI exposure-based proxy)		
				DOR (95% CI) (vs. non-exposed; reference group)		R-DOR (95% CI)
		IGRA QFT (GIT/G) and/or TSPOT	TST (by threshold)	IGRA QFT (GIT/G) and/or T-SPOT	TST (by threshold)	IGRA (QFT-GIT/G or T-SPOT) vs. TST (by threshold)
	up QFT-GIT/G: 169 TST: 169					

Abbreviations: N = number; SN = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; DOR = diagnostic odds ratio; DORa = adjusted diagnostic odds ratio; R-DOR = ratio of diagnostic odds ratio; R-DORa = adjusted ratio of diagnostic odds ratio; TB = tuberculosis; 95% CI = 95 percent confidence interval; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test

Based on the meta-analysis of the three studies,[143-145] the pooled R-DOR for IGRA (QFT-GIT) vs. TST-10mm (contact with TB case, exposure to TB, birth in TB burden country) was not statistically significant suggesting that there is no evidence that IGRA performs better than TST in identifying LTBI in this population. (Figure 47) (R-DOR = 0.96 CI: 0.69, 1.33).

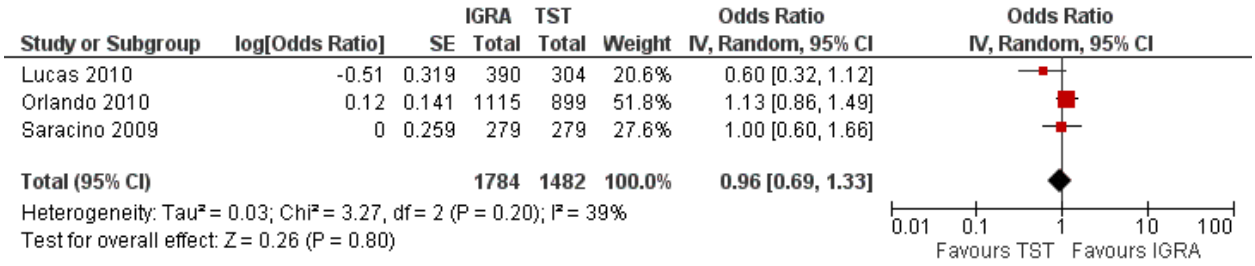


Figure 47. Pooled ratio of diagnostic odds ratio (R-DOR) of IGRA vs. TST 10mm based on high risk and low risk exposure in recent arrivals from countries with a high incidence of TB

4.5.4.1.2 Sensitivity, specificity, PPV, and NPV:

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

4.5.4.1.3 Influence of BCG vaccination status on test positivity:

Of the three newly identified studies,[143-145] only one reported the association between test positivity and BCG vaccination status.[143] Given the study results, there was no evidence indicating a differential effect of BCG vaccination status on IGRA (QFT, TSPOT) and TST positivity. Namely, the odds of test positivity for QFT-GIT (OR = 1.70, 95% CI: 0.80, 3.60), TSPOT (OR = 1.80, 95% CI: 0.80, 4.00), and TST (OR = 1.70, 95% CI: 0.80, 3.50) were not significantly different between the BCG vaccinated vs. non-vaccinated groups (see Table 24).

Table 24. Association between test positivity and BCG vaccination (exposure studies) in recent arrivals from countries with a high incidence of TB

Subgroup of interest – – newly arrived people				
Study ID (Author name, year, and 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[143] Australia [Low]	420	QFT-GIT	1.70 (95% CI: 0.80, 3.60)	NR
	460	T-SPOT	1.80 (95% CI: 0.80, 4.00)	NR
	304	TST: ≥10mm	1.70 (95% CI: 0.80, 3.50)	NR
Orlando, 2010[144] Italy [Low]	1130	QFT-GIT	NR	NR
	1129	TST: ≥10mm	NR	NR
Saracino, 2009[145] Australia [Low]	452	QFT-GIT	NR	NR
	452	TST: ≥10mm	NR	NR

Abbreviations: TB = tuberculosis; NR = not reported; N = number; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test; 95% CI = 95 percent confidence interval

4.5.4.2 Between-test concordance, discordance, and agreement

This relevant evidence was reported for nine CG117 studies[164, 181-186, 188, 189] (see Appendix 6) and three newly identified studies[143-145] (see Appendix 9). In overall samples, the percent concordance between IGRA and TST-10mm ranged from 63.6%[186] to 84.2%.[188] The corresponding concordance between IGRA and TST-5mm was similar and ranged from 60.7%[186] to 90%.[189] The kappa values between IGRA and TST (regardless of TST threshold and BCG vaccination status) ranged from 0.08 to 0.68,[186] most of them below the value of 0.45. Both concordance and kappa were greater amongst BCG unvaccinated (or total sample) vs. vaccinated only[144, 164, 181-184, 186, 188] (see Table 25 for agreement; see Appendix 6 for CG117 studies).

Table 25. Between-test concordance and discordance (exposure studies and incidence studies) in recent arrivals from countries with a high incidence of TB

Study ID (Author name, year, and country) [burden]	Sample size (N) total or by subgroup	Type of IGRA vs. TST induration threshold	Concordance (%) 95% CI	Discordance (%) 95% CI	Agreement kappa 95% CI
Lucas, 2010[143] Australia [Low]	NR	T-SPOT vs 10mm	NR	NR	0.45 (0.38, 0.53)
	NR	QFT-GIT vs 10mm	NR	NR	0.46 (0.39, 0.53)
Orlando, 2010[144] Italy [Low]	887	QFT-GIT vs 10mm	70.46 (67.32, 73.43)	29.53 (NR)	0.38 (NR)
	56 BCG vaccinated	QFT-GIT vs 10mm	66.07 (52.09, 77.84)	33.92 (NR)	0.35 (NR)
	789 unvaccinated	QFT-GIT vs 10mm	71.36 (68.04, 74.46)	28.64 (NR)	0.40 (NR)
Saracino, 2009[145] Australia [Low]	279 total	QFT-GIT vs 10mm	70.97 (65.39, 75.98)	29.03 (24.02, 34.61)	0.35 (0.23, 0.46)
Harstad, 2010[141] Norway [Low]	823	QFT-GIT vs 10mm	NR	NR	NR
	823	QFT-GIT vs 15mm	NR	NR	NR
Kik, 2010[142] The Netherlands [Low]	433	QFT-GIT vs 10mm	NR	NR	NR

Abbreviations: 95% CI = 95 percent confidence interval; QFT = QuantiFERON-TB; GIT = Gold In-Tube; TST = tuberculin skin test

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

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

Seven of the 10 studies reviewed in CG117 found significant strong associations presented as DORs for both IGRA and TST (5mm, 10mm, 15mm) across exposure gradient groups defined as place of birth, racial group, country prevalence. However, the R-DORs comparing IGRA to TST across these studies ranged from 0.14 to 0.98. Since the CG117 report did not provide the 95% confidence intervals, 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) vs. TST-10mm (contact with TB case, exposure to TB, birth in TB burden country) was not statistically significant, suggesting no evidence of IGRA performing better than TST in identifying LTBI.

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

Based on nine CG117 and three newly identified studies, overall percent concordance between IGRA and TST-10mm ranged from 63.6% to 84.2%. The corresponding concordance between IGRA and TST-5mm was similar (range: 60.7%-90%). Most kappa values between IGRA and TST (regardless of TST threshold and BCG vaccination status) were below the value of 0.45. Both concordance and kappa were greater amongst BCG unvaccinated.

4.6 Overall summary of results

We identified 53 more recent studies. Risk of bias was assessed for 15 studies which evaluated the incidence of active TB and methodological quality was assessed for the remaining 38 studies which correlated test results with prior TB exposure. Seven of the 15 studies (incidence group studies) were identified as having high risk of bias, six as moderate risk of bias and the remaining two as low risk of bias. All had important drawbacks in design, methods, and poor reporting. Of the 38 studies (exposure group studies), 29 were generally of lower quality, six were of moderate quality and three were of high quality.

Children

Although the limited evidence in children showed no significant difference between QFT-GIT and TST-5mm (pooled R-CIR = 1.12, 95% CI: 0.72, 1.75), QFT-GIT performed significantly better than TST-10mm in predicting risk of active TB (pooled R-CIR = 4.33, 95% CI: 1.32, 14.23). IGRA (QFT-GIT/G) demonstrated a similar sensitivity (range: 48%-100%) and a slightly better specificity (range: 49%-90%) when compared to TST 5mm (sensitivity range: 57%-100%; specificity range: 45%-65%). Although, sensitivities of IGRA and TST 5mm were higher than that for TST 10mm (range: 30%-56%), the corresponding specificities of these tests were lower compared to TST 10mm (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: 2.15, 10.44) as compared to the high TB settings (pooled R-DOR = 1.13, 95% CI: 0.78, 1.65).

Immunocompromised people

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

Recent arrivals

Overall, based on studies of incidence, there was no significant difference between the performance of QFT-GIT and TST 5mm/10mm in identifying LTBI among newly arrived people from high TB burden countries (Pooled R-CIR = 1.57, 95% CI: 0.52, 4.76). Similarly, there was no significant difference between T.SPOT.TB and TST-10mm in predicting LTBI (R-CIR=0.37, 95% CI: 0.10, 1.41). Likewise, the pooled result showed no significant difference between QFT-GIT and TST 10mm for the associations with prior TB exposure (Pooled R-DOR = 0.96 CI: 0.69, 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 prior TB exposure for defining LTBI. Prior exposure to TB was highly variable and ill-defined, lacking a description of duration and proximity of contact to index TB cases. Overall, while 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 definition) precluded a more meaningful subgroup analysis due to the scarcity of evidence for each subgroup.

5 Systematic review of economic evaluation studies

5.1 Identification and selection of studies

5.1.1 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 the literature on the suitability of existing cost-effectiveness models and model design, and also to identify studies which reported costs and health-related quality of life (HRQL) 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 which aimed to compare both the clinical effectiveness and cost-effectiveness of screening tests (IGRAs and TST) for LTBI in high risk groups: in children, in immunocompromised people or those at risk from immunosuppression, and in people who are recent arrivals 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 run for the clinical effectiveness review and focussed on the diagnosis of LTBI using IGRAs compared to other methods. Searches were limited to articles in English and included articles that have been added to databases since the health economics searches for the equivalent questions in the NICE clinical guideline CG117 were run (5 – 6 January 2010, Appendix 1).[10] These searches automatically picked up comparisons between IGRAs and TSTs, therefore it was not necessary to search independently for comparator technologies (e.g., TSTs). These searches were not restricted by study type, therefore an economics search filter was not required. The search strategies are provided in Appendix 1. Details of the databases and other sources searched are provided in the clinical effectiveness section (Section 3.1). Additional databases searched for cost-effectiveness were:

- Research Papers in Economics (REPEC)
- CEA Registry
- HEED (Wiley)

A separate search in Medline was performed to identify existing cost-effectiveness model designs for LTBI. The search strategy is available in Appendix 1.

5.1.1.1 Inclusion and exclusion of relevant studies

5.1.1.1.1 Inclusion criteria

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

5.1.1.1.2 Population

- Research question #1: Children (both genders, age < 18 years, immunocompetent)
- Research question #2: People (both genders, any age) who are immunocompromised or at risk from immunosuppression (e.g., transplant recipients or those with HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, or who are on or about to start anti-TNF-α treatment, steroids, or cyclosporins)
- Research question #3: People (both genders, 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 or greater e.g. those in Africa, Central/South America, Eastern Europe, and Asia)

5.1.1.1.3 Intervention

- InterFERON gamma release assays (IGRAs) (QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold In Tube (QFT-GIT) and T-SPOT.TB

5.1.1.1.4 Comparator

- Tuberculin skin test (TST) (Mantoux method)

5.1.1.1.5 Outcome measures

- The main outcome measure is the cost per quality adjusted life-year. Other outcomes such as correct diagnosis of LTBI and cost per active TB case prevented were also considered

5.1.1.1.6 Study design

- Studies comprising a formal economic evaluation involving direct comparison between IGRAs (QFT-G, QFT-GIT or T-SPOT.TB) with TST and include a decision analytic model in identifying people with LTBI

5.1.1.1.7 Type and language of publication

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

From the initial search of the literature, two reviewers (PA and AT) reviewed the titles and abstracts from the citations retrieved. Full texts of potentially relevant articles were read, and those that were considered model-based economic evaluations were reviewed (see Figure 48).

5.1.2 Data extraction

The 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 from the included studies 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 generalizability) and other (source of funding and conflicts of interests). The completed data extraction sheets are presented in Appendix 12.

5.1.3 Quality assessment

The quality of the studies included in the current review was assessed against the Consolidated Health Economic Reporting Standards (CHEERS)[191] and the Philips' checklist,[192] respectively.

The economic evaluations were appraised against a framework for best practice for reporting economic evaluation studies developed by the CHEERS task force.[191] The CHEERS assessment tool comprises six dimensions which include title and abstract, introduction, methods, results, discussion and other. Under these dimensions, a series of questions check whether the criteria have been clearly reported (see Appendix 13). Additionally, the models were critically appraised against a framework for best practice for reporting decision-analytical models developed by Phillips and colleagues.[192] The Phillips' quality assessment tool comprises two main dimensions, structure of the model and data used to parameterize the model. Under these dimensions several questions assess whether the criteria has been clearly reported (see Appendix 14).

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.

5.1.4 Data synthesis

Information extracted from the included studies were summarised and presented in Table 26. These findings on individual studies were compared narratively, and recommendations for the future modelling of LTBI are discussed.

5.2 Results

The literature search identified 5,959 records through electronic database searches and other sources. After removing duplicates, 3057 records were screened for inclusion. On the basis of title and abstract, 3,032 records were excluded. The remaining 25 records were included for full-text

screening. A further 15 articles were excluded at the full-text stage, and the reasons for exclusion are shown in Figure 48 and presented in Appendix 11. The literature search identified 10 studies[10, 76, 193-200] which included a decision-analytical model to estimate the cost-effectiveness of IGRAs compared with TST in diagnosing people who are at high risk of LTBI.

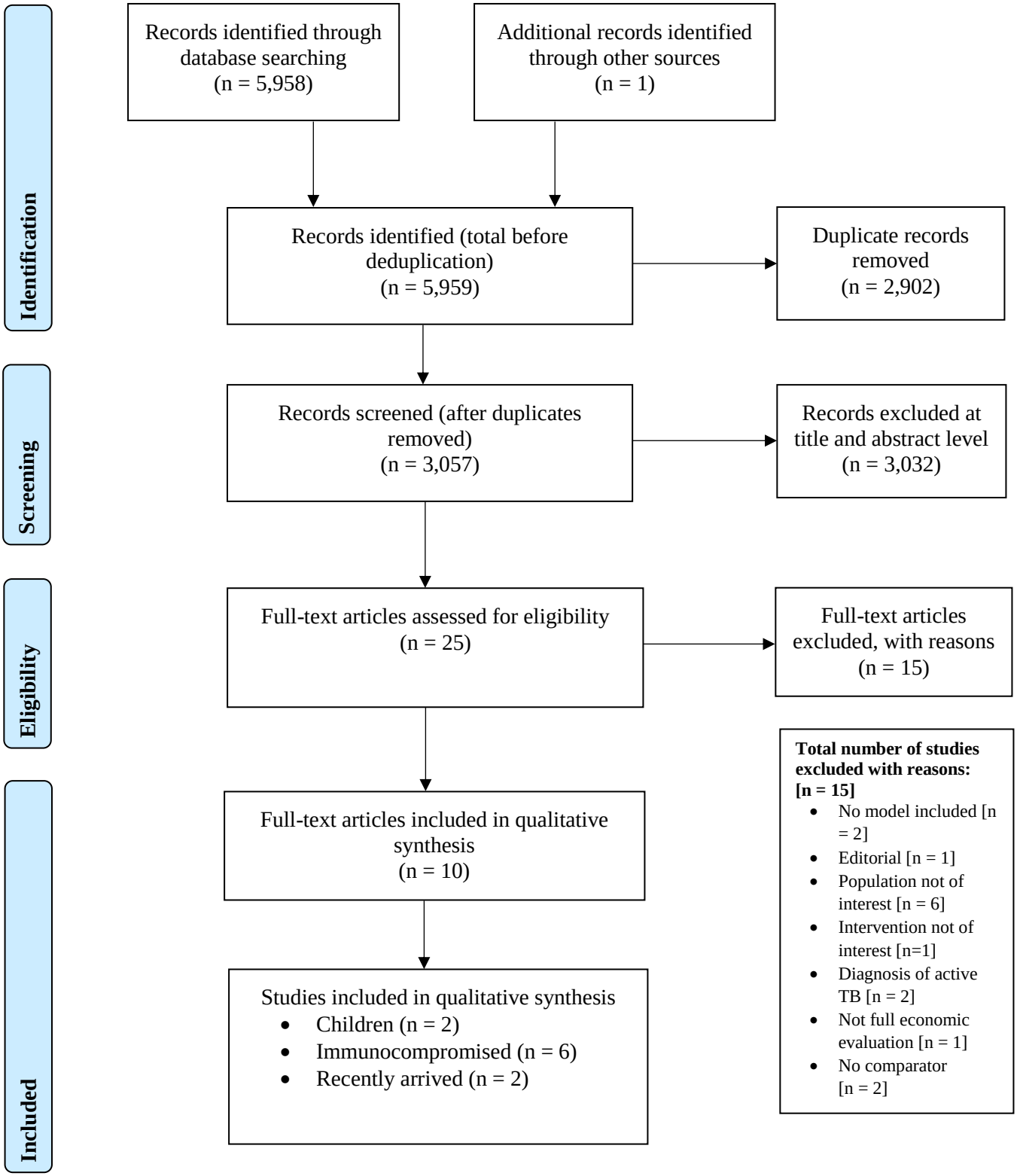


Figure 48. PRISMA study flow diagram

5.3 Summary of the general approaches to modelling LTBI

Below we present the general modelling approaches used for the diagnosis of LTBI by population of interest.

5.3.1 Children

Kowada (2012)

Kowada et al. (2012)[194] estimated the cost-effectiveness of using Quantiferon Gold-In-Tube compared with the tuberculin skin test and chest x-ray for the diagnosis of LTBI in children. The author developed a decision tree structure with Markov nodes to demonstrate the clinical pathway 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 x-ray). The model structure continued with children being in the 'LTBI'/'initial active TB' or no 'LTBI' health states, characterised by the prevalence of the disease. On positive test results, children received a chest x-ray to confirm initial active TB. Children who received a negative result on the chest x-ray were treated for LTBI. Children who adhered to LTBI treatment could develop isoniazid-induced hepatotoxicity (INH-induced hepatotoxicity). For the state-transition model, children entered the model at the 'no LTBI' health state and could remain or progress to 'LTBI', 'TB' or 'dead' health states overtime. Data required to populate the model were obtained from published sources. Estimates on 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 quality-adjusted life-years (cost per QALY) gained. Kowada et al. (2012)[194] 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 (2013)

Mandalakas et al. (2013)[200] used a decision tree structure with Markov nodes to estimate the health and economic outcomes of five screening strategies for the diagnosis of *M tuberculosis* 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 states, characterised by the prevalence of the disease. Children with positive test results were eligible for treatment for LTBI, and could either

accept of 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 due to 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 cost per life-year saved (LYS). Base-case results indicate that for 0-2 year olds, the no testing strategy was the dominant strategy whilst for 3-5 year olds, an IGRA following a negative TST was the most effective strategy but not cost-effective compared to no testing. The authors conducted one-way sensitivity analyses to determine the impact of data uncertainties on the results.

5.3.2 Immunocompromised

Kowada (2010)

Kowada et al. (2010)[193] 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 the 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 received a chest x-ray to detect active TB. If active TB was detected people received treatment for active TB. If active TB was not detected, people received treatment for LTBI. Here the author assumed that chest-ray to diagnose initial active TB was 100% sensitive and specific. People who adhered to LTBI treatment were at risk of developing INH-induced hepatotoxicity. Kowada et al. (2010)[193] 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 states.

The information required to populate the model were obtained from published sources. However, the author has not provided comment/discussion on the sources of prevalence of LTBI in this population. Information on the sensitivity and specificity of the tests were 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 has not elaborated 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 presented in terms of an incremental cost-effectiveness ratio expressed as cost per QALYs gained. Kowada 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, but the distributions and the cost-effectiveness acceptability curve 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 100% probability of being cost-effective compared to TST at society's willingness-to-pay of US$50,000 per QALY.

Kowada (2013)

In this study Kowada et al. (2013)[195] used a decision tree structure with Markov nodes to assess the costs and effects of using QFT-GIT alone, TST alone and chest x-ray alone to diagnose LTBI in patients being screened for haemodialysis. The model simulated a pathway for a hypothetical cohort of people with haemodialysis being screened, and the cost-effectiveness was estimated over a lifetime horizon. The model started with a cohort of people who received one of three diagnostic tests. People with positive results on the TST or QFT-GIT received a chest x-ray to detect active TB. If active TB was detected people received treatment for active TB. If active TB was not detected, people received treatment for LTBI. The author assumed that chest-ray 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 et al. (2013)[195] did not present the illustrative Markov structure, but stated the clinical health states, but 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 if the accuracy of the tests was derived from a meta-analysis. The primary outcome measure of effectiveness was QALYs gained, however, the author has not elaborated on the descriptive tools used to value these health states. The analysis was conducted from the societal perspective and results presented in terms of an incremental cost-effectiveness ratio expressed as cost per QALYs gained. Kowada et al. (2013)[195] 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, but the distributions and the cost-effectiveness acceptability curve were not presented. The author demonstrated that QFT-GIT alone was the most cost-effective strategy for the diagnosis of LTBI in haemodialysis people.

Laskin (2013)

Laskin et al. (2013)[197] 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 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 three-month cycle lengths. The starting point of the model was a hypothetical cohort of new-onset of nephrotic syndrome being tested. 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 proportion of children with negative TST/IGRA results, children who LTBI treatment was successful, and those who 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 that other strategies. The results from this study should be interpreted with caution because the discounted and undiscounted costs were similar. Results from the sensitivity analysis showed that the results were robust when indirect medical costs were excluded from the analysis. Results were sensitive to changes in the prevalence of LTBI in this population, with the questionnaire followed by IGRA screening strategy to be the most cost-effective strategy at a prevalence of >4.9%. Results from the probabilistic analysis showed that at a prevalence of 1.1%, no screening compared with IGRA was the preferred screening option, but the authors have not stated at what willingness-to-pay value.

Swaminath (2013)

Swaminath et al. (2013)[199] used a decision tree structure to estimate the costs and benefits of using QuantiFERON-Gold (QFT-G) alone compared to TST alone for the diagnosis of LTBI in people with inflammatory bowel disease (IBD). 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 INH-induced hepatitis, and survived or died from this event. People who were false negative, could have re-activated TB, and could survive or die from this event. People who were false positive received treatment and could further develop INH-induced hepatitis. The authors suggested that people with indeterminate results on the QFT-G would immediately receive a second QFT-G test immediately. 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 World Health Organization (WHO). Sensitivity and specificity of tests were derived based on information obtained from a few sources, and not a literature review. The analysis was conducted from the health payer perspective and results presented in terms costs of false negative cases avoided, TB reactivations and deaths avoided. The authors conducted one-way

sensitivity analyses around key model input parameters. Swaminath and colleagues suggested that QFT-G was less costly and more effective than the TST in this population.

5.3.3 Recently arrivals from countries with high incidence of TB

Pareek (2013)

Pareek et al. (2013)[76] 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. Hence, further comment/appraisal on the structure/pathways could not be made. The authors suggested that immigrants who were symptomatic at initial screening or had a positive IGRA/TST result were referred for a chest x-ray and further clinical assessment. Immigrants with a positive IGRA and/or positive TST result and a normal chest x-ray without any symptoms of suggesting active TB were considered to have LTBI. For a positive TST test, cut-offs of ≥ 6mm and ≥ 15mm were used for BCG-unvaccinated and BCG-vaccinated participants, respectively. Additionally, the authors used a non-stratified cut-off of ≥ 10mm 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 were recently arrived (within the last five years) immigrants to the UK, aged ≥ 16 years (with symptoms of TB) or from a country with a TB incidence of ≥ 40/100, 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 are presented as cost per active TB cases avoided. Both costs and benefits were discounted at 3.5% per annum. Pareek et al. (2013)[76] conducted sensitivity analyses on key model input parameters (prevalence of LTBI, progression rate from LTBI to active TB, reducing the specificity, proportion of immigrants accepting and adhering to LTBI treatment). Base-case results showed that the screening strategy of 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 active TB avoided, in 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 or lower, the strategy was not cost-effective (at £30,000 per QALY. Results from the sensitivity analyses showed that varying the prevalence of the cohort and the progression rate from LTBI to active TB increased the cost-effectiveness of using the one-step QFT-GIT. Reducing the specificity of 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 lead to higher cost-effectiveness estimates.

CG117

The authors of CG117[10] used a decision tree structure to compare the costs and effects between 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 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 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 negative results, a proportion were given a BCG vaccination. The end-point of the model is 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 tests were derived based on two publications, and an average value was used as an estimate. Costs included in the model were those related to the UK NHS and Personal Social Services (PSS). All costs were presented in pounds sterling in 2008/09 prices. Costs obtained from published sources were inflated using the hospital and community Health Services Pay and Price Index. The results showed that TST positive followed by IGRA, and IGRA alone 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) changed the direction of the cost-effectiveness results.

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

Study ID (First author, year, and 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,[194] Japan	To assess the cost-effectiveness of school-based TB screening using QFT-GIT versus the 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 strategy
Mandalakas, 2013,[200] 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 due to future exposures, pulmonary TB, disseminated TB, TB death and death from other causes	In the 0-2 cohort, no testing strategy dominated other strategies In the 0-3 cohort, the TST –ve followed by IGRA was the most - effective with a reported ICER of approximately US$233 000 per LYS versus no testing
Immunocompromised							
Kowada, 2010,[193] Japan	To assess the cost-effectiveness of QFT-GIT versus TST for TB screening of RA patients prior to	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 strategy. At society's WTP per QALY, the

Study ID (First author, year, and 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)
	initiation of TNFα antagonist therapy						probability of QFT-GIT testing strategy has a 100% probability of being cost-effective compared to the TST
Kowada, 2013,[195] Japan	To assess the cost-effectiveness of QFT-GIT compared with the TST and the CXR for TB screening of haemodialysis	Cost-effectiveness, 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 to TST testing strategy. Results from the SA showed that the base-case results were sensitive to the BCG vaccination rate. At all WTP thresholds, the probability of QFT-GIT testing strategy has a 100% probability of being cost-effective compared to the TST
Kowada, 2014,[196] Japan	To assess the cost effectiveness for TB screening of high risk HIV positive pregnant women by using IGRAs compared to the TST in low	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 dead	Base-case results showed that the T-SPOT.TB is less costly and was more effective compared to other strategies. SA showed that the

Study ID (First author, year, and 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)
	incidence countries						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
Laskin, 2013,[197] 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 compared to universal TST
Linas, 2011,[198] 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, INH related hepatitis, < six months INH, 6-8 months INH, nine months INH, Active TB, post active TB and death	Base-case results showed that people who are taking immunosuppressive medications, neither TST nor IGRA screening was cost-effective versus the no screening strategy. Similar results were reported for people with ESRD.
Swaminath, 2013,[199]	To compare the	Cost-	QFT-G	Cost per false	Decision tree	True positive,	Base-case results

Study ID (First author, year, and 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)
USA	performance of TST and QFT-G got screening LTBI among immunosuppressed IBD patients based on prevalence, mortality risk reactivation TB, and costs	effectiveness, health care payer, setting not reported		negative cases of LTBI avoided, cost per TB deaths avoided, cost per reactivation TB avoided (this can be derived from the information provided)	model	true negative, false positive, false negative, hepatitis, survive/death hepatitis	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 TST
Recently arrived							
CG117, 2011,[10] UK	To compare the cost and effects of four strategies of testing for people suspected with LTBI in England and Wales	Cost-effectiveness analysis, NHS and Personal Social Services (PSS)	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 +ve followed by IGRA and IGRA testing strategies were associated with ICERs below £30, 000 per QALY compared with no testing. 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
Pareek, 2013,[76] UK	To assess the cost-effectiveness of LTBI screening using different	Cost-effectiveness analysis, NHS, primary care setting	1) T-SPOT.TB alone, 2) QFT-GIT alone, 3) TST plus	Cost per case of active TB avoided	Decision tree model	The illustrative modelling structure was presented in a	Results showed that screening of recently arrived immigrants from

Study ID (First author, year, and 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)
	screening modalities at different incidence thresholds in a primary care setting, with and without CXR screening on arrival at port of entry		confirmatory T-SPOT.TB (if TST positive), and 4) TST plus confirmatory QFT-GIT (if TST positive)			supplementary web-appendix, but unfortunately, these structures were illegible	countries of origin with moderate (not defined) TB incidence is likely to be cost-effective by the use of one-step IGRA testing compared to other screening strategies

BCG, Bacillus Calmette–Guérin; CXR, Chest x-ray, ESRD, End-stage renal disease; HIV, Human immunodeficiency virus; IGRA, Interferon-gamma release assay; INH, Isoniazid; LTBI, Latent tuberculosis infection; LYS, Life-year saved; NHS, National Health Service; PSS, Personal Social Services; QALY, Quality adjusted life-years, QFT-G, QuantiFERON-Gold; QFT-GIT, QuantiFERON Gold-In-Tube; RA, Rheumatoid arthritis; SA, Sensitivity analysis; TB, Tuberculosis; TST, Tuberculin skin test; WTP, Willingness-to-pay

5.4 Characteristics of included studies

The characteristics of the models included in these evaluations are summarised in Table 26. All of the ten included studies used an economic model to determine the cost-effectiveness of various strategies for the diagnosis of LTBI. Four[193-196] economic evaluations were conducted in Japan, three[197, 199, 201] studies in USA, two[10, 76] studies in the UK, and one study[200] in South Africa. Three studies[193-195] compared QFT-GIT only with TST only, two studies[197, 201] compared IGRA with TST, but have not suggested the type of IGRA being used, one study[199] compared QFT-G only with TST only and four studies[10, 76, 196, 200] compared various testing strategies (TST alone, QFT alone, QFT-GIT alone, T-SPOT.TB, TST followed by QFT and TST followed by T-SPOT.TB, TST –ve followed by IGRA) for the diagnosis of LTBI. Two[194, 200] economic evaluations were conducted in a population with children, six[193, 195-197, 199, 201] evaluations were conducted in the immunocompromised population and two[10, 76] were conducted in the recently arrived population.

From the outcomes reported, six[10, 193-197] studies reported their results in terms of cost per quality-adjusted life-years only, three studies[76, 199, 200] reported their results in terms of cost per life-year saved (LYS), cost per false negative cases of LTBI avoided, cost per TB deaths avoided, cost per reactivation TB avoided or cost per TB avoided and one study,[201] their outcomes were based on number needed to screen to prevent one case of active TB, life expectancy, quality-adjusted life-years gained. From the base-case results reported in these studies, the general consensus was that IGRAs were less costly and more effective than other strategies.

Most of the decision-analytical models[193-197, 200] used for the analyses were decision tree structures with Markov nodes, three studies[10, 76, 199] used decision tree structures alone and one study[201] used a Markov model alone to show diagnostic strategies for detecting LTBI and progression to active TB overtime. Three models started from individuals with LTBI which progresses to active TB/no LTBI, followed by the probability of test results, four models started from test result followed by LTBI diagnosis and one model was unclear. The health states included in the models, represented those that people would experience while being screened for LTBI. In the model with a cohort of children, the health states included healthy, LTBI, TB and dead. There was some variation in the health states for the immunocompromised population, this may be due to 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 people, 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 one year to lifetime. In the models with children, the time horizon was lifetime (up to 80-years) with cycle lengths of six months'[200] and one-year.[194] In the models with immunocompromised cohorts, the time horizons ranged from one-year to lifetime, with three-month

or one-year cycle lengths and in the recently arrived cohort, the time horizons ranged from 15-years to 20-years, with annual cycle lengths. Authors justified that their time horizons chosen were long enough to measure the costs and benefits of these diagnostic strategies.

Resource use and costs included in the economic analysis depended on the perspective taken. All studies clearly stated the perspective or viewpoint the analysis was undertaken. Five studies[10, 76, 196, 199, 201] conducted their analyses from the UK NHS or other national health payer perspective, and the remaining five studies[193-195, 197, 200] conducted their analyses from the societal perspective. The five models[10, 76, 196, 199, 201] that presented results based on the health payer perspective, included direct costs related to the health service (cost of diagnostic tests, chest x-ray and sputum examinations, treatment for LTBI/active TB and treatment for INH-induced hepatotoxicity). From the five models[193-195, 197, 200] that presented results based on the societal perspective, three models[193-195] have not included indirect costs or loss of productivity.

From the outcomes reported, six studies[10, 193-197] reported their results in terms of cost per quality-adjusted life-years only, three studies[76, 199, 200] reported their results in terms of cost per life-year saved (LYS), cost per false negative cases of LTBI avoided, cost per TB deaths avoided, cost per reactivation TB avoided or cost per TB avoided and one study[201] their outcomes were based on number needed to screen to prevent one case of active TB, life expectancy and cost per QALYs gained. From the studies that reported results in terms of QALYs, utility values were obtained based on published sources in order to derive QALY estimates. These studies have referenced the original source of utility values, but have not elaborated on which descriptive system was used to values these health states.

Due to the uncertainty around key model input parameters and assumptions made in the models, all authors conducted sensitivity analyses. Five studies[10, 76, 199-201] conducted deterministic (one- and two-way) sensitivity analyses alone. The remaining studies[193-197] conducted both deterministic and probabilistic sensitivity analyses (PSAs). Sensitivity analyses were conducted around changing the prevalence of LTBI in these populations, test accuracies (sensitivity and specificity) of diagnostic tests, cost of IGRAs, return rates for TST and varying the progression rate from LTBI to active TB.

This review will be used to inform model development for the diagnosis of LTBI in three populations. Here we outline an appraisal of the modelling structures, data used to parameterize these models, and the handling of uncertainty. We also consider issues when deriving key model input parameters (prevalence, sensitivity/specificity of diagnostic tests and combination strategies).

5.5 Quality assessment of the modelling methods

We present a summary of the reporting quality of the studies included in the current review against the Philips' checklist in Appendix 14.[192]

5.5.1 Structure

The structure of the models included in this review were generally of good quality. According to best practice for developing model structures, studies clearly stated their decision problems and perspective of the analysis, their objectives of the model, which were consistent with the decision problem, and the structures which represented the clinical pathway people will follow while being screened for LTBI. However, there were some structural issues noticed; three studies Kowada 2010,[193] Kowada 2012[194] and Kowada 2013[195]) conducted their analyses from the societal perspective, but have not included indirect costs or loss of productivity in the analyses. Studies general stated the location of their analyses, but not their setting, and this may have the impact on the generalizability of results. Illustrative model structures were also presented in the majority of the studies, but one study[76], their 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, 193-197] used decision tree structures with Markov nodes for their analyses, three studies[76, 199, 200] used decision tree structures alone and one study[201] used a Markov model alone. From the studies identified, four studies[10, 76, 195-197] modelled from the test result first, followed by LTBI diagnosis, while six studies[76, 193, 194, 199-201] modelled from LTBI, followed by test result. One study (CG117[10]) included a proportion of people returning to have their TST result read. One study[199] 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 a chest x-ray to confirm if active TB was present. All studies included treatment for LTBI and TB. As a result of adhering to LTBI treatment, all studies included a proportion of people developing INH-induced hepatotoxicity, but have not included any other adverse event from adhering to TB treatment. Studies[193-197, 200] which included a Markov model generally used similar health states (no LTBI, LTBI, active TB, re-infection, disseminated TB and dead) to show the possible transitions over time.

5.5.2 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, i.e., to search the literature to inform on the data inputs and/or to inform on their model

structure or model design. All studies provided references for their model inputs, but 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 six models[76, 193, 194, 199-201] which started from known disease status, information required at this point was the prevalence of LTBI in the population. Most models used secondary sources to obtain a point estimate or to derive an estimate on the prevalence of LTBI, but have not elaborated on what the prevalence represents (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 have used multiple sources were not transparent on the methods used to derive an estimate on the prevalence of LTBI.

Test characteristics on TST and IGRAs were required for the majority of the models. Most studies have undertaken a literature review, and derived an estimate on sensitivity and specificity based on sources identified. Most studies have 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 on sensitivity and specificity based on confirmed TB cases. All studies 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, for example, TST +ve followed by IGRA have not elaborated 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 have been 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 have not elaborated on the resource use 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, the costs included did not reflect the viewpoint/perspective of the analyses. All authors, where necessary, discounted costs and benefits using the appropriate rates.

In the models that reported their results in terms of QALYs, authors provided references used to obtain the utility weights. However, the majority of the authors have not elaborated on the descriptive tools/measures used to value these health states in these populations. Hence, uncertainty arises concerning the methods/tools used to value these health states. Additionally, authors have not elaborated on if the source of utility information obtained was relevant to their population of interest.

5.5.3 Uncertainty and assumptions

Uncertainty is unavoidable in economic modelling. Briggs and Gray (1999) and Philips et al. (2004) have outlined methods to handle the four main types of uncertainty (methodological, structural, parameter and generalizability).[192, 202] All models have attempted to address uncertainty, but none of these studies addressed all types of uncertainty. All models have undertaken univariate or multivariate sensitivity analysis on key model input parameters. Four studies[193-196] have also undertaken probabilistic sensitivity analysis for joint uncertainty in model parameters to assess the impact on base-case results.

In order to have a workable model structure to conduct these analyses, most studies clearly stated their simplifying assumptions, except the model developed by Kowada et al. (2014),[196] these assumptions were unclear. In general, these assumptions outlined in the studies appeared to be feasible, but strong in some cases. One study[76] assumed that testing with an IGRA would not lead to an indeterminate result. Whilst in NICE (2011),[10] the authors assumed that treatment of LTBI/TB was adhered by the population, and it would not lead to any adverse events.

5.6 Conclusion

The evidence-base here offers insight on the decision analytical models available to determine the cost-effectiveness of IGRA compared with TST for the diagnosis of LTBI in children, immunocompromised and people from countries with high incidence of active TB. We identified ten model-based economic evaluations across these three populations. The majority of these models were in the immunocompromised or immunosuppressed population. These results highlight that the evidence available for the other two populations is 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 existing literature, but are subject to limitations. First, the majority of the studies indicated the location of the study but have not stated the setting of the analysis and this may limit the generalizability of the results. Second, the majority of the studies used QALYs as their outcome measure and have referenced the source of their utility values. However, authors have not provided 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 of the methods used to identify information to populate the models, but it was unclear on any assessment used on the

quality of the information. Finally, all models have explored uncertainty around key model input parameters, but no attempt was made to explore methodological, structural or generalizability. Other concerns relate to the derivation of prevalence, test accuracy and transition probabilities; most studies have not elaborated on these statistical/pre-model analyses.

In chapter 6, we outline the development of a de novo model which is structured against two stages to inform on the cost-effectiveness of various strategies for the diagnosis of LTBI in our populations of interest.

6 Health economics methods and results

6.1 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:

Children

- Offer a Mantoux test to children aged 2-15 years. If positive, follow-up with an interferon-gamma test.

Immunocompromised

- For people who are HIV negative, offer an interferon-gamma test alone or an interferon-gamma test with a concurrent Mantoux test. If either test is positive, perform a clinical assessment to exclude active TB and treat

Recently arrived

- Offer an interferon-gamma test alone or a dual strategy for people aged 16-35 years. If either test is positive, refer to TB specialist to exclude active TB and treat

General population

- Offer interferon-gamma test alone or interferon-gamma testing for people whose Mantoux testing shows positive results

6.2 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 model was developed with clinical input, and represents, as far as possible, the clinical pathways people would take whilst being screened for LTBI. The model structure 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 people would take in a one-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:

- Tuberculin skin test (TST) alone
- Interferon-gamma release assay (IGRA) alone
- Combinations of TST and IGRA
- Simultaneous testing

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. People begin in one of the possible health states to the right of the chance node (circle symbol). 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.[203] Below we describe each strategy in detail.

TST alone strategy: When screening with TST, an individual may or may not return to have the test result interpreted (TST not read). Adults with positive TST results (induration ≥ 5mm/10mm) are assessed for initial active TB by a chest x-ray and sputum examination. Children with positive TST results are assessed for active TB by a chest x-ray and, if that is positive, a gastric lavage procedure. People who have a positive result on the chest x-ray and sputum examination are treated for active TB. We assumed here that the chest x-ray and sputum examination are 100% accurate at diagnosing people who have initial active TB. People who adhered 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's a rare adverse event in this population.[200] People who have a negative result on the chest x-ray and sputum examination (LTBI) can either accept or refuse to be treated for LTBI. People who have accepted LTBI treatment may adhere/not adhere to treatment. If the TST is not read or the TST is negative, the individual is not followed-up.

IGRA alone strategy: When screening with IGRA alone, an individual may have a determinate or indeterminate result. Adults with determinate results and who are IGRA positive are assessed for initial active TB by a chest x-ray and sputum examination. Children with positive TST results are assessed for active TB by a chest x-ray and, if that is positive, a gastric lavage procedure. People who have a positive result on the chest x-ray and sputum examination are treated for active TB. People who have a negative result on the chest x-ray and sputum examination (LTBI) can either accept or refuse to be treated for LTBI. People who have accepted 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. If the IGRA is negative or both IGRAs are indeterminate, the individual is not followed-up.

Combined strategy: For the children and recently arrived population, people who had their TST results interpreted and are positive, receive an IGRA test. Children with determinate, positive IGRA results receive a chest x-ray, and if positive, receive the gastric lavage procedure before a sputum examination for the assessment of active TB. Children with negative chest x-ray/sputum examination results are either treated or not treated for LTBI. Children with indeterminate results receive a second IGRA, which is the same as the initial IGRA. 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 a chest x-ray and sputum examination. If there is a positive result on the chest x-ray and sputum examination, people are treated for active TB. People who have a negative result on the chest x-ray 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. These people follow similar pathways as those who received one IGRA test. At most, people will receive two IGRAs. If the TST result has not been read, the TST result is negative, the IGRA is negative or both IGRAs are indeterminate, the individual is not followed-up.

Conversely, in the immunocompromised group, people receive an IGRA test first. If the result on the IGRA is positive, people receive a chest x-ray and sputum examination to detect initial active TB. If there is a positive result on the chest x-ray and sputum examination people are treated for active TB. If the result is negative, people 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 negative IGRA results undergo a TST test. People here follow similar pathways for those who received the TST alone strategy. People with an indeterminate IGRA result receive a second IGRA test which is the same as the initial IGRA. These people follow similar pathways as those who received one IGRA test. At most, people will receive two IGRAs. People with a negative IGRA or two indeterminate results, a negative TST result or the TST result has not been read are not followed up.

Simultaneous testing strategy: When screening with an IGRA and TST, people can have a combination of test results: a determinate result on the IGRA and TST read, a determinate result and TST not read, an indeterminate result and TST read or an indeterminate result and TST not read. Children with positive results on either test receive a chest x-ray, and if positive, receive the gastric lavage procedure and sputum examination to detect initial active TB. For the other populations,

people with a positive result on either test receive a chest x-ray, and if positive, receive 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 two 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/aren't being treated for latent/active TB, though the transmission probabilities are different in each of these cases. The outputs of the decision tree are used to determine 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 identical cohort of 500,000 individuals in each arm, was run using the mean values of each parameter. In order to account for parameter uncertainty, we also ran a Monte Carlo simulation, consisting of 2,000 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 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 are treated for LTBI have a certain probability of not developing active TB in the future (the effectiveness of the treatment – assumed to be six months of isoniazid), with activation times for those whose treatment is unsuccessful sampled as above.

Age specific all-cause mortality rates are taken from UK-specific data in the Human Mortality Database,[204] 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.[205] 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 probabilities as the initial episode.

For each TB activation (primary or relapse), individuals generate a certain numbers 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.

As the model is run, any new cases of LTBI infection generated are included in the disease progression model from that time forward. Costs and QALYs are accrued by individuals according to the lengths of time 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 will be 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 28, Table 70 and Table 71 for the children, immunocompromised and recently arrived populations, respectively.

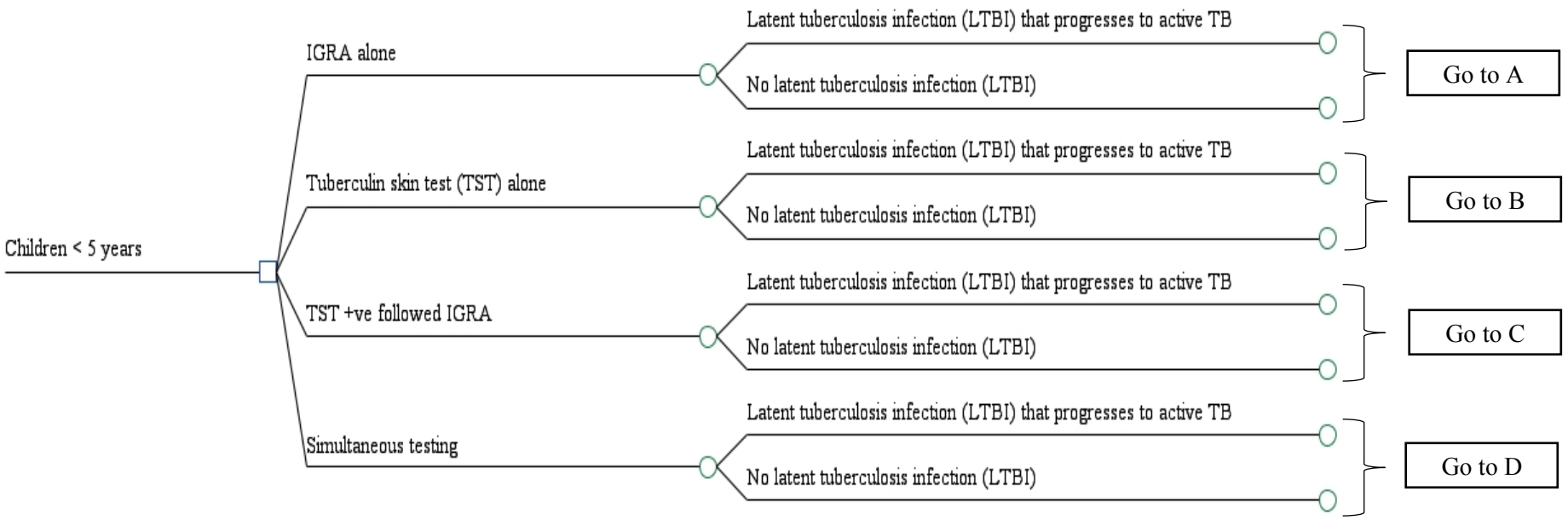


Figure 49. Decision tree structure for the children population

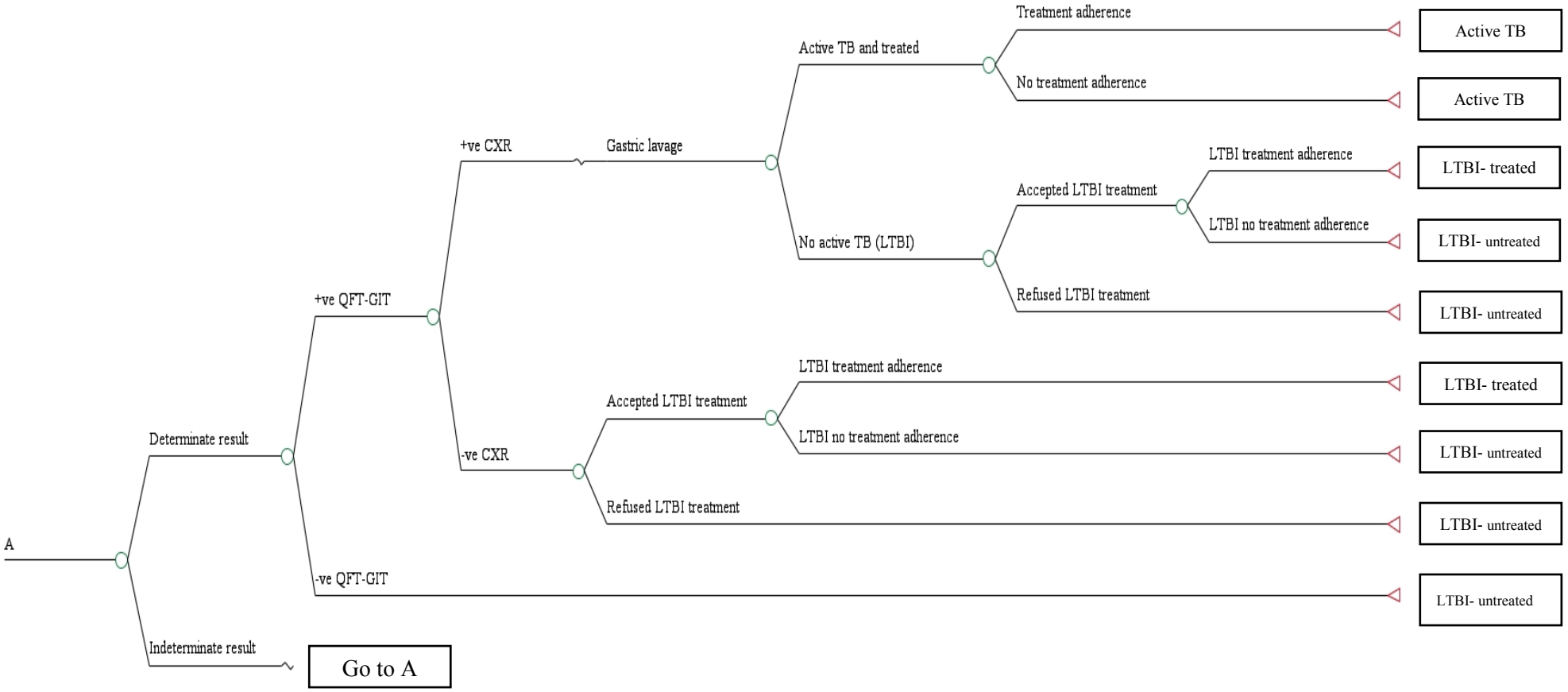


Figure 50. Pathway for the IGRA alone diagnostic strategy (IGRA alone strategy) in children

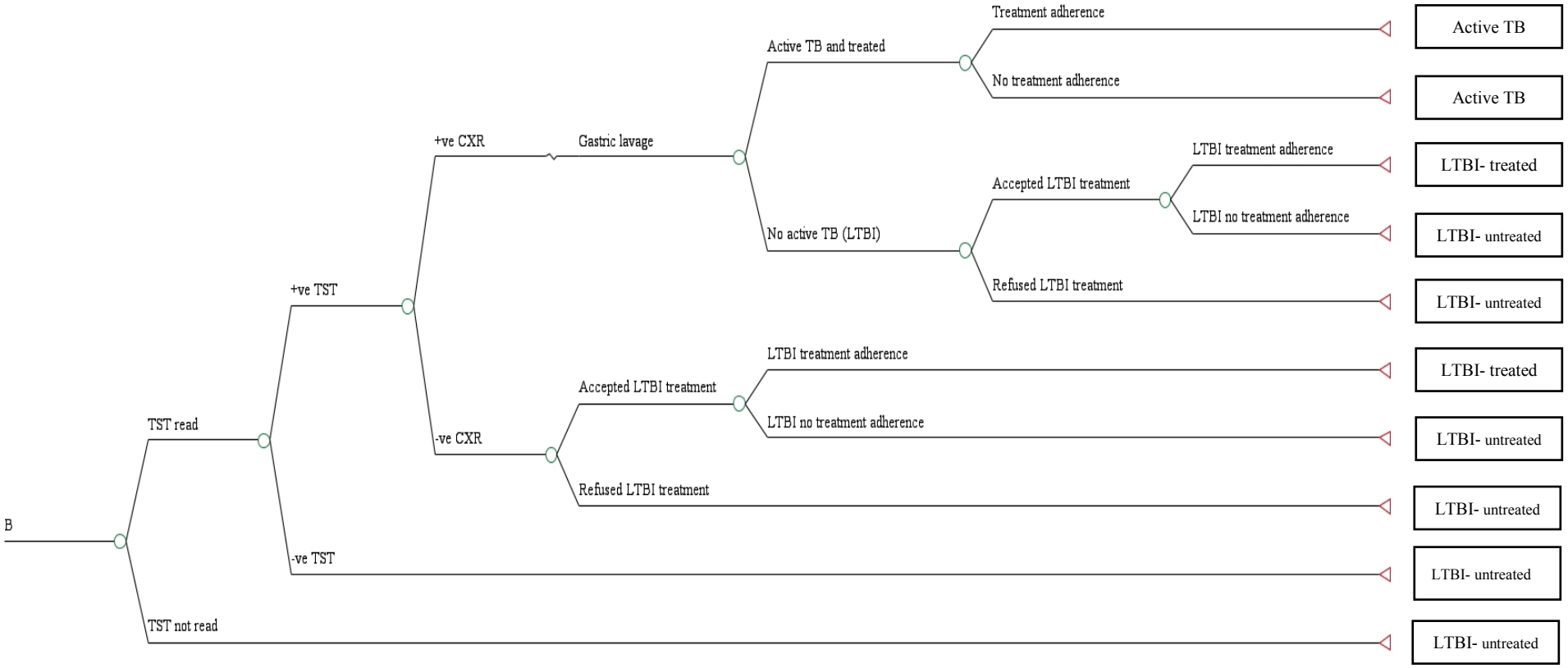


Figure 51. Pathway for the TST alone diagnostic strategy (TST alone strategy) in children

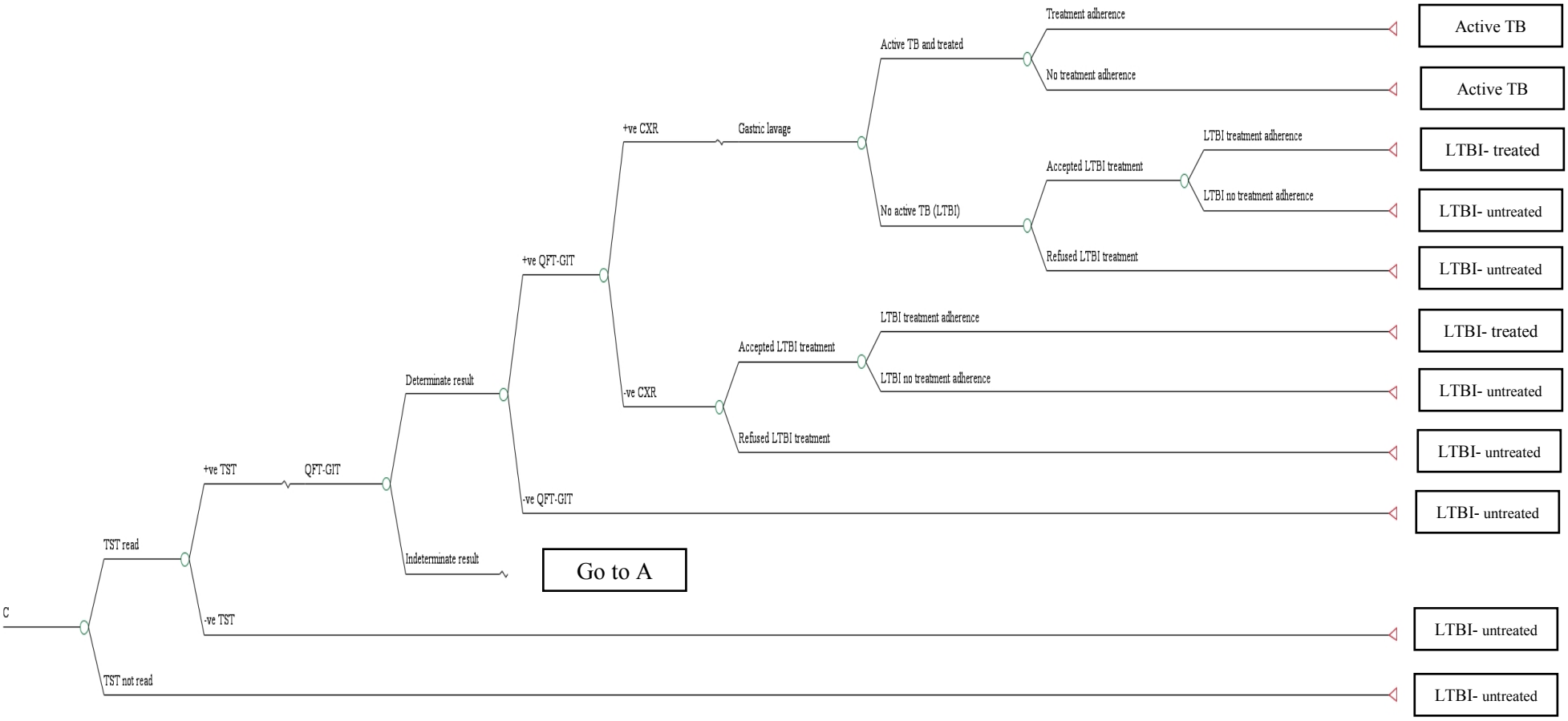


Figure 52. Pathway for the diagnostic strategy TST positive followed by IGRA in children

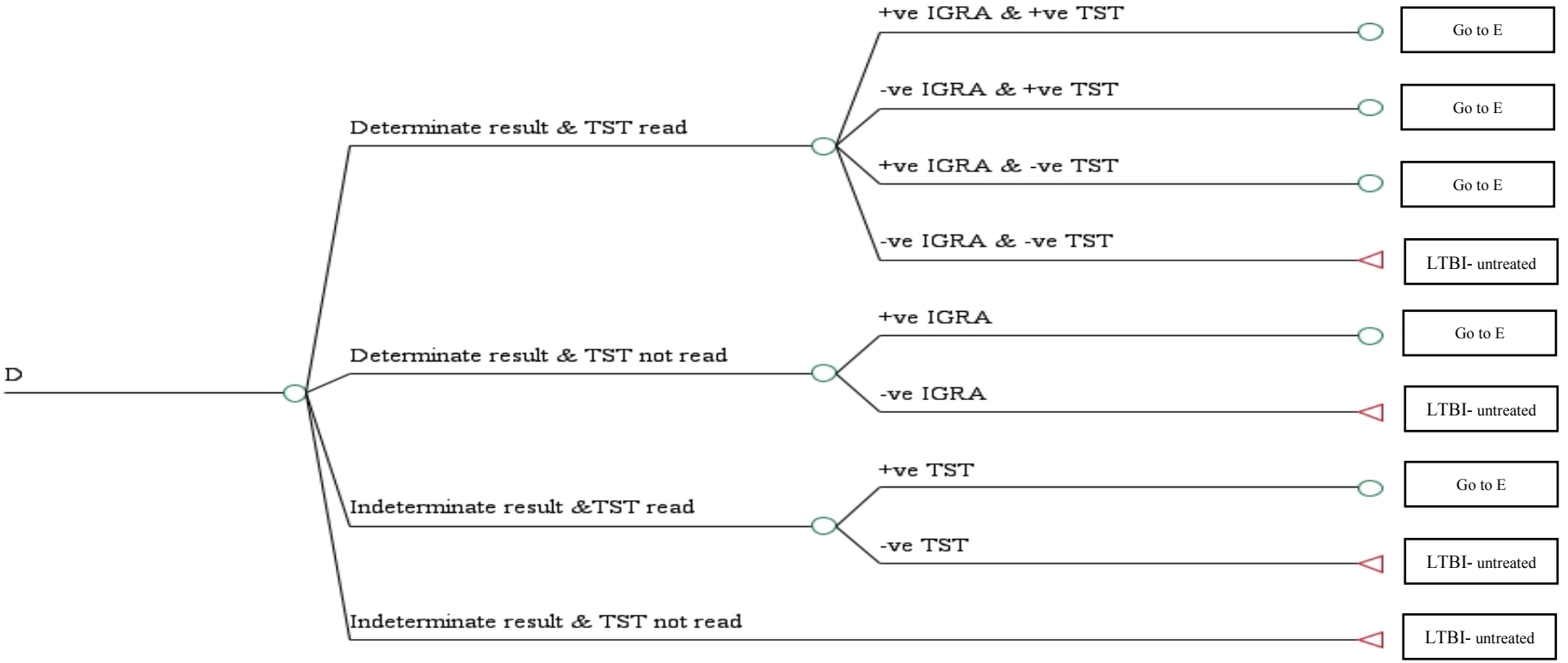


Figure 53. Decision tree structure for the children population receiving simultaneous testing strategy

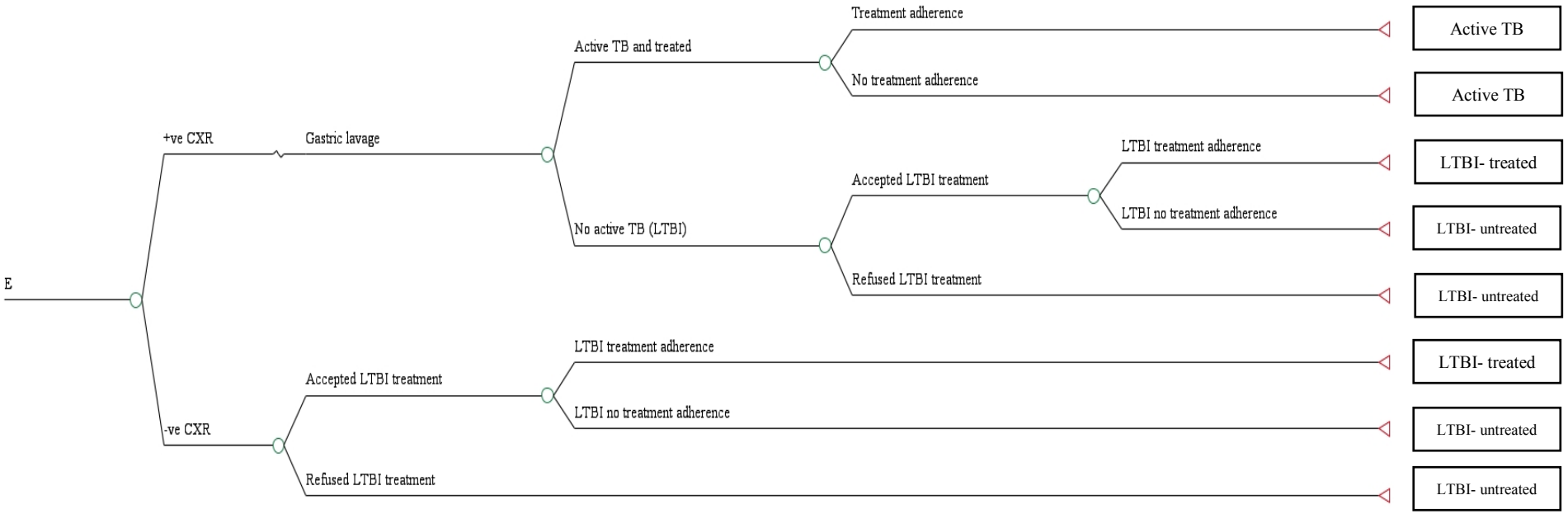


Figure 54. Pathway for the children population receiving simultaneous testing strategy

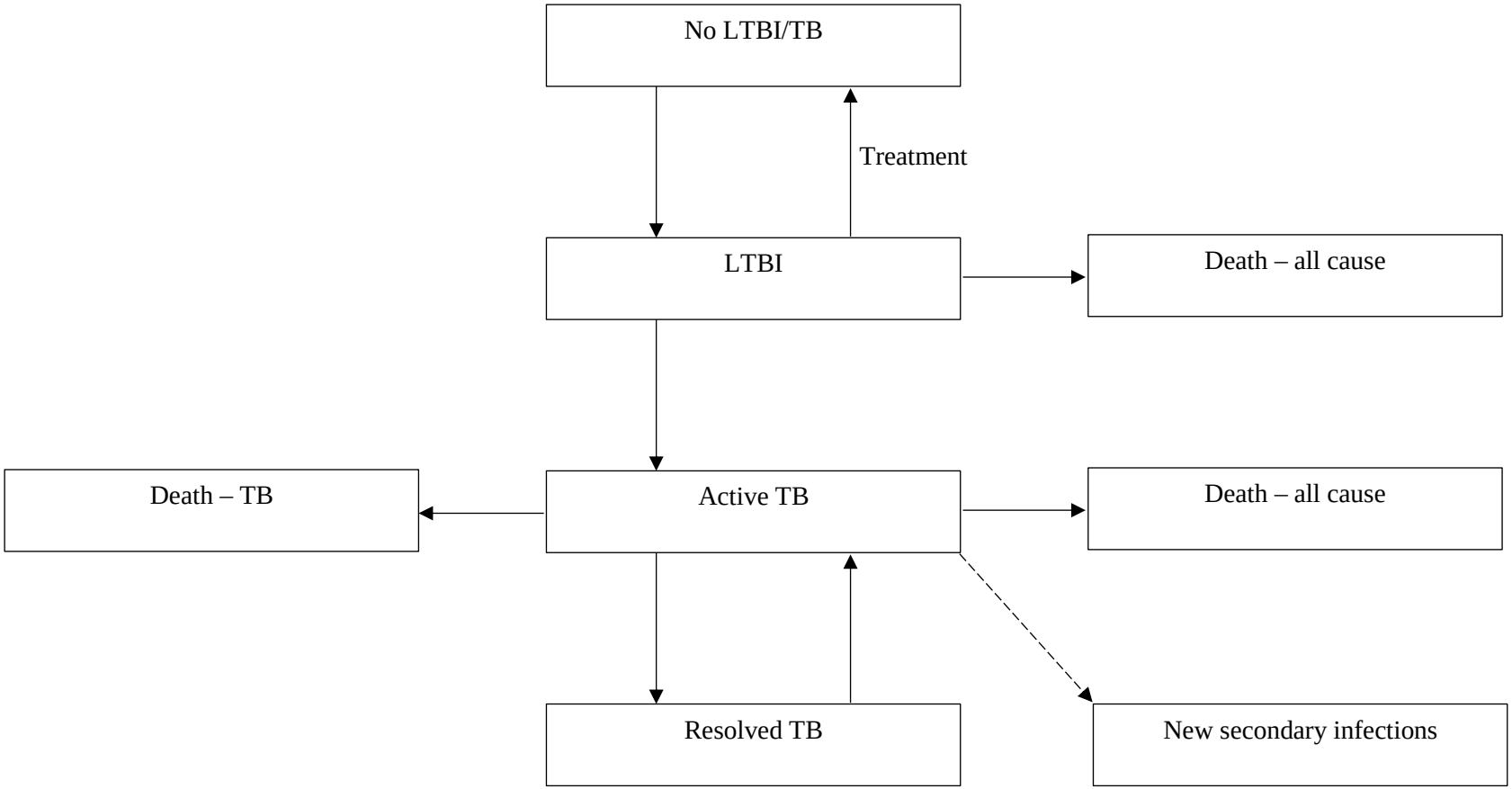


Figure 55. Dynamic transmission model

6.2.1 Model assumptions

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

1. We assumed that our population is similar to the population in the clinical effectiveness studies, but excluding studies with a high incidence of active TB
2. People being assessed for initial active TB have a chest x-ray, and if positive, receive a sputum examination
3. Children being assessed for initial active TB have a chest x-ray, 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 or false negative result on the IGRA test are at the same risk of developing active TB
6. People who have been diagnosed with initial TB accept treatment
7. People who do not adhere to LTBI treatment take medication for one month
8. People who do not adhere to LTBI treatment are not at risk of developing INH-induced hepatotoxicity
9. People who do not adhere to active TB treatment, take medication for one month
10. Children are not at risk of developing hepatitis as a result of treatment for active TB or LTBI
11. No health loss experienced by people with LTBI who do not progress to active TB

6.3 Data required for the model

The model was populated with clinical information from the current 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 LTBI diagnosis. Hence, we have used clinical information from studies in this review which report information on the confirmed cases of active TB (incidence to active TB for untreated LTBI).

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

6.3.1 Prevalence

In this analysis, prevalence was defined as the proportion of people who have LTBI that will progress to active TB, assuming they are not treated. We derived estimates for this LTBI prevalence criteria,

based on empirical data from the three cohorts separately. We used WinBUGS software (version 1.4.3) to conduct Bayesian Markov chain Monte Carlo simulation to derive the prevalence of LTBI in each cohort using the following formula:
*Probability of a positive result = (Test sensitivity*Prevalence of LTBI) + ((1-Test specificity)*(1-Prevalence of LTBI))*

Re-arranging the above equation for prevalence of LTBI:
Prevalence of LTBI = Probability of a positive result – (1- Test specificity)/((Test sensitivity) - (1 – Test specificity))

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

6.3.2 Performance of screening tests (sensitivity and specificity)

The sensitivity and specificity of various strategies were derived based on information obtained information from longitudinal studies on people who received testing and further developed active and further developed active TB. Therefore, our calculated sensitivity and specificity represent sensitivity and specificity of detecting people with LTBI that will progress to active TB, not the sensitivity and specificity 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 diagnostic tests by population. Estimates for sensitivity and specificity were derived for TST (≥ 5mm), TST (≥ 10mm), QFT-GIT and T-SPOT.TB.

To synthesize the clinical evidence in WinBUGS, there were three main components of the model: the statistical model, priors and data. See Appendix 18 for the WinBUGS code for our three populations of interest.

Statistical model

In our models we have used distributions to represent the unknown variables in the model. For the evidence synthesis for children, immunocompromised, and recent arrivals we have used the binomial distribution in order to derive the sensitivity and specificity of TST, QFT-G, QFT-GIT and T-SPOT.TB. We have chosen 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. Second, the probability p_{apos} of the number of positive results that progressed to active TB from n number of positive test results. Likewise, we are interested in the probability p_{aneg} of the negative results that progressed to active TB.

Logical expressions were built into the model to represent the relationship between the probability of a positive result, prevalence of LTBI, test sensitivity and test specificity (see Appendix 18).

We initially explored both fixed- and random-effects models. However, for two of the populations (children and immunocompromised), the random effects models did not converge (most likely due to a number of studies where either zero or only a very small number of people 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 have chosen the uniform distribution because the number of positive/negative test results are equally likely to be observed, and these results have an equal probability of occurring. In our WinBUGS code, we have added a logic expression to inform the model that the sensitivity of TST (≥ 5mm) > TST (≥ 10mm) > TST (≥ 15mm). Likewise, the specificity of TST (< 5mm) < TST (< 10mm) < TST (< 15mm). We have included this logic expression because the TST is a single test with various cut-off thresholds for a positive result, and by definition, the TST (≥ 5mm) would be more sensitive and less specific than TST (≥10/15mm).

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, number of people with positive results, number of people with positive results, and untreated, that developed active TB and the number of people with negative results who further developed active TB. Table 62 - Table 67 in the appendices show the information obtained from the clinical effectiveness studies. The term NA (Not applicable) was used to represent any missing values. After compiling the model, we provided values in order to generate initial values.

In order to get 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 18).

Results of the meta-analysis are presented in Table 27. The sensitivity and specificity of TST (≥ 5mm) for the diagnosis of LTBI in children was 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 (≥ 5mm), respectively. In the recently arrived group, we derived estimates of 93.56% and 50.11% for the sensitivity and specificity of TST (≥ 5mm), respectively. In the models we have not stratified by BCG-status, hence, we used a cut-off of ≥ 5mm to define a positive TST.

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

Table 27. Diagnostic accuracy of various tests for diagnosing LTBI that progresses to active TB

	Sensitivity, % (95% credible interval)	**Specificity, % (95% credible interval)**
Children		
TST (≥ 5mm)	72.80 (60.59 – 72.94)	49.03 (47.96 – 50.08)
TST (≥ 10mm)	53.51 (38.21 – 67.69)	74.81 (34.34 – 76.18)
QFT-GIT	68.84 (58.56 – 78.20)	61.03 (60.30 – 61.76)
T-SPOT.TB	50.00 (2.45 – 97.64)	77.58 (67.38 – 86.40)
Immunocompromised		
TST (≥ 5mm)	32.42 (11.19 – 58.48)	74.22 (72.88 – 75.57)
TST (≥ 10mm)	16.82 (2.52 – 38.99)	83.97 (78.99 – 88.31)
QFT-GIT	55.48 (24.73 – 83.73)	82.27 (80.52 – 83.96)
T-SPOT.TB	66.65 (35.17 – 0.9144)	68.46 (63.46 – 73.37)
Recently arrived		
TST (≥ 5mm)	93.56 (77.86 – 99.77)	50.11 (47.90 – 52.29)
QFT-GIT	59.15 (35.84 – 81.42)	79.29 (77.80 – 80.73)
T-SPOT.TB	70.01 (39.78 – 92.42)	39.92 (34.39 – 45.54)

6.3.3 Resource use and costs

The resource use and cost included were those directly incurred by the NHS. Costs for diagnostic tests, chest x-rays, gastric lavage, sputum examination, treatment of LTBI/TB and Isoniazid (INH)-induced hepatitis were all included in the analysis. Societal costs: indirect costs, loss of productivity or cost of death were not included in the analysis. Unit costs are presented in Table 28. The majority of the cost information used in the analyses was obtained from secondary sources. Cost for QFT-GIT (testing kit, consumables, processing and phlebotomy) and TST (disposables, administration and reading) were obtained from Pooran et al. (2010).[206] Estimated costs for the chest x-ray, gastric lavage procedure and sputum examination were obtained from the NHS reference costs 2012/13[207]. Estimated costs for the treatment of LTBI were obtained from the NHS drug tariff 2014 and in consultation with a clinical expert (see Appendix 17).[208] Cost for the treatment of TB were obtained from Bothamley et al. (2002) (see Appendix 17).[209] Management of LTBI included further blood tests (full blood count and liver function tests), outpatient visits to doctor and nurse, and treating with Isoniazid 300mg daily for six months. Estimated costs for treating INH-induced hepatitis were obtained from Pareek et al. (2013).[76] All costs were adjusted to 2012/2013 prices using the Hospital and Community Health Service (HCHS) pay and price index Curtis et al. (2013)[210] and discounted at a rate of 3.5% per annum, as recommended by National Institute for Health and Care Excellence (NICE).

Table 28. Model input parameters required for the population with children

Variable	Base-case value	Range for SA	PSA distribution	Reference(s)
Probabilities				
Prevalence of LTBI	0.0288	0.0206 - 0.0384	#	
Sensitivity TST (≥5mm)	0.7280	0.6059 - 0.7294	#	
Specificity TST (<5mm)	0.4903	0.4796 - 0.5008	#	
Sensitivity TST (≥10mm)	0.5351	0.3821 - 0.6769	#	
Specificity TST (>10mm)	0.7481	0.3434 - 0.7618	#	
Sensitivity QFT-GIT	0.6884	0.5856 - 0.7820	#	
Specificity QFT-GIT	0.6103	0.6030 - 0.6176	#	Derived from clinical effectiveness
Sensitivity T-SPOT.TB	0.500	0.0245 - 0.9764	#	
Specificity T-SPOT.TB	0.7758	0.6738 - 0.8640	#	
Sensitivity of QFT-GIT conditional on +ve TST (LTBI arm)	0.6775	0.4674 - 0.9233	#	
Specificity of	0.3213	0.3073 - 0.3353	#	

Variable	Base-case value	Range for SA	PSA distribution	Reference(s)
QFT-GIT conditional on +ve TST (No LTBI arm)				
Sensitivity of QFT-GIT conditional on -ve TST (LTBI arm)	0.7031	0.1122 – 0.9921	#	
Specificity of QFT-GIT conditional on -ve TST (No LTBI arm)	0.9108	0.9013 – 0.9200	#	
Sensitivity of CXR for diagnosing active TB	0.7800	Not reported	Not varied	Kumar et al. (2005)[211]
Specificity of CXR for diagnosing active TB	0.5100	Not reported	Not varied	Kumar et al. (2005)[211]
Determinate QFT-GIT	0.97	-	Beta (873,27)	Derived from Laskin et al. (2013)[197]
Determinate T-SPOT.TB	0.97	-	Beta (873,27)	Derived from Laskin et al. (2013)[197]
Probability of TST read	0.9400	0.6 – 1.00	Beta (164,10.5)	Pareek et al. (2013)[76]
Probability of initial active TB	0.00001	-	Not varied	Laskin et al. (2013)[197]
TB treatment adherence	1.0000	-	Not varied	Pareek et al. (2013)[76]
Accepting LTBI treatment	0.9400	0.50 – 1.00	Beta (141,9)	CG117 (2011)[10]
Adherence to LTBI treatment	0.8000	0.50 – 0.90	Beta (41,10)	Kowada (2013)[195]
INH hepatitis after TB treatment	0.0040	0.001 - 0.010	Beta (2.7,664)	Assumption
Death from INH hepatitis	0.00002	0.00001 - 0.0001	Beta (0.5,25125)	Pooran et al. (2010)[206]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	-	Lognormal (-1.065,0.842)	White and Jit (2015)[212]
Average number of secondary cases from one index case	0.2	0.1-0.3	Lognormal (-1.609,0.354)	Pareek et al. (2011)[6]
Average delay from infection to activation (secondary cases)	2.88	-	Lognormal (1.058,0.333)	Okuonghae et al., (2013)[213]
Annualised reactivation rate from resolved TB	0.013	0.004 – 0.025	Beta (7,513)	Oxlade et al. (2011)[214]
Case fatality rate	0.0477	-	Beta (628,12543)	Croft et al. (2008)[215]

Variable	Base-case value	Range for SA	PSA distribution	Reference(s)
for active TB (0-4 years)				
Case fatality rate for active TB (5-14 years)	0.0034	-	Beta (1,290)	Croft et al. (2008)[215]
Case fatality rate for active TB (15-44 years)	0.0018	-	Beta (1,564)	Croft et al. (2008)[215]
Case fatality rate for active TB (45-64 years)	0.0476	-	Beta (125,2500)	Croft et al. (2008)[215]
Case fatality rate for active TB (65+years)	0.1755	-	Beta (413,1940)	Croft et al. (2008)[215]
Resource use and costs				
TST	17.48		Not varied	Pooran et al. (2010)[206]
QFT-GIT	48.73		Not varied	Pooran et al. (2010)[206]
T-SPOT.TB	59.57		Not varied	Pooran et al. (2010)[206]
Chest x-ray	35.00		Not varied	NHS costs 2012/13[207]
Gastric lavage procedure	916.00		Not varied	NHS costs 2012/13[207]
Sputum examination	7.00		Not varied	NHS costs 2012/13[207]
Cost of adherence to active TB treatment	5461.12		Gamma (10.41,524.6)	Bothamley et al. (2002)[209]
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 (2014)[208]
Cost of non-adherence to LTBI treatment	112.85		Uniform (85.24,140.41)	Assumption
Treatment of INH-induced hepatitis	389.51		Gamma (7.13,55.64)	Pareek et al. (2013)[76]
Utility decrements				
Active TB (whilst on treatment)	0.15[†]	Not reported	Gamma (11.2,0.0134)	Derived from Kowada (2012)[194]
Treatment for LTBI	0.001	-	Uniform (0,0.002)	Derived from Kowada (2012)[194]
Other				
Discount rate per annum (costs and QALYs)	3.5%			

IGRA, Interferon-gamma release assay; INH, Isoniazid; LTBI, Latent tuberculosis infection; QFT-G, QuantiFERON Gold; QFT-GIT, QuantiFERON Gold-In-Tube; SA, Sensitivity analysis; TB, tuberculosis; TST, Tuberculin skin test;
[†] QALY decrement for people being treated for active TB
Calculated from posterior distributions generated by Markov Chain Monte Carlo (MCMC)

6.4 Outcomes

Two different outcome measures were used in the analysis, QALYs and diagnostic error avoided. To calculate QALYs, the age-related utility weights for the general population were obtained from the Health Survey for England 2012,[205] and the utility decrement of 0.15 for people who received treatment for active TB was derived from the published literature.[194] 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 one and we reserved the value of zero for an error (false positives and false negatives) in the diagnosis.

6.5 Analysis

The models were constructed to assess the cost-effectiveness of various strategies for the diagnosis of LTBI in three populations (children, immunocompromised and recently arrived). The models estimated the mean costs and effects associated with each diagnostic strategy. For the children population, we began with a hypothetical cohort of children aged five years, whilst for the recently arrived and immunocompromised populations, the starting distributions were representative of the UK recent arrival, and UK general populations, respectively.[216] The analysis was undertaken from an NHS perspective in a primary care setting, and outcomes reported as incremental cost effectiveness ratios (ICER), expressed in terms of cost per diagnostic error avoided and cost per QALY gained. Since using QALYs allows trade-offs between the harms of false negatives and false positives, which are treated as equal in a cost per error avoided analysis, our primary conclusions are drawn from the ICERs for QALYs. Univariate and probabilistic sensitivity analyses were undertaken to assess to impact of the uncertainty of model input parameters.

6.5.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to determine the joint uncertainty in key model input parameters of prevalence, sensitivity and specificity, and expected QALYs. We have undertaken PSA based on an outcome of cost per QALY only. In probabilistic sensitivity analysis, 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. 2,000 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, 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 2,000 PSA simulations. The

distributions used in the PSA are presented in Table 28. We also calculated probabilities that each strategy is the most cost-effective, at a willingness-to-pay of £20,000/QALY.

6.6 Results of the cost-effectiveness modelling

The base-case results of the diagnostic strategies based on the outcomes cost per diagnostic error avoided and cost per QALY gained cost for the population with children, immunocompromised and recent arrivals from countries with a high incidence of active TB are presented in Table 29 to Table 43.

6.6.1 Model 1: Children

Results from our 250,000 patient simulations, based on the mean values of each parameter, are presented in tables A and B. 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 breakdowns of the total into diagnosis, LTBI treatment, active TB and hepatitis costs. Table 30 shows incidence rates of active TB in the initial cohort, numbers of secondary infections, mean life years and mean QALYs, for each of the strategies.

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

Strategy	Mean costs (£)	Mean diagnosis costs (£)*	Mean LTBI costs (£)*	Mean active TB costs (£)*	Mean hepatitis costs (£)*
TST (≥ 5mm)	362.47	58.28	192.57	111.55	0.07
TST (≥ 10mm)	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 (≥ 5mm) +ve then QFT-GIT	360.47	83.16	134.23	142.98	0.10
TST (≥ 5mm) –ve then QFT-GIT	389.24	114.98	196.17	78.03	0.06

*Percentages are all relative to the costs of the TST (≤ 5mm) strategy

Table 30. Mean QALYs and LYG (discounted) and 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 (≥ 5mm)	23.095	27.036	4722	1133
TST (≥ 10mm)	23.090	27.035	5521	1332
QFT-GIT	23.093	27.036	4804	1149
T-SPOT.TB	23.091	27.036	5620	1349
TST (≥ 5mm) +ve then QFT-GIT	23.091	27.036	5653	1367

TST (≥ 5mm) –ve then QFT-GIT	23.097	27.037	4150	996

*Percentages are all relative to the outcomes of the TST (≤ 5mm) strategy

Our primary results, based on our 2,000 Monte Carlo simulations, are presented in Table 31 (diagnostic accuracy) and Table 32 (QALYs). Considering diagnostic accuracy, the TST (≥ 10mm) alone strategy dominated the TST (≥ 5mm) –ve followed by QFT-GIT, TST (≥ 5mm), QFT-GIT, TST (≥ 5mm) +ve followed by QFT-GIT strategies. The TST strategy has a mean cost of approximately £272 with corresponding diagnostic errors of 0.2449, compared with a mean cost of approximately £306 and 0.2322 diagnostic errors for the T-SPOT.TB alone strategy. The ICER of T-SPOT.TB compared to TST (≥ 10mm) presented indicates the additional cost required to avoid one diagnostic error. Results for the simultaneous testing strategy and the TST (≥ 10mm) followed by QFT-GIT are not presented because these results have been dominated by sequential and TST (≥ 5mm) followed by QFT-GIT, respectively.

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

Strategy	Mean cost* (£)	Incremental costs (£)	False positives	False negatives	Effectiveness (diagnostic errors)*	Incremental diagnostic error	ICER (£)
TST –ve followed by QFT-GIT	361.42	N/A	0.5032	0.0040	0.5072	N/A	Dominated
TST (≥ 5mm)	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 +ve followed by QFT-GIT	324.12	0.05	0.3040	0.0154	0.3194	-0.0686	Dominated
TST (≥ 10mm)	271.66	-52.46	0.2307	0.0142	0.2449	-0.0745	N/A
T-SPOT.TB	306.09	34.43	0.2172	0.0150	0.2322	-0.0127	2,711.02

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

The QALY outcomes of our Monte Carlo simulations showed that the TST (≥ 10mm) diagnostic strategy alone was the least costly and TST (≥ 5mm) –ve 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 compared with a mean cost of £371 and 23.0968 QALYs for the TST (≥ 5mm) alone strategy. The ICER of £11,255 presented indicates the additional cost required to gain an extra QALY. Results in terms of the joint uncertainty in the expected mean costs and QALYs showed that TST (≥ 5mm) –ve followed by QFT-GIT the most cost-

effective strategy, at a willingness-to-pay of £20,000 per QALY, in 32% of the simulations, followed by the TST (≥ 5mm) (27%) and the QFT-GIT (21%).

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

Strategy	Mean cost* (£)	Incremental costs (£)	Mean QALYs*	Incremental QALYs	ICER (£)	Probability most cost-effective
TST(≥ 10mm)	300.21	N/A	23.088	N/A	N/A	0.032
T-SPOT.TB	332.46	32.25	23.091	0.003	Extended dominated	0.122
TST (≥ 5mm) +ve 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	8,249 (versus TST(≥ 10mm)	0.210
TST (≥ 5mm)	371.14	10.09	23.096	0.001	11,255 (versus QFT-GIT)	0.269
TST (≥ 5mm) -ve followed by QFT-GIT	393.03	21.89	23.097	0.001	18,871	0.322

*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.
#Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.

Results of our univariate sensitive analyses are presented in

Table 33. We present costs and QALYs, in each scenario, for each of the three most effective strategies (QFT-GIT, TST (≥ 5mm) and (TST ≥ 5mm -ve followed by QFT-GIT). We also show which of the three strategies was the most cost-effective, assuming a willingness-to-pay of £20,000 per QALY, in each of these scenarios. In the majority of scenarios, as in our base case, the TST (≥ 5mm) -ve followed by QFT-GIT was the most cost-effective strategy, at a threshold of £20,000 per QALY. 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 the QFT-GIT, all lead to the QFT-GIT being the most cost-effective option. Conversely, decreases in the sensitivity of the QFT-GIT lead to the TST (≥ 5mm) being selected as the most cost-effective option.

Table 33. Univariate sensitivity analyses

Parameter varied	Value	Costs (QFT-GIT)	QALYs (QFT-GIT)	Costs (TST ≥ 5mm)	QALYs (TST ≥ 5mm)	Costs (TST ≥ 5mm -ve followed by QFT-GIT)	QALYs (TST ≥ 5mm -ve followed by QFT-GIT)	Most cost-effective strategy (£20,000 per QALY)
Base-case		361.03	23.095	371.17	23.096	393.03	23.097	TST (≥ 5mm) -ve followed by 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 (≥ 5mm) -ve followed by QFT-GIT
Sensitivity: IGRAs	QFT-GIT: 0.5856 QFT-GIT following –ve TST: 0.1122	368.16	23.089	363.76	23.096	397.13	23.095	TST (≥ 5mm)
	QFT-GIT: 0.7820 QFT-GIT following –ve 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 –ve TST: 0.9013	368.46	23.095	363.76	23.096	393.43	23.097	TST (≥ 5mm) -ve followed by QFT-GIT
	QFT-GIT: 0.6176 QFT-GIT following –ve TST: 0.9200	354.02	23.095	379.48	23.096	393.98	23.097	TST (≥ 5mm) -ve followed by QFT-GIT
Sensitivity: TST ≥ 5mm	TST: 0.6059	361.03	23.095	379.54	23.095	395.48	23.096	QFT-GIT
	TST: 0.7294	361.03	23.095	368.47	36.098	392.62	23.099	TST (≥ 5mm) -ve followed by QFT-GIT
Specificity: TST ≥ 5mm	TST: 0.4796	361.03	23.095	374.27	23.096	395.75	23.097	QFT-GIT
	TST: 0.5008	361.03	23.095	361.28	23.096	383.20	23.097	TST (≥ 5mm)

Parameter varied	**Value**	**Costs (QFT-GIT)**	**QALYs (QFT-GIT)**	**Costs (TST ≥ 5mm)**	**QALYs (TST ≥ 5mm)**	**Costs (TST ≥ 5mm -ve followed by QFT-GIT)**	**QALYs (TST ≥ 5mm -ve followed by QFT-GIT)**	**Most cost-effective strategy (£20,000 per QALY)**
								-ve followed by QFT-GIT
Effectiveness of LTBI treatment	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 (≥ 5mm) -ve followed by QFT-GIT
Cost of LTBI treatment	511.69	321.89	23.095	324.13	23.096	345.11	23.097	TST (≥ 5mm) -ve followed by QFT-GIT
	842.45	400.17	23.095	418.21	23.096	440.95	23.097	TST (≥ 5mm) -ve followed by QFT-GIT
Cost of active TB treatment	2664.38	302.91	23.095	314.25	23.096	343.07	23.097	TST (≥ 5mm)
	9244.44	419.15	23.095	428.09	23.096	432.99	23.097	TST (≥ 5mm) -ve followed by QFT-GIT
Utility decrement – active TB	0.75	361.03	23.090	371.17	23.091	393.03	23.092	TST (≥ 5mm) -ve followed by 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

Finally, Figure 56 presents cost-effectiveness acceptability curves 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.

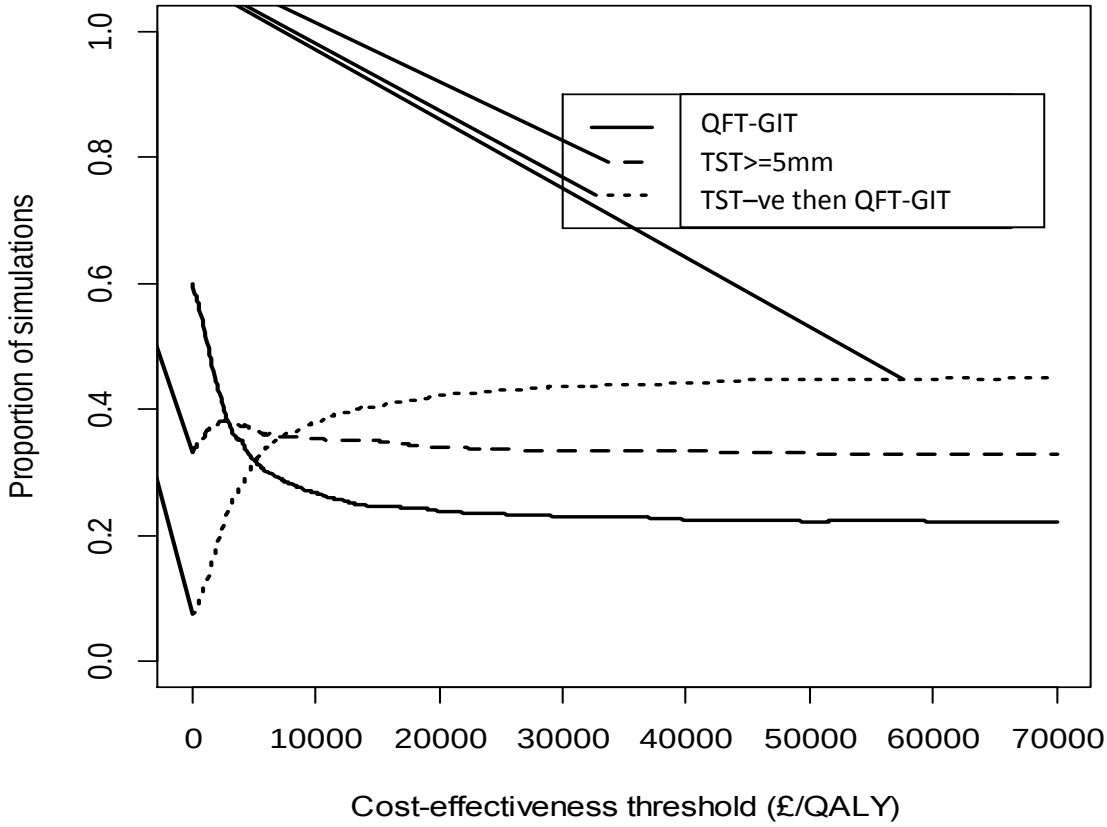


Figure 56. Cost-effectiveness acceptability curve for the children population, showing the proportion of simulations in which each strategy is the most cost-effective, at different willingness-to-pay thresholds

6.6.2 Model 2: Immunocompromised

Results from our 250,000 patient simulations, based on the mean values of each parameter, are presented in Table 34 and Table 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 breakdowns of the total into diagnosis, LTBI treatment, active TB and hepatitis costs. Table 35 shows incidence rates of active TB in the initial cohort, numbers of secondary infections, mean life years and mean QALYs, for each of the strategies.

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

Strategy	Mean costs (£)	Mean diagnosis costs (£)*	Mean LTBI costs (£)*	Mean active TB costs (£)*	Mean hepatitis costs (£)*
TST (≥ 5mm)	272.79	28.59	127.86	116.00	0.35
TST (≥ 10mm)	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 +ve then TST (≥ 5mm)	286.49	67.91	63.95	154.51	0.12
QFT-GIT –ve then TST (≥ 5mm)	315.00	79.99	145.50	89.08	0.43

Table 35. Mean QALYs and LYG (discounted) and 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 (≥ 5mm)	15.527	33.018	4826	1158
TST (≥ 10mm)	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 +ve then TST (≥ 5mm)	15.526	33.017	5271	1254
QFT-GIT –ve then TST (≥ 5mm)	15.534	33.018	3671	886

Our primary results, based on our 2,000 Monte Carlo simulations, are presented in Table 36 (diagnostic accuracy) and Table 37 (QALYs). Considering diagnostic accuracy, QFT-GIT dominated the QFT-GIT -ve followed by TST (≥ 5mm), T-SPOT.TB and TST (≥ 5mm) strategies. The TST (≥ 10mm) strategy has a mean cost of approximately £236 with corresponding diagnostic errors of 0.1641, compared with a mean cost of approximately £253 and 0.1047 diagnostic errors for the QFT-GIT +ve followed by TST (≥ 5mm) strategy. The ICER of £297 per diagnostic error avoided for the QFT-GIT +ve followed by TST (≥ 5mm) strategy versus the TST (≥ 10mm) 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 36. Results from the analysis based on cost per diagnostic error avoided (2012/13 prices)

Strategy	Mean cost* (£)	Incremental costs (£)	False positives	False negatives	Effectiveness (diagnostic errors)*	Incremental diagnostic error	ICER (£)
QFT-GIT –ve TST (≥ 5mm)	287.77	N/A	0.3100	0.0066	0.3166	N/A	Dominated
T-SPOT.TB	252.01	-35.76	0.3080	0.0072	0.3152	-0.0018	Dominated
TST (≥ 5mm)	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	N/A
TST (≥ 10mm)	236.11	1.70	0.1474	0.0167	0.1641	-0.0173	98.27 (versus QFT-GIT)
QFT-GIT +ve TST	253.77	17.66	0.0876	0.0171	0.1047	-0.0594	297.31 (versus TST (≥ 10mm)

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

The QALY outcomes of our Monte Carlo simulations showed that TST (≥ 10mm), QFT-GIT +ve followed by TST (≥ 5mm), and TST (≥ 5mm) were dominated by the QFT-GIT alone strategy which has a mean cost of £259 with corresponding QALYs of 15.526. The ICER reported for the T-SPOT.TB alone strategy shows the additional costs required to gain one extra QALY, versus the QFT-GIT strategy. At a willingness-to-pay of £20,000 per QALY, the QFT-GIT –ve followed by TST (≥ 5mm) had the highest net-benefit in the largest proportion of simulation (40%), followed by the T-SPOT.TB (25%) and the QFT-GIT alone (20%). All other strategies had the largest net benefit in fewer than 7% of the simulations.

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

Strategy	Mean cost* (£)	Incremental costs (£)	Mean QALYs*	Incremental QALYs	ICER (£)	Probability most cost-effective
TST (≥ 10mm)	269.42	N/A	15.516	N/A	Dominated	0.046
QFT-GIT +ve TST (≥ 5mm)	289.31	19.89	15.516	0.000	Dominated	0.052
TST (≥ 5mm)	276.01	-13.30	15.517	0.001	Dominated	0.067
QFT-GIT	258.61	-17.40	15.523	0.006	N/A	0.187
T-SPOT.TB	280.90	12.29	15.524	0.001	10,402.63 (versus QFT-GIT)	0.249
QFT-GIT –ve TST (≥ 5mm)	318.26	37.36	15.526	0.002	18,746.01 (versus T-SPOT.TB)	0.399

*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.
[#]Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.

Results of our univariate sensitive analyses are presented in Table 38. We present costs and QALYs, in each scenario, for each of the three strategies which were not strictly dominated by another strategy in our primary results. We also show which of the three strategies was the most cost-effective, assuming a willingness-to-pay of £20,000 per QALY, in each of these scenarios. In scenarios where the importance of test sensitivity is equal to or higher than the base case, the QFT-GIT -ve followed by TST (≥ 5mm) is consistently the most cost-effective strategy, at £20,000 per QALY. In scenarios where the relative importance of test specificity is 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), the QFT-GIT often becomes the most cost-effective strategy.

Table 38. Univariate sensitivity analyses

Parameter varied	**Value**	**Costs (QFT-GIT)**	**QALYs (QFT-GIT)**	**Costs (T-SPOT.TB)**	**QALYs (T-SPOT.TB)**	**Costs (QFT-GIT – ve TST (≥ 5mm))**	**QALYs (QFT-GIT – ve TST (≥ 5mm))**	**Most cost-effective strategy (£20,000 per QALY)**
Base-case		258.61	15.523	280.90	15.524	318.26	15.526	QFT-GIT –ve TST (≥ 5mm)
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 –ve TST (≥ 5mm)
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 –ve TST (≥ 5mm)
	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 –ve TST (≥ 5mm)
	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 ≥ 5mm	TST following –ve IGRA: 0.0121	258.61	15.523	280.90	15.524	321.89	15.526	QFT-GIT –ve TST (≥ 5mm)
	TST	258.61	15.523	280.90	15.524	314.87	15.526	QFT-GIT

Parameter varied	Value	Costs (QFT-GIT)	QALYs (QFT-GIT)	Costs (T-SPOT.TB)	QALYs (T-SPOT.TB)	Costs (QFT-GIT – ve TST (≥ 5mm))	QALYs (QFT-GIT – ve TST (≥ 5mm))	Most cost-effective strategy (£20,000 per QALY)
	following –ve IGRA: 0.7989							–ve TST (≥ 5mm)
Specificity: TST ≥ 5mm	TST following –ve IGRA: 0.3909	258.61	15.523	280.90	15.524	342.16	15.526	T-SPOT.TB
	TST following –ve IGRA: 0.4993	258.61	15.523	280.90	15.524	291.20	15.526	QFT-GIT –ve TST (≥ 5mm)
Effectiveness of LTBI treatment (proportion 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 –ve TST (≥ 5mm)
Cost of LTBI treatment	511.69	235.90	15.523	249.62	15.524	284.37	15.526	QFT-GIT –ve TST (≥ 5mm)
	842.45	281.32	15.523	312.18	15.524	352.15	15.526	QFT-GIT
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 –ve TST (≥ 5mm)
Utility decrement – active TB	0.75	258.61	15.520	280.90	15.522	318.26	15.524	QFT-GIT –ve TST (≥ 5mm)
	0.95	258.61	15.526	280.90	15.526	318.26	15.528	QFT-GIT –ve TST (≥ 5mm)
Number of secondary TB cases per index case	0	234.41	15.536	252.01	15.536	287.77	15.38	QFT-GIT

Finally, Figure 57 presents cost-effectiveness acceptability curves 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.

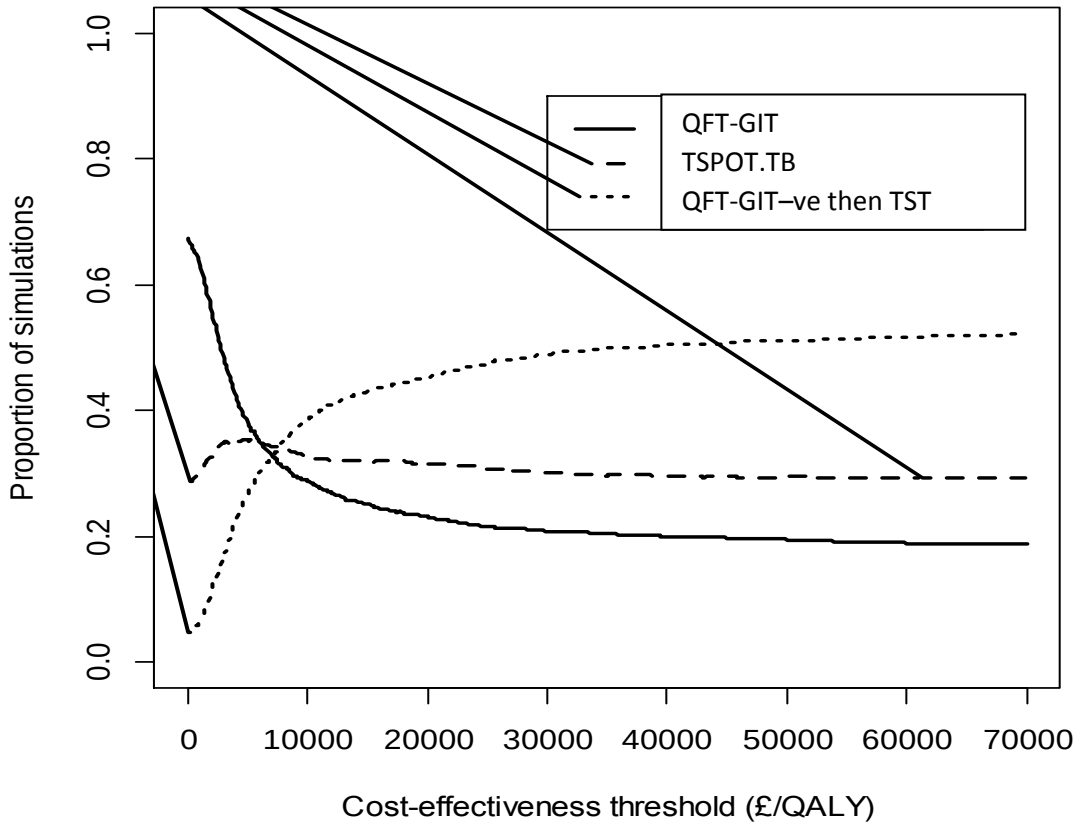


Figure 57. Cost-effectiveness acceptability curve for the immunocompromised population, showing the proportion of simulations in which each strategy is the most cost-effective, at different willingness-to-pay thresholds

6.6.3 Model 3: Recent arrivals from countries with a high incidence of Tuberculosis

Model 3: Recently arrived

Results from our 250,000 patient simulations, based on the mean values of each parameter, are presented in Table 39 and Table 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 breakdowns of the total into diagnosis, LTBI treatment, active TB and hepatitis costs. Table 40 shows incidence rates of active TB in the initial cohort, numbers of secondary infections, mean life years and mean QALYs, for each of the strategies.

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

Strategy	Mean costs (£)	Mean diagnosis costs (£)*	Mean LTBI costs (£)*	Mean active TB costs (£)*	Mean hepatitis costs (£)*
TST (≥ 5mm)	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 (≥ 5mm) +ve then QFT-GIT	310.83	78.88	101.04	130.07	0.84
TST (≥ 5mm) -ve then QFT-GIT	363.64	74.15	219.87	68.91	0.72

*Percentages are all relative to the costs of the TST (≤ 5mm) strategy

Table 40. Mean QALYs and LYG (discounted) and 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 (≥ 5mm)	19.929	24.160	2883	705
QFT-GIT	19.924	24.158	4329	1041
T-SPOT.TB	19.922	24.158	4289	998
TST (≥ 5mm) +ve then QFT-GIT	19.915	24.157	4522	1091
TST (≥ 5mm) -ve then QFT-GIT	19.931	24.160	2756	660

*Percentages are all relative to the outcomes of the TST (≤ 5mm) strategy

Our primary results, based on our 2,000 Monte Carlo simulations, are presented in Table 41(diagnostic accuracy) and Table 42 (QALYs). Considering diagnostic accuracy, the QFT-GIT alone strategy was the least costly and the TST (≥ 5mm) +ve followed by the QFT-GIT strategy was the most effective. The QFT-GIT strategy has a mean cost of approximately £266 with corresponding diagnostic errors of 0.2113, compared with a mean cost of approximately £277 and 0.1955 diagnostic errors for the QFT-GIT alone strategy. The ICER reported for the TST (≥ 5mm) +ve followed by the QFT-GIT strategy compared to QFT-GIT alone strategy shows the additional cost of £692 for avoiding one diagnostic error. We have not presented the results for the simultaneous testing strategies because these strategies were dominated by the equivalent sequential strategies.

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

Strategy	Mean cost* (£)	Incremental costs (£)	False positives	False negatives	Effectiveness (diagnostic errors)*	Incremental diagnostic error	ICER (£)
T-SPOT.TB	374.60	N/A	0.5669	0.0071	0.5740	N/A	Dominated
TST (≥ 5mm) -ve QFT-GIT	325.81	-48.79	0.4680	0.0016	0.4696	-0.1044	Dominated
TST (≥ 5mm)	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	N/A
TST (≥ 5mm) +ve QFT-GIT	276.80	10.93	0.1846	0.0109	0.1955	-0.0158	691.77

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

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

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

Strategy	Mean cost* (£)	Incremental costs (£)	Mean QALYs*	Incremental QALYs	ICER (£)	Probability most cost-effective
TST (≥ 5mm) +ve QFT-GIT	300.10	N/A	19.909	N/A	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	N/A	0.177
TST (≥ 5mm)	298.75	7.62	19.922	0.005	1,524	0.469
TST (≥ 5mm) -ve QFT-GIT	353.47	54.72	19.923	0.001	58,720	0.280

*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.
[#]Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.

Results of our univariate sensitive analyses are presented in Table 43. We present costs and QALYs, in each scenario, for both of the strategies which were not strictly dominated by another strategy in our primary results. We also show which of the three strategies was the most cost-effective, assuming a willingness-to-pay of £20,000 per QALY, in each of these scenarios. In the majority of scenarios,

as in our base case, the TST (≥ 5mm) alone was the most cost-effective strategy. However, decreases in the prevalence of LTBI, increases in the sensitivity of the QFT-GIT, and decreases in the sensitivity of the TST, all led to strategies involving the QFT-GIT becoming the most cost-effective.

Table 43. Univariate sensitivity analyses

Parameter varied	**Value**	**Costs (QFT-GIT)**	**QALYs (QFT-GIT)**	**Costs (TST ≥ 5mm)**	**QALYs (TST ≥ 5mm)**	**Costs (TST ≥ 5mm -ve followed by QFT-GIT)**	**QALYs (TST ≥ 5mm -ve followed by QFT-GIT)**	**Most cost-effective strategy (£20,000 per QALY)**
Base-case		291.13	19.917	298.75	19.922	353.47	19.923	TST (≥ 5mm)
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 (≥ 5mm)
Sensitivity: IGRAs	QFT-GIT: 0.3584 QFT-GIT following –ve TST: 0.0225	309.31	19.913	298.75	19.922	354.82	19.922	TST (≥ 5mm)
	QFT-GIT: 0.8172 QFT-GIT following –ve 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 –ve TST: 0.9555	299.23	19.917	298.75	19.922	355.66	19.923	TST (≥ 5mm)
	QFT-GIT: 0.8073 QFT-GIT following –ve TST: 0.9893	283.62	19.918	298.75	19.922	349.92	19.923	TST (≥ 5mm)
Sensitivity: TST ≥ 5mm	TST: 0.7786	291.13	19.917	303.86	19.920	354.48	19.922	(TST ≥ 5mm -ve followed by QFT-GIT)
	TST: 0.9977	291.13	19.917	297.08	19.924	352.08	19.924	TST (≥ 5mm)
Specificity: TST ≥ 5mm	TST: 0.4790	291.13	19.917	311.44	19.922	363.91	19.923	TST (≥ 5mm)
	TST: 0.5229	291.13	19.917	288.84	19.922	344.32	19.923	TST (≥ 5mm)

Parameter varied	**Value**	**Costs (QFT-GIT)**	**QALYs (QFT-GIT)**	**Costs (TST ≥ 5mm)**	**QALYs (TST ≥ 5mm)**	**Costs (TST ≥ 5mm -ve followed by QFT-GIT)**	**QALYs (TST ≥ 5mm -ve followed by QFT-GIT)**	**Most cost-effective strategy (£20,000 per QALY)**
Effectiveness of LTBI treatment	0.392	302.35	19.915	311.22	19.918	369.71	19.919	TST (≥ 5mm)
	0.805	283.73	19.919	279.48	19.925	334.96	19.926	TST (≥ 5mm)
Cost of LTBI treatment	511.69	264.48	19.917	251.46	19.922	302.26	19.923	TST (≥ 5mm)
	842.45	317.78	19.917	346.04	19.922	404.68	19.923	TST (≥ 5mm)
Cost of active TB treatment	2664.38	228.40	19.917	261.83	19.922	318.18	19.923	TST (≥ 5mm)
	9244.44	375.99	19.917	348.69	19.922	401.21	19.923	TST (≥ 5mm)
Utility decrement – active TB	0.75	291.13	19.911	298.75	19.917	353.47	19.918	TST (≥ 5mm)
	0.95	291.13	19.923	298.75	19.926	353.47	19.927	TST (≥ 5mm)
Number of secondary TB cases per index case	0	265.87	19.928	277.46	19.931	325.81	19.932	TST (≥ 5mm)

Finally, Figure 58 presents cost-effectiveness acceptability curves 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.

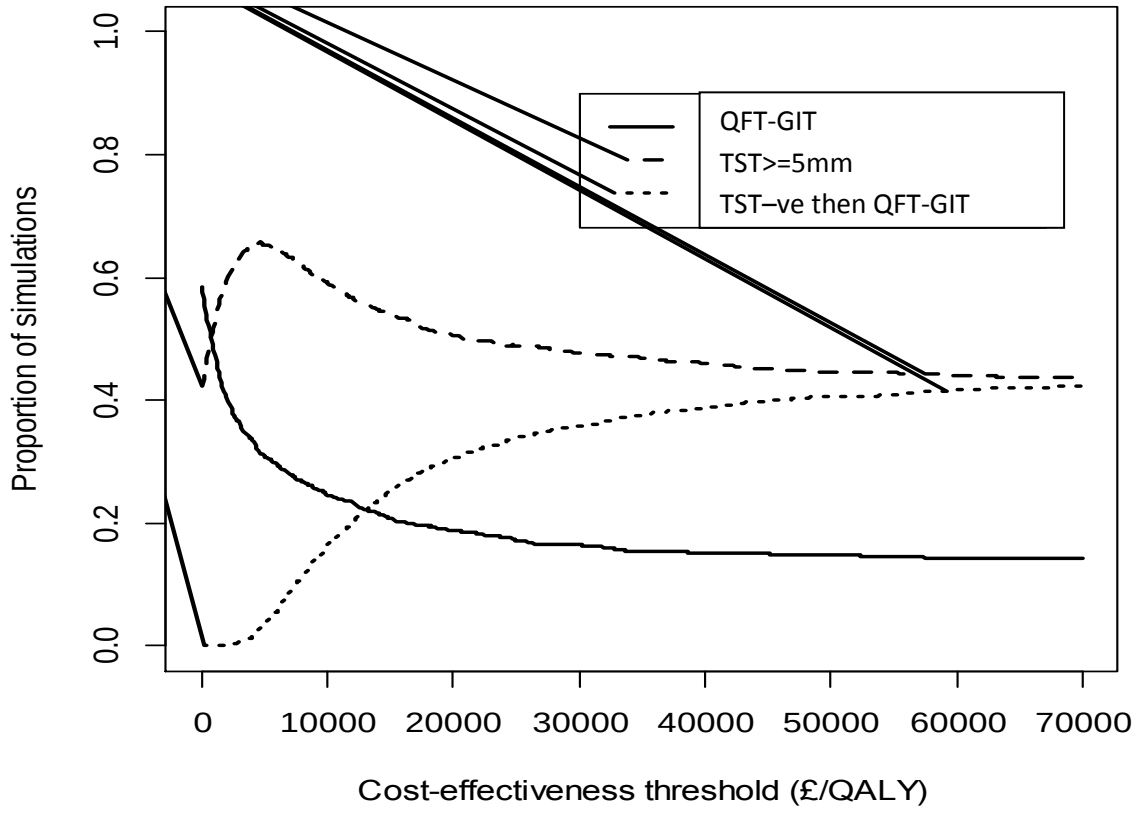


Figure 58. Cost-effectiveness acceptability curve for the recently arrived population, showing the proportion of simulations in which each strategy is the most cost-effective, at different willingness-to-pay thresholds

6.7 Exploring sensitivity and specificity

Clearly, one of the key drivers of differences between models is sensitivity and specificity. To illustrate the impact these parameters have on the outputs of our model, 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 children population.

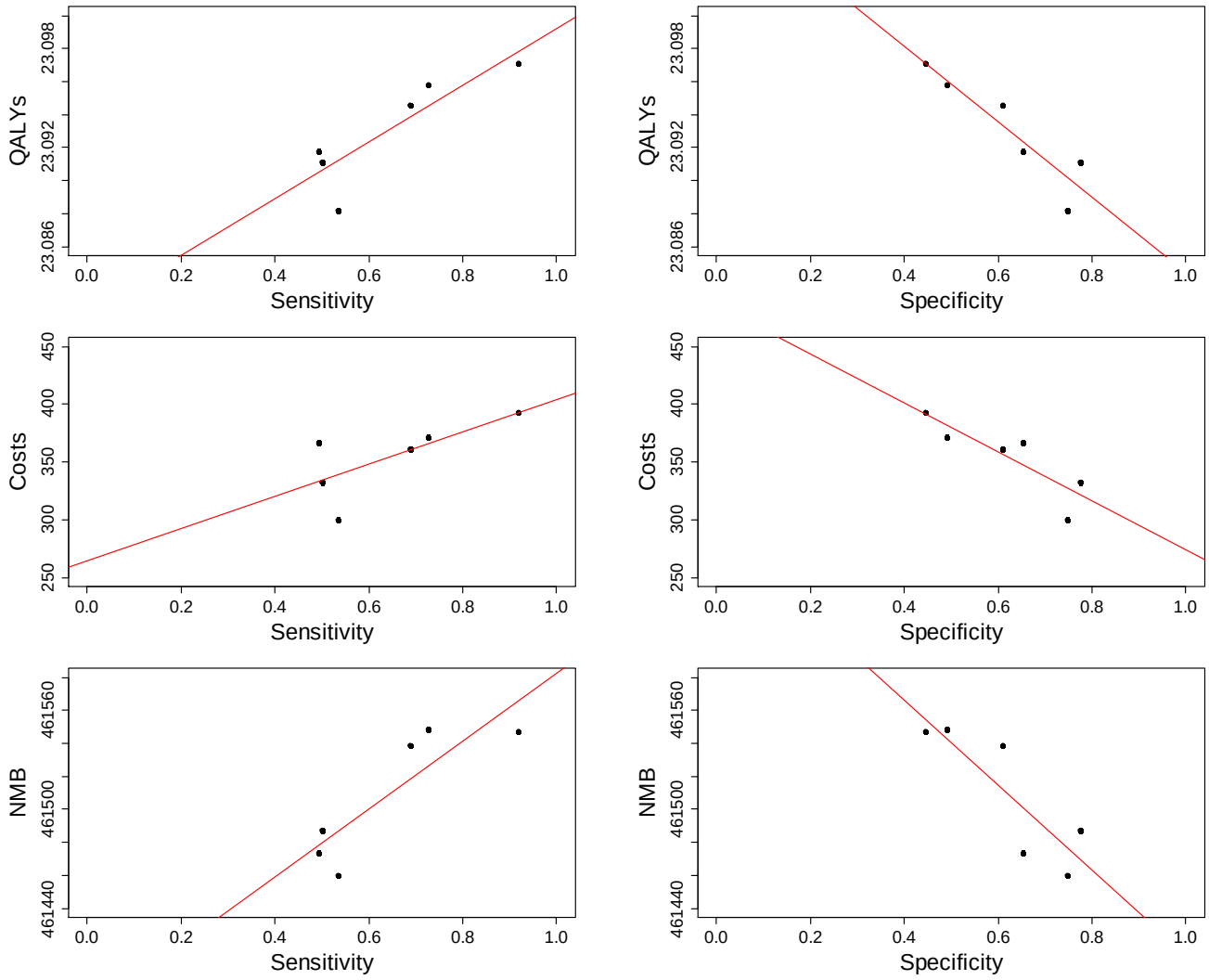


Figure 59. Sensitivity and specificity, plotted against costs, QALYs and net monetary benefit (at £20,000 per QALY), for each of the six strategies in the children population

These graphs show the, at first sight, counter intuitive result that increased specificity is associated with lower QALYs and lower NMB, whilst higher sensitivity is associated with higher costs. This is due to 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 we, instead of using the different strategies, can use the outputs of the PSA simulations for one of these strategies. This gives us 2,000 realisations of sensitivity, specificity, cost and QALYs, and since each of these sensitivity/specificity pairs is a sample from the posterior distribution of our MCMC, we would expect lower correlations between sensitivity and specificity than from comparing between different strategies. We then run a

linear regression model, with sensitivity and specificity as the predictor variables, for costs and QALYs. The results of this regression model are shown in Table 44.

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

In this model, where we have 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 due to the impact of varying other parameters, 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.

6.8 Discussion and conclusion

The results based on the outcome of cost per diagnostic error avoided showed that the TST (≥ 10mm) dominated all strategies except T-SPOT.TB strategy alone in the children population. T-SPOT.TB compared to TST (≥ 10mm) was more effective, but more expensive, with an ICER of approximately £2,711 per diagnostic error avoided. A breakdown of the effectiveness showed that T-SPOT.TB had less false positive cases (0.2172) compared to TST (≥ 10mm) (0.2307), but a larger number of false negative cases (0.0150) in a cohort of children. If T-SPOT.TB strategy were to be used in this population to diagnose LTBI that progress to active TB, this would lead to a slight reduction in the number of children being over treated for LTBI. In the immunocompromised population, QFT-GIT dominated QFT-GIT negative followed by TST, T-SPOT.TB and TST (≥ 5mm) in terms of diagnostic errors avoided. Results showed that QFT-GIT resulted in less false positives and less false negatives compared to these strategies. With the use of TST (≥ 10mm) in this population, this strategy was more effective, with overall diagnostic errors avoided of 0.1641. A breakdown of this effectiveness showed that TST (≥ 10mm) resulted in less false positives, but more false negative results. Likewise, with the use of the combination strategy QFT-GIT positive followed by TST (≥ 5mm) produced less false positive results, but more false negative results. In the recent arrivals from countries with a high incidence of TB, QFT-GIT dominated the T-SPOT.TB, TST (≥ 5mm) negative followed by QFT-

GIT, and TST (≥ 5mm) strategies. TST (≥ 5mm) positive followed by QFT-GIT had an ICER of £692 per diagnostic error avoided versus QFT-GIT, with more false negatives and less 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 threshold of £20,000 per QALY, a standard threshold that is used in the UK. Results in terms of the children population shows that TST (≥ 5mm) 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 £20,000 per QALY. The most effective strategy is TST (≥ 5mm) negative followed by QFT-GIT, which is the most cost-effective strategy in 32% of the simulations. Results in the immunocompromised population shows that QFT-GIT negative followed by TST (≥ 5mm) was the most effective strategy with an ICER of approximately £18,746 compared to T-SPOT.TB, and is the most cost-effective strategy in 40% of the simulations. In the recent arrivals population, TST (≥ 5mm) dominated the TST (≥ 5mm) positive followed by QFT-GIT, T-SPOT.TB and QFT-GIT alone strategies and had a probability of 47% of being cost-effective at £20,000 per QALY.

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

7 Discussion

The purpose of the current review was to compare the clinical- and cost-effectiveness of new screening tests for LTBI (IGRAs with 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 and cost-effective in accurately identifying latent TB in children?
2. Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB in people who are immunocompromised or at risk of immunosuppression?
3. Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB in people who are recent arrivals from countries with a high incidence of TB?

In this Chapter, the principal findings of the clinical and cost-effectiveness review 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.

7.1 Main findings

7.1.1 Clinical effectiveness review

There is no gold standard for 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 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, 55, 56] 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, 57, 59]

This review identified and appraised a large amount of evidence (53 new studies since CG117 and 37 studies from CG117) comparing IGRAs with TST for identifying LTBI in children, immunocompromised people, and recently arrived immigrants from countries with high TB incidence. Overall, the limited evidence from prospective studies in children showed no significant difference between the performance of QFT-GIT and TST 5mm in predicting LTBI. However, QFT-GIT was significantly better than TST 10mm in predicting LTBI. In children, IGRA (QFT-GIT/G) demonstrated similar sensitivity and slightly better specificity compared to TST 5mm. Moreover,

IGRAs tended to have a greater sensitivity but lower specificity compared to TST 10mm/15mm. Since the predictive value of the test is a function of its sensitivity, the greater predictive ability of IGRA compared to TST 10mm in predicting LTBI (as proxy of developing active TB) could be explained by better sensitivity of the former. Based on the exposure studies in children, IGRAs outperformed TST in identifying LTBI in the settings of low TB burden but not in the settings of high TB burden. This finding is consistent with growing body of evidence showing reduced sensitivity and specificity of IGRAs in high vs. low TB burden areas, the former represented mostly by developing countries where BCG vaccination is given at birth.[43, 58, 217-219] This heterogeneity in the test performance could be explained by higher frequency of exposure to MTB, different transmission dynamics, malnutrition, co-morbidity, people co-infected with HIV, exposure to NTMs, and helminthic infection in high TB burden settings.[103, 218, 219] Moreover, in high TB burden settings (mostly developing countries), specificity of TST is not greatly reduced because BCG is given mostly at birth without repeating it. In contrast, in some low burden settings (e.g., developed countries), BCG vaccination with booster shots may be offered after infancy which is known to compromise TST specificity.[218]

Evidence comparing IGRAs to TST in predicting the incidence of active TB in immunocompromised people was insufficient and inconclusive. The meta-analytic forest plot of 21 exposure-based studies showed large variation in the performance of IGRA compared to TST across different clinical subgroups. In general, QFT-GIT and T-SPOT.TB performed better than TST 5mm/10mm in identifying LTBI among people undergoing haemodialysis and those with hepatitis C. In contrast, in patients with HIV/AIDS, QFT-GIT was significantly worse than TST 10 mm in identifying LTBI. One explanation of this finding would be reduced sensitivity of IGRA to detect LTBI due to CD4+ T lymphocyte depletion in people with HIV-induced immunosuppression, leading to high proportion of indeterminate IGRA results. Interestingly, it is not clear if QFT-GIT and TST are differentially affected by CD4 depletion.[39, 218, 220, 221] Evidence on the comparative performance of IGRAs to TST in people with lupus erythematosus, immune-mediated inflammatory diseases before anti-TNF-α therapy, solid organ transplantation candidates, and kidney transplant recipients was inconclusive due to high uncertainty around the statistically non-significant effect estimates. The agreement between IGRA and TST in immunocompromised people was low.

There was no significant difference in the performance of IGRAs compared to TST in identifying LTBI amongst recently arrived people from countries with high TB burden. QFT-GIT demonstrated greater specificity but lower sensitivity compared to TST. Similarly, there was no evidence indicating differential effect of BCG vaccination status on IGRA (QFT, T-SPOT.TB) and TST positivity. Limited evidence indicated that both concordance and kappa were greater amongst BCG unvaccinated (or total sample) vs. BCG vaccinated people.

In general, the degree of agreement (measured by kappa statistic) between IGRAs and TST across the three subgroups of children, immunocompromised people, and recently arrived people from high TB burden areas was low. Several studies indicated better between-test (IGRAs vs. TST) concordance percent and agreement in unvaccinated vs. BCG vaccinated people. The higher rates of discordance between IGRAs and TST in BCG vaccinated populations could be explained by TST having reduced specificity (i.e., higher false positive rates) due to its cross-reactivity with antigens that are common to both MTB and BCG vaccine.[217] Overall, there was no clear and convincing evidence indicating a differential effect of BCG vaccination status 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 IGRAs and TST between BCG vaccinated vs. BCG non-vaccinated people.

7.1.2 Cost-effectiveness review

Ten studies 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.[10, 76, 193-197, 199-201] The majority of these models were in the immunocompromised population. These results highlight that there is a paucity pf 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 evaluation. 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 existing literature, but were subjected 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 generalizability of the results. Second, the majority of the studies used QALYs as their 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 have explored uncertainty around key model input parameters, but no attempt was made to explore methodological, generalizability or structural uncertainty. Other concerns relate to the derivation of prevalence, test accuracy and transition probabilities; most studies have not elaborated on these statistical/pre-model analyses.

7.1.3 Economic evaluation

In the children population, the TST –ve followed by QFT-GIT had the lowest proportion of false negatives, and the T-SPOT.TB the lowest proportions of false positives and overall errors. The TST(≥

10mm) was the strategy with the lowest overall cost, whilst the TST (≥ 5mm) -ve followed by QFT-GIT had the highest QALYs, was the most cost-effective (at £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 (≥ 5mm) had the lowest proportion of false negatives, and the QFT-GIT positive followed by TST the lowest proportions of false positives and overall errors. The QFT-GIT was the strategy with the lowest overall cost, whilst the QFT-GIT negativee followed by TST (≥ 5mm) had the highest QALYs, was the most cost-effective (at £20,000 per QALY), and had the highest probability of being the most cost-effective strategy.

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

7.2 Current findings compared to those from other systematic reviews

In general, our findings agreed with those from the other three systematic reviews[58, 89, 219] in showing IGRAs' improved specificity and a greater ability to predict LTBI relative to TST in the settings 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 which were reviewed.

The findings of this review could not be directly compared to those of several previously published systematic reviews due to the following reasons: a) our review results were stratified by children, immunocompromised people, and recently arrived people from high TB burden countries, whereas others do not use these three populations[18, 43, 56, 57, 217, 222]; b) we do not use prevalent culture-positive active TB as a proxy for LTBI;[39, 217, 220] c) one review included in-house IGRAs which we did not;[222] d) one review QFT-GIT compared to T-SPOT.TB only;[220] or e) two reviews reported no relevant outcomes.[223, 224]

7.3 Current results compared to 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 previous published papers, and hence the numbers derived for sensitivity and specificity are not comparable. Also, most of these other papers did not include sequential testing as a possible strategy, so we are only able to restrict our comparisons to the results for the TST and IGRA alone strategies.

In the immunocompromised population, previous studies[193, 195, 197, 199] indicated that when using a single test, IGRAs were preferable to TST, a conclusions which our results concur with. In the children population our results agree with those of Mandalakas et al[200] in finding that the TST negative followed by IGRA strategy was the most effective, but disagree with those of Kowada et al[194], who found the QFT-GIT to be more cost-effective than the TST, the opposite of our conclusion. Finally, in the recently arrived population, Pareek et al[76] found QFTs to be more cost-effective than TST, whilst we found the reverse, with the TST (≥ 5mm) the most cost-effective strategy.

Reasons for these differences, other than those which always apply (different populations modelled, different parameter values used etc.) can also be found in the different underlying structures of the models. First, Kowada et al[194] only considered primary cases of TB and not secondary infections, From our univariate sensitivity analyses in the children population, we see that when we set our seconadry infection rate to zero, we also find the QFT-GIT to be the most cost-effective strategy. When comparing IGRAs to TST, Pareek and colleagues used TST measured indurations of 10mm and 6/15mm (stratified by BCG status). Our results for the recently arrived population are based on an induration of 5mm, a value not modelled in the Pareek study, and therefore differences in conclusions may be explained by these thresholds used.

It is important to note that our model is designed only to evaluate which is the most cost-effective diganostic strategy, conditional on a decision having been made to test. It does not say anything about whether testing itself, versus no testing, is cost-effective and should be undertaken in these populations. Research addressing this question (testing/no testing) has recently been published [212]. Their model and ours 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 (ours included only TSTs versus IGRAs, theirs only treatment versus 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 costs of active TB, it differing by only 2%. Costs of managing hepatitis differed more substantially (aound £200), but since Isoniazid-induced hepatitis contributed only a small fraction to the costs in

our model, this is unlikely to make a major impact. Since progression to active TB was calculated using different methods in the two models, it is not possible to compare the input parameters direcetly. However, by restricting to a subsample of the full population which can be extracted from both models, we can compare the number of active TB cases each predicts, to see if these numbers are similar. In particular, for a sample of 51-65 years olds with a positive TST, the Imperial model presdicts 2,091 cases per 100,000 in treated patiens, and 5,928 per 100,000 in untreated. Our model, in contrast, predicts 1,736 cases per 100,000 in treated, and 5,372 per 100,000 in untreated. These differenes are most likely explained simply from the different data used to populate the two models. However, if one were to believe the incidence from their study to be more accurate, this would have the effect of increasing the prevalance of LTBI in the starting population of ours, the net effects of which can be explored from our uniariate sensitivity analyses.

7.4 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 provide 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 prior BCG vaccination, inter-/intra-rater 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 due to 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 the test performance (IGRA vs. TST) in correctly detecting LTBI is the inconsistent use of definitions for high vs. low risk for LTBI (i.e., construct of validity). The heterogeneity in the measures of association between test results and prior exposure to TB observed even at within-study level could be due to inadequate definition of construct of validity for LTBI (e.g., prior 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, diagnostic odds ratios, between-test agreement) could be explained by study setting, type of population, type of test, and the outcome characteristics.

Heterogeneity especially with regards to the sensitivity and specificity estimates derived from prior 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 stratified analyses by population, type of IGRA test, and TST threshold.

Another concern in interpreting the evidence relates to risk of bias and methodological quality of the individual studies. In general, most studies were rated as being at high or moderate risk of bias (incidence studies) or 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 we reviewed may have been biased due to diagnostic review bias (i.e., lack of blinding or knowledge of IGRA/TST result influencing the ascertainment of exposure status or diagnosis of incident active TB), selection bias (i.e., study sample distorted with respect to prior TB exposure or disease spectrum due to inadequate sampling frame, participant recruitment, non-participation, and exclusions at study baseline), partial verification bias (incomplete outcome data assessment due to indeterminate IGRA results, missing TB exposure, withdrawals and/or losses to follow-up), and incorporation bias (i.e., incorporation of IGRA/TST result as criteria for the diagnosis of LTBI or incident active TB).[18, 43, 88, 225]

Although 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 were of small sample size, and their follow-up was not long enough to document and evaluate the test predictive ability 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 since not all LTBI cases will develop into active TB or some seemingly incident active TB cases (assumed to have developed from LTBI) may actually be people with newly acquired TB infection (prevalent active TB cases).

7.5 Strengths and limitations of the current reviews and economic evaluation

We undertook a systematic review to identify all relevant studies providing evidence on clinical-effectiveness of IGRAs compared to TST for identifying LTBI in the pre-specified populations. The main strength of the current review was the application of systematic comprehensive search, study screening, data extraction, use of relevant quality/ROB assessment tools for different study designs, and stratified analyses (by children, immunocompromised people, recently arrived people from high TB burden countries, subgroups defined by clinical condition, type of IGRAs, TST threshold, high vs. low TB burden area, study setting). Our review, unlike other systematic reviews,[39, 217, 220] avoided including studies which used invalid constructs for LTBI such as culture-confirmed active TB. Instead, this review focused on studies which defined the construct of LTBI either through incidence

of active TB or study participants' prior exposure to respective 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 which 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 was not undertaken for studies included in CG117.[10] Moreover, due to a lack of relevant reported evidence, it was not possible to evaluate the effectiveness of the two-step testing procedure (using both IGRAs plus TST) for identifying people with LTBI. Another limitation was our inability to stratify the study findings by BCG vaccination status, since even though this may have been an important distinguishing feature in the effectiveness of the different tests, the individual study publications failed to report their results separately for vaccinated and un-vaccinated populations. The proportion of people vaccinated with BCG varied considerably in the included studies such that, it was not possible to dichotomize populations into e.g., vaccinated vs. non-vaccinated. And further stratification by BCG status was anyway not feasible due to the scarcity of the data. With regards to the economic evaluation, we applied a unit cost for people being tested with TST. Unit cost includes the cost of test, consumables, administering the test and reading the result. We applied this cost to people who had their TST result read and those who did not have their result read. This has the effect of inflating the cost of an unread TST. In addition, the model takes into account the need for two clinic visits for TST, however, it does not take into account the need for skilled operators and the wide intra-observer variability in interpretation. IGRAs require one visit, need less 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 x-ray for identifying people who have active TB. In our model, we have used the sensitivity and specificity from Kumar et al. (2005)[211] on the accuracy of chest x-ray for identifying the presence/absence of active TB in our three populations. This may have the impact of over/underestimating the diagnostic accuracy of chest x-rays in these populations. Third, detailed resource use information on the treatment for LTBI was unavailable in the literature. We therefore estimated resource use for LTBI treatment using input from our clinical advisors derive and this may result in either over or under estimation.

8 Conclusion

The review draws attention to the clinical effectiveness evidence published since CG117. The research adds to the existing literature but highlights the poor quality in the evidence. Surprisingly, the results show that the two different generations of tests are broadly equivalent, although results vary in the number of different settings and sub-groups. The limitations in evidence (e.g., absence of gold standard in LTBI diagnosis, risk of bias in individual studies, scarcity of evidence, test administration/interpretation, variation in the exposure-based definitions of LTBI construct, limitations of the screening tests) and heterogeneity in IGRA performance relative to TST limits 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 immunocompromised population, thereby limiting the extent of applicability of test results from one subgroup (e.g., HIV, rheumatoid arthritis) to another (e.g., hepatitis C, lupus erythematosus) within immunocompromised people.

The review of the cost-effectiveness evidence brings attention to the methods available, prior to developing a model structure to determine the cost-effectiveness of IGRA 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, derivation of prevalence, test accuracy and transition probabilities; most studies have not elaborated on these statistical/pre-model analyses.

In the population of children who have had contact with an index case, the results based on the outcome cost per diagnostic error avoided showed that the TST (≥ 10mm) dominated all strategies except T-SPOT.TB strategy alone. T-SPOT.TB compared to TST (≥ 10mm) was more effective, but more expensive, with an ICER of approximately £2710 per diagnostic error avoided. Results in terms of the children population showed that TST (≥ 5mm) was slightly more effective than QFT-GIT alone strategy, with an ICER of approximately £11,260 per QALY, and has a 26.9% probability of being cost-effective at £20,000 per QALY.

In the immunocompromised population, QFT-GIT dominated QFT-GIT negative followed by TST, T-SPOT.TB and TST (≥ 5mm) in terms of diagnostic errors avoided. With the use of the combination strategy QFT-GIT positive followed by TST (≥ 5mm) was the most effective strategy. Results in terms of cost per QALY showed that QFT-GIT negative followed by TST (≥ 5mm) was the most

effective strategy with an ICER of approximately £18,750 compared to T-SPOT.TB, and had a 40% probability of being cost-effective.

In the recent arrivals from countries with a high incidence of TB, QFT-GIT dominated all strategies except TST (≥ 5mm) positive followed by QFT-GIT. TST (≥ 5mm) positive followed by QFT-GIT strategy was more costly and resulted in more diagnostic errors avoided with an ICER of approximately £690 compared to the QFT-GIT alone strategy. Results in terms of cost per QALY, QFT-GIT dominated T-SPOT.TB and TST (≥ 5mm) 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 (≥ 5mm) had the highest (47%) probability of being cost-effective at a willingness-to-pay of £20,000.

8.1 Implications for service provision and local commissioning

The results of the health economic analysis shows which diagnostic strategy is likely to be the most cost-effective for the diagnosis of LTBI which progresses to active TB.

Our results do not show if screening compared with no screening is likely to be cost-effective nor does it 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 gold standard diagnostic test and assumptions made. Clinicians should be mindful of the variation in performance of the different testing strategies amongst different populations.

8.2 Suggested research priorities

A key priority is to conduct research in both high and low TB burden in order to explore and confirm whether the inconsistent performance of IGRAs in high vs. low TB burden countries 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 TST for diagnosis of LTBI; future studies need to evaluate the utility of two-step vs. single testing in order to maximise both sensitivity and specificity for identifying people with LTBI.

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 the component exposures to classify people into high vs. low risk for LTBI. This would improve retrospective or cross-sectional studies of prior TB exposure by facilitating standardized definitions across different studies, and would allow for more objective comparison of IGRAs with TST in terms of detecting LTBI in subgroups of interest.

There is very little evidence on the roles of IGRAs and TST for the diagnosis of LTBI in different clinical subgroups of immunocompromised people (e.g., HIV, hepatitis C, solid organ transplant recipients, rheumatoid arthritis) and future research could be directed at clarifying this. Finally, more efforts need to be directed at identifying new more accurate markers of LTBI.

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11 Appendices

11.1 Appendix 1. Search strategies and results 2011

Main searches

Diagnosis of latent TB using M. tuberculosis-specific antigens interferon gamma release assays

The following sources were searched to answer questions relating to the diagnosis of latent TB using *M. tuberculosis*-specific antigens (ESAT-6, CFP 10, and TB7.7) interferon gamma release assays (IGTs), including the following commercially available assays:

- QuantiFERON-TB Gold In-Tube
- QuantiFERON-TB Gold
- I T-SPOT.TB.

The diagnostic utility of these assays, alone or in combination with a tuberculin skin test, will be compared with tuberculin skin test alone.

The database searches were undertaken between the 7th and 14th December 2009.

Databases searched:

- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- Cinahl (EBSCO)
- DARE (CRD)
- HTA (CRD)
- Cochrane Library (Wiley)
- Cochrane Register of Diagnostic Test Accuracy Studies (Wiley)
- Medion
- ARIF

The MEDLINE search strategy is presented below. It was translated for use in the databases listed above.

Ovid MEDLINE(R) <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 interferon gamma release assays (IGTs) for latent tuberculosis:

- Health Economic Evaluations Database – HEED (Wiley)
- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The searches were undertaken on 5th and 6th January 2009.

The MEDLINE search strategy is presented below. It was translated for use in other databases.

Ovid MEDLINE(R) <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$.tw.
70 Health Status Indicators/
71 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
72 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
[Double click to insert footer here] 24 of 315
73 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
74 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
75 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
76 (euroqol or euro qol or eq5d or eq 5d).tw.
77 (qol or hql or hqol or hrqol).tw.
78 (hye or hyes).tw.
79 health$ 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

11.2 Appendix 2. Search strategies and results 2014

The objective of the search strategy was to identify literature on the diagnosis of LTBI using IGRAs compared to other methods. The following sources were searched: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, 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 9th and 10th April, 2014 and were updated on 2nd December 2014 using the same strategies. Supplementary searches were undertaken between 10th June and 5th August 2014.

Table 45. Ovid MEDLINE(R) 1946 to April Week 1 2014, searched on 09/04/2014

1	(laten* adj3 (tb* or tubercul*)).tw.	2701
2	ltb*.tw.	6939
3	tubercul*.tw.	158617
4	Tuberculosis/	51049
5	Latent Tuberculosis/	866
6	Tuberculosis, Pulmonary/	63874
7	Mycobacterium tuberculosis/	35401
8	1 or 2 or 3 or 4 or 5 or 6 or 7	195420
9	quantiferon*.tw.	819
10	QFT*.tw.	557
11	t spot*.tw.	261
12	exp Enzyme-Linked Immunosorbent Assay/	122317
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	126234
18	8 and 17	3840
19	Latent Tuberculosis/di	576
20	18 or 19	4061
21	Animals/ not Humans/	3812070
22	20 not 21	3480
23	limit 22 to english language	3014
24	limit 23 to ed=20091207-20140409	**1288**

Update search Dec 2014
Ovid MEDLINE(R) 1946 to November Week 3 2014, searched on 02/12/20
Search above re-run with the following limit:

Line 24 = limit 23 to ed=20140312-20141202: **222**

Total
1288 + 222 = **1510**

Table 46. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 08, 2014, searched on 09/04/2014

1	(laten* adj3 (tb* or tubercul*)).tw.	312
2	ltb*.tw.	340
3	tubercul*.tw.	10405
4	1 or 2 or 3	10625
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

Update search Dec 2014
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 01, 2014, searched on 02/12/2014
Search above re-run with the following limit:
Line 15 = limit 14 to ed=20140312-20141202: 19

Total
263 + 19 = **282**

Table 47. Ovid Embase 1980 to 2014 Week 14, searched on 09/04/2014

1	(laten* adj3 (tb* or tubercul*)).tw.	3880
2	ltb*.tw.	8397
3	tubercul*.tw.	175055
4	tuberculosis/	87819
5	latent tuberculosis/	1696
6	lung tuberculosis/	62789
7	Mycobacterium tuberculosis/	47234
8	1 or 2 or 3 or 4 or 5 or 6 or 7	227447
9	quantiferon*.tw.	1477
10	QFT*.tw.	871

11	t spot*.tw.	442
12	enzyme linked immunospot assay/	5911
13	*enzyme linked immunosorbent assay/	14220
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	23387
19	8 and 18	3410
20	latent tuberculosis/di	573
21	19 or 20	3619
22	animal/ not human/	1176853
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

Update search Dec 2014
Embase 1980 to 2014 Week 48, searched on 02/12/2014
Re-ran search above with the following limits:
Line 25 = limit 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 48. Cochrane Library via Wiley, searched on 09/04/2014

#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**

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 Dec 2014
Cochrane Library via Wiley, searched on 02/12/2014
Search above re-run with the following limit:
Line 21= #18 or #19 Publication Year from 2014 to 2014: **11**
All Results (**11**)
Cochrane Reviews (0)
All Review Protocol
Other Reviews (**3**)
Trials (**7**)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (**1**)
Cochrane Groups (0)

Total
108 + 11 = **119**

Table 49. Science Citation Index Expanded (SCI-EXPANDED) --1970-present and Conference Proceedings Citation Index- Science (CPCI-S) --1990-present via Web of Knowledge, searched on 09/04/2014

# 14	(#13) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2014	1,608
# 13	#4 and #12 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	3,139
# 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	5,812
# 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	464

	Timespan=All years	
# 6	TS=QFT* Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	1,894
# 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	6,278
# 1	TS=(laten* NEAR/3 (tb or tubercul*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	3,314

Update search Dec 2014
Science Citation Index Expanded (SCI-EXPANDED) --1970-present and Conference Proceedings Citation Index- Science (CPCI-S) --1990-present via Web of Knowledge, searched on 02/12/2014
Search above re-run with the following limit:
Timespan=2014
#14 = **277**

Total
3,314 + 277 = **3591**

Medion, searched on 10/06/2014
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 Word 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

WHO ICTRP, searched on 05/08/2014
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 on 05/08/2014
(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, were checked for the last five years. Search date: 24th and 25th June 2014.

- European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) http://ecdc.europa.eu/en/ESCAIDE/about_ESCAIDE/Pages/previous_conferences.aspx
- Public Health England Annual Conference (previously HPA Annual Conference) https://www.phe-events.org.uk/hpa/frontend/reg/thome.csp?pageID=117557&eventID=286&eventID=286 (previously HPA Annual Conference)
- 5 Nations Health Protection Conference http://5nations.org.uk/?page_id=44
- Federation of Infection Society http://fis-infection.org.uk/ (eg http://www.actiononinfection.com/abstracts-and-poster-walk/)
- British Thoracic Society https://www.brit-thoracic.org.uk/bts-learning-hub/bts-summer-and-winter-meetings/summer-meeting-2014/
- Annual Conferences of the Union North America Region http://www.bc.lung.ca/association_and_services/union.html

Websites
Websites of specific organisations, selected with input from a clinical expert, were checked for relevant literature. Search date: 25th June 2014.

- Public Health England (including old Health protection Agency site) https://www.gov.uk/government/organisations/public-health-england and http://www.hpa.org.uk/
- CDC (Atlanta) http://www.cdc.gov/
- European Centre for Disease Prevention and Control (ECDC) http://www.ecdc.europa.eu/en/Pages/home.aspx and http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/programme_tuberculosis/Pages/index.aspx
- World Health Organization (WHO) http://www.who.int/en/ and http://dosei.who.int/uhtbin/cgisirsi/tXRt5oo9vL/245820007/60/86/X
- British Thoracic Society (BTS) - https://www.brit-thoracic.org.uk/
- Cellestis (manufacturer of QuantiFERON-TB Gold) www.cellestis.com/
- Oxford Immunotec (manufacturer of T-SPOT.TB test) www.oxfordimmunotec.com/

11.3 Appendix 3. Data extraction sheet 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		

11.4 Appendix 4. Quality assessement and risk of bias

Table 50. Quality assessment for the exposure studies (adapted from Dinnes et al., 2007)[43]

First author, Year, Study ID	**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]#, inadequate or unreported [no]*	**Overall score of satisfactory features (%)** [£]

[#] ≥ 90% of participants were included in the follow-up analysis [yes response] and < 90% were classified as "no response"

[£] Studies with 1 or 2 "yes" ratings = Low quality; studies with 3 "yes" ratings = Moderate quality; studies with 4 or 5 "yes" ratings = High quality

Please note the following item has been removed from the original Dinnes et al., (2007) checklist: "study design" (as all studies were considered are retrospective), this item has been removed. Furthermore, the following item has been added: "sample attrition"

Risk of bias (ROB) for the incidence studies (adapted from Hayden et al., 2013)[89]

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 it is that relationship between test result and outcome is different for participants vs. eligible non-participants?**	The source population is adequately described			
		The sampling frame and recruitment is adequately described			
		The period and place of recruitment are adequately described			
		Inclusion and exclusion criteria is adequately described			
		The baseline study sample is adequately described			
		Adequate participation in the study by eligible individuals			
		Participants were consecutively enrolled			
Study Attrition (risk of selection bias)	**Does the study data available (participants not lost to follow-up) adequately represent the study sample?** **How likely it is that relationship between test results and outcome are different for completing and non-**	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			

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)
	completing participants)?	outcomes in 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?**	A clear definition or description of the test is provided (e.g., type, assay, threshold for positivity, and method of measurement)			
	How likely it is that the measurement or knowledge of outcome influenced the test results?	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 is the same for all study participants			
		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			
Outcome/Construct Measurement (risk of bias 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**	A clear definition of outcome 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			

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)
	for all participants? **How likely is differential measurement of outcome (e.g., outcome measurement related to the test results)?**	measurement, adequate methods of outcome/construct ascertainment – exposure proximity plus duration considered)			
		The method and setting of outcome/construct measurement is the same for all study participants			
Study Confounding (risk of bias due to confounding)	**Were important potential confounding factors appropriately accounted for?** **How likely is bias due to confounding?**	All important confounders, including treatments (key variables in conceptual mode) are defined and measured			
		All important confounders are accounted for at the design and/or analysis stage			
Statistical Analysis and Reporting (risk of bias due to analysis and selective reporting)	**Was the statistical analysis appropriate, and all primary outcomes were reported?** **How likely is bias related to the statistical analysis and presentation of 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)	
ROB = risk of bias					

Table 51. Definition for risk of bias ratings for each domain of bias – The Quality In Prognosis Studies (QUIPS) tool (adapted from Hayden et al., 2013)[89]

Domain of bias	Definition for ROB ratings		
	High risk of bias	**Moderate risk of bias**	**Low risk of bias**
Study Design	Case-control study	Cross-sectional study	Prospective cohort study
Study Participation	The relationship between the test results and construct/outcome is very likely to be different for participants and eligible nonparticipants	The relationship between the test results and outcome may be different for participants and eligible nonparticipants	The relationship between the test results and outcome is unlikely to be different for participants and eligible nonparticipants
Study Attrition	The relationship between the test results and construct/outcome is very likely to be different for completing and noncompleting participants	The relationship between the test results and construct/outcome may be different for completing and noncompleting participants	The relationship between the test results and outcome is unlikely to be different for completing and noncompleting 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 PF 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

11.5 Appendix 5. Literature review list of excluded studies and reason(s) for exclusion (N = 424)

Table 52. List of excluded studies from the clinical effectiveness review

N	Study	Reason(s) for exclusion
1.	Abud-Mendoza, C., et al. (2010). "Should tuberculin skin test be positive to give latent tuberculosis treatment before tumor necrosis factor-alpha inhibitors in selected patients in developing countries?" Journal of Rheumatology 37(3): 672-673; author reply 673.	Letter
2.	Abu-Taleb, A. M., et al. (2011). "Interferon-gamma release assay for detection of latent tuberculosis infection in casual and close contacts of tuberculosis cases." Eastern Mediterranean Health Journal 17(10): 749-753.	Mixed population and/or no subgroup of interest
3.	Ahmadinejad, Z., et al. (2012). "Diagnosis of latent tuberculosis infection in candidates for kidney transplantation (comparison of two tests)." Acta Medica Iranica 50(5): 305-310.	No construct validity
4.	Altet-Gomez, N., et al. (2011). "Diagnosing TB infection in children: analysis of discordances using in vitro tests and the tuberculin skin test." European Respiratory Journal 37(5): 1166-1174.	Combined test positive result (TST and IGRA tests +s) for ORs
5.	American College Health, A. (2011). "Tuberculosis screening and targeted testing of college and university students." Journal of American College Health 59(7): 670-677.	Guideline
6.	Andrisani, G., et al. (2013). "Comparison of Quantiferon-TB Gold versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease patients." Journal of Gastrointestinal & Liver Diseases 22(1): 21-25.	No construct validity
7.	Anibarro, L., et al. (2011). "Tuberculin skin test and interferon-release assay show better correlation after the tuberculin 'window period' in tuberculosis contacts." Scandinavian Journal of Infectious Diseases 43(6-7): 424-429.	Mixed population and/or no subgroup of interest
8.	Anonymous (2010). "Proceedings of the Second Global Symposium on Interferon-Gamma Release Assays. Dubrovnik, Croatia. May 30-June 1, 2009." International Journal of Tuberculosis & Lung Disease 14 Suppl 1: S3-70.	Abstract
9.	Baboolal, S., et al. (2010). "Comparison of the QuantiFERON-TB Gold assay and tuberculin skin test to detect latent tuberculosis infection among target groups in Trinidad & Tobago." Pan American Journal of Public Health 28(1): 36-42.	Inappropriate proxy for LTBI
10.	Basu Roy, R., et al. (2012). "Identifying predictors of interferon-release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette-Guerin?: a pTB-NET collaborative study." American Journal of Respiratory & Critical Care Medicine 186(4): 378-384.	No construct validity
11.	Belard, E., et al. (2011). "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." Inflammatory Bowel Diseases 17(11): 2340-2349.	No construct validity

12.	Bergot, E., et al. (2012). "Observational study of QuantiFERON-TB gold in-tube assay in tuberculosis contacts in a low incidence area." PLoS ONE [Electronic Resource] 7(8): e43520.	Mixed population and/or no subgroup of interest
13.	Bienek, D. R. and C. K. Chang (2009). "Evaluation of an interferon-gamma release assay, T-SPOT.TB, in a population with a low prevalence of tuberculosis." International Journal of Tuberculosis & Lung Disease 13(11): 1416-1421.	Mixed population and/or no subgroup of interest
14.	Bottger, E. C. (2012). "Interferon- release assays and the risk of developing active tuberculosis." American Journal of Respiratory & Critical Care Medicine 185(7): 786-787; author reply 787.	Letter
15.	Bua, A., et al. (2013). "Tuberculin skin test and QuantiFERON in children." New Microbiologica 36(2): 153-156.	No construct validity
16.	Camlar, S. A., et al. (2011). "Performance of tuberculin skin test and interferon gamma assay for the diagnosis of latent tuberculosis infection in juvenile idiopathic arthritis." Clinical Rheumatology 30(9): 1189-1193.	No construct validity
17.	Campainha, S., et al. (2012). "Negative predictive value of TST and IGRA in anti-TNF treated patients." European Respiratory Journal 40(3): 790-791.	Letter
18.	Carvalho, A. C., et al. (2013). "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 41(4): 827-831.	IGRA vs. IGRA only (no TST)
19.	Cassone, A., et al. (2012). "High rate of Quantiferon positive and tuberculin negative tests in infants born at a large Italian university hospital in 2011: a cautionary hypothesis." Pathogens and Global Health 106(1): 8-11.	Review
20.	Cheallaigh, C. N., et al. (2013). "Interferon gamma release assays for the diagnosis of latent TB infection in HIV-infected individuals in a low TB burden country." PLoS ONE [Electronic Resource] 8(1): e53330.	No construct validity
21.	Chou, C. H., et al. (2009). "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." Journal of Microbiology, Immunology & Infection 42(3): 251-257.	IGRA vs. IGRA only (no TST)
22.	Chung, W. K., et al. (2010b). "Serial testing of interferon-gamma-release assays for the diagnosis of latent tuberculosis in hemodialysis patients." Journal of Infection 61(2): 144-149.	Serial testing, conversion and reversion rates
23.	Connell, D. W., et al. (2011). "A comparison between interferon gamma release assays and the tuberculin skin test in the contact tracing of patients with chronic kidney disease." Thorax 66(8): 729-730; author reply 730.	Letter
24.	Connell, T. G., et al. (2010). "Indeterminate interferon-gamma release assay results in children." Pediatric Infectious Disease Journal 29(3): 285-286.	Letter
25.	Critselis, E., et al. (2012). "The effect of age on whole blood interferon-gamma release assay response among children investigated for latent tuberculosis infection." Journal of Pediatrics 161(4): 632-638.	No construct validity
26.	Dagnew, A. F., et al. (2012). "Diagnosis of latent tuberculosis infection in healthy young adults in a country with high tuberculosis burden and BCG vaccination at birth." BMC	Mixed population and/or no subgroup of interest

	Research Notes 5: 415.	
27.	Davies, M. A., et al. (2009). "Detection of tuberculosis in HIV-infected children using an enzyme-linked immunospot assay." AIDS 23(8): 961-969.	Active TB
28.	de Andrade Lima, E., et al. (2011). "Evaluation of an IFN-gamma assay in the diagnosis of latent tuberculosis in patients with psoriasis in a highly endemic setting." Acta Dermato-Venereologica 91(6): 694-697.	No construct validity
29.	de Kantor, I. N. (2011). "Diagnosis of latent tuberculosis infection in BCG-vaccinated subjects in China." International Journal of Tuberculosis & Lung Disease 15(11): 1560-1561; author reply 1561.	Letter
30.	Del Tedesco, E., et al. (2011). "Does anti-TNF therapy influence the performance of mycobacterium tuberculosis antigen-specific interferon-gamma assays? A French multicenter experience." Inflammatory Bowel Diseases 17(8): 1824.	Letter
31.	Denholm, J. T. (2013). "Immigration screening for latent tuberculosis infection." Medical Journal of Australia 199(10): 654.	Letter
32.	Denholm, J. T. (2013). "Immigration screening for latent tuberculosis infection." Medical Journal of Australia 198(10): 524.	Letter
33.	Deuffic-Burban, S., et al. (2010). "Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection." International Journal of Tuberculosis & Lung Disease 14(4): 471-481.	Economic study
34.	Diel, R., et al. (2009). "Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany." Respiratory Medicine 103(12): 1838-1853.	Economic study
35.	Dilektasli, A. G., et al. (2010). "Is the T-cell-based interferon-gamma releasing assay feasible for diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country?" Japanese Journal of Infectious Diseases 63(6): 433-436.	Mixed population and/or no subgroup of interest
36.	Doberne, D., et al. (2011). "Preanalytical delay reduces sensitivity of QuantiFERON-TB gold in-tube assay for detection of latent tuberculosis infection." Journal of Clinical Microbiology 49(8): 3061-3064.	No relevant outcomes; population ineligible
37.	Dowdy, D. W. and Golub, J. E. (2012). "Tests for latent tuberculosis infection and isoniazid preventive therapy." The Lancet Infectious Diseases 12(11): 827-828.	Letter
38.	Dyrhol-Riise, A. M., et al. (2010). "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 10: 57.	Mixed population and/or no subgroup of interest
39.	Garcia-Elorriaga, G., et al. (2013). "Interferon in patients with HIV/AIDS and suspicion or latent tuberculosis infection." Asian Pacific Journal of Tropical Medicine 6(2): 135-138.	No construct validity
40.	Garcia-Gasalla, M., et al. (2013). "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." Enfermedades Infecciosas y Microbiologia Clinica 31(2): 76-81.	No construct validity
41.	Garcovich, S., et al. (2012). "Clinical applicability of	No construct validity

	Quantiferon-TB-Gold testing in psoriasis patients during long-term anti-TNF-alpha treatment: a prospective, observational study." Journal of the European Academy of Dermatology & Venereology 26(12): 1572-1576.	
42.	Gautam, M., et al. (2012). "Tuberculosis infection in the indigenous elderly White UK population: a study of IGRAs." International Journal of Tuberculosis & Lung Disease 16(4): 564.	Letter
43.	Gilham, L., et al. (2011). "Tuberculosis screening before biologics – T-SPOT for all?" Journal of Rheumatology 38(1): 179.	Letter
44.	Girlanda, S., et al. (2010). "ELISPOT-IFN-gamma assay instead of tuberculin skin test for detecting latent Mycobacterium tuberculosis infection in rheumatic patients candidate to anti-TNF-alpha treatment." Clinical Rheumatology 29(10): 1135-1141.	Non-standard or in-house IGRA
45.	Gogus, F., et al. (2010). "Comparison of tuberculin skin test and QuantiFERON-TB gold in tube test in patients with chronic inflammatory diseases living in a tuberculosis endemic population." Clinical & Experimental Medicine 10(3): 173-177.	No construct validity
46.	Gonzalez-Salazar, F., et al. (2011). "Snapshot of Quantiferon TB gold testing in Northern Mexico." Tuberculosis 91 Suppl 1: S34-37.	Mixed population and/or no subgroup of interest
47.	Goujon, C., et al. (2012). "Diagnosis of latent tuberculosis infection (LTBI) before anti-TNF-alpha treatment--the tuberculin skin test is useful." European Journal of Dermatology 22(5): 701-702.	Case report
48.	Grare, M., et al. (2010). "QuantiFERON-TB Gold In-Tube as help for the diagnosis of tuberculosis in a French pediatric hospital." Diagnostic Microbiology & Infectious Disease 66(4): 366-372.	No construct validity
49.	Greveson, K., et al. (2013). "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." Journal of Crohn's & colitis 7(5): 412-418.	IGRA only (no TST)
50.	Griffin, D. W. and Kelly, M. D. (2013). "Immigration screening for latent tuberculosis infection." Medical Journal of Australia 199(10): 654.	Editorial
51.	Grinsdale, J. A., et al. (2011). "Programmatic impact of using QuantiFERON-TB Gold in routine contact investigation activities." International Journal of Tuberculosis & Lung Disease 15(12): 1614-1620.	Mixed population and/or no subgroup of interest
52.	Gupta, D., et al. (2011). "Interferon gamma release assay (QuantiFERON-TB Gold In Tube) in patients of sarcoidosis from a population with high prevalence of tuberculosis infection." Sarcoidosis Vasculitis & Diffuse Lung Diseases 28(2): 95-101.	Active TB
53.	Hanta, I., et al. (2012). "Detection of latent tuberculosis infection in rheumatologic diseases before anti-TNFalpha therapy: tuberculin skin test versus IFN- assay." Rheumatology International 32(11): 3599-3603.	No construct validity
54.	Hardy, A. B., et al. (2010). "Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the	Economic study

	QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries." Thorax 65(2): 178-180.	
55.	Hatemi, G., et al. (2012). "Quantiferon-TB Gold in tube assay for the screening of tuberculosis before and during treatment with tumor necrosis factor alpha antagonists." Arthritis Research & Therapy 14(3): R147.	No construct validity
56.	He, D., et al. (2013). "High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy." Clinical & Vaccine Immunology: CVI 20(6): 842-847.	IGRA only (no TST)
57.	Helwig, U., et al. (2012). "Corticosteroids and immunosuppressive therapy influence the result of QuantiFERON TB Gold testing in inflammatory bowel disease patients." Journal of Crohn's & colitis 6(4): 419-424.	IGRA only (no TST)
58.	Hernandez-Garduno, E. (2011). "The positive predictive value of T-spot.TB and tuberculin skin test in patients with silicosis." American Journal of Respiratory & Critical Care Medicine 183(2): 277; author reply 277-278.	Letter
59.	Hernandez-Garduno, E. (2011). "An update: the predictive value of QuantiFERON-TB-Gold In-Tube assay and the tuberculin skin test." American Journal of Respiratory & Critical Care Medicine 183(3): 414; author reply 414-415.	Letter
60.	Hernandez-Garduno, E. and G. G. Huitron Bravo (2013). "The predictive value of interferon- release assays and tuberculin skin test: what about those not vaccinated with Bacillus Calmette-Guerin?" Chest 143(5): 1514-1515.	Letter
61.	Higuchi, K., et al. (2012). "Comparison of specificities between two interferon-gamma release assays in Japan." International Journal of Tuberculosis & Lung Disease 16(9): 1190-1192.	IGRA vs. IGRA only (no TST)
62.	Hill, P. C., et al. (2006). "Surprisingly high specificity of the PPD skin test for M. tuberculosis infection from recent exposure in The Gambia." PLoS ONE [Electronic Resource] 1: e68.	Old pre-2009 study
63.	Hoffmann, M., et al. (2010). "Assessment of an Interferon-gamma release assay for the diagnosis of latent tuberculosis infection in haemodialysis patient." Swiss Medical Weekly 140(19-20): 286-292.	No construct validity
64.	Huang, Y. W., et al. (2010). "Latent tuberculosis infection among close contacts of multidrug-resistant tuberculosis patients in central Taiwan." International Journal of Tuberculosis & Lung Disease 14(11): 1430-1435.	Mixed population and/or no subgroup of interest
65.	Inanc, N., et al. (2009). "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." Journal of Rheumatology 36(12): 2675-2681.	Included/excluded in CG117
66.	Ingram, P. R., et al. (2009). "Latent tuberculosis infection in travelers: is there a role for screening using interferon-gamma release assays?" Journal of Travel Medicine 16(5): 352-356.	Review
67.	Jacobs, S., et al. (2011). "The tuberculin skin test is unreliable in school children BCG-vaccinated in infancy and at low risk of tuberculosis infection." Pediatric Infectious Disease Journal 30(9): 754-758.	No relevant outcomes; only TST+ included
68.	Jeong, Y. J., et al. (2012). "Positive tuberculin skin test or interferon-gamma release assay in patients with radiographic	Mixed population and/or no subgroup of

	lesion suggesting old healed tuberculosis." Journal of Korean Medical Science 27(7): 761-766.	interest
69.	Jo, K. W., et al. (2012). "Poor correlation between tuberculin skin tests and interferon- assays in close contacts of patients with multidrug-resistant tuberculosis." Respirology 17(7): 1125-1130.	Mixed population and/or no subgroup of interest
70.	Katsenos, S., et al. (2011). "Use of interferon-gamma release assay for latent tuberculosis infection screening in older adults exposed to tuberculosis in a nursing home." Journal of the American Geriatrics Society 59(5): 858-862.	Mixed population and/or no subgroup of interest
71.	Kawamura, L. M., et al. (2012). "Interferon- release assays for prediction of tuberculosis." The Lancet Infectious Diseases 12(8): 584.	Letter
72.	Kim, E. Y., et al. (2009). "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 9: 207.	No construct validity
73.	Kim, J. H., et al. (2013a). "Factors influencing discrepancies between the QuantiFERON-TB gold in tube test and the tuberculin skin test in Korean patients with rheumatic diseases." Seminars in Arthritis & Rheumatism 42(4): 424-432.	No construct validity
74.	Klein, M., et al. (2013). "Quantiferon TB Gold and tuberculin skin tests for the detection of latent tuberculosis infection in patients treated with tumour necrosis factor alpha blocking agents." Clinical & Experimental Rheumatology 31(1): 111-117.	No construct validity
75.	Kleinert, S., et al. (2010). "Comparison of two interferon-gamma release assays and tuberculin skin test for detecting latent tuberculosis in patients with immune-mediated inflammatory diseases." Annals of the Rheumatic Diseases 69(4): 782-784. Endnote Record ID: 623 [1]	Letter
76.	Kowada, A. (2010). "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 14(6): 367-373.	Economic study
77.	Kowada, A. (2012). "Cost effectiveness of interferon-gamma release assay for school-based tuberculosis screening." Mol Diagn Ther 16(3): 181-190.	Economic study
78.	Kowada, A. (2013). "Cost effectiveness of the interferon- release assay for tuberculosis screening of hemodialysis patients." Nephrology Dialysis Transplantation 28(3): 682-688.	Economic study
79.	Kwakernaak, A. J., et al. (2011). "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." Clinical Rheumatology 30(4): 505-510.	No construct validity
80.	Lange, B., et al. (2010). "Indeterminate results of a tuberculosis-specific interferon-gamma release assay in immunocompromised patients." European Respiratory Journal 35(5): 1179-1182.	Letter
81.	Laskin, B. L., et al. (2013). "Cost-effectiveness of latent tuberculosis screening before steroid therapy for idiopathic nephrotic syndrome in children." American Journal of Kidney Diseases 61(1): 22-32.	Economic study
82.	Latorre, I., et al. (2010). "IFN- response on T-cell based assays in HIV-infected patients for detection of tuberculosis infection." BMC Infect Dis 10: 348.	No construct validity

83.	Lee, S. S., et al. (2010). "High prevalence of latent tuberculosis infection in dialysis patients using the interferon-gamma release assay and tuberculin skin test." Clinical Journal of The American Society of Nephrology: CJASN 5(8): 1451-1457.	No construct validity
84.	Legesse, M., et al. (2011). "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 11: 89.	Mixed population and/or no subgroup of interest
85.	Legesse, M., et al. (2012). "Association of the level of IFN-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." International Immunology 24(2): 71-78.	Mixed population and/or no subgroup of interest
86.	Leung, C. C. (2012). "Tests for prediction of active tuberculosis." The Lancet Infectious Diseases 12(1): 6-8.	Editorial
87.	Lienhardt, C., et al. (2010). "Evaluation of the prognostic value of IFN-gamma release assay and tuberculin skin test in household contacts of infectious tuberculosis cases in Senegal.[Erratum appears in PLoS One. 2010;5(12) doi: 10.1371/annotation/6aa24f81-7f3a-4163-b8bc-731c6112fcf7 Note: Diadhiou, Roger [corrected to Diadhiou, Raymond]]." PLoS ONE [Electronic Resource] 5(5): e10508.	Mixed population and/or no subgroup of interest
88.	Lighter-Fisher, J. and A. M. Surette (2012). "Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy.[Erratum appears in Obstet Gynecol. 2012 Aug;120(2 Pt 1):399]." Obstetrics & Gynecology 119(6): 1088-1095.	Mixed population and/or no subgroup of interest
89.	Linas, B. P., et al. (2011). "Priorities for screening and treatment of latent tuberculosis infection in the United States." American Journal of Respiratory & Critical Care Medicine 184(5): 590-601.	Economic study
90.	Losi, M., et al. (2011). "Tuberculosis infection in foreign-born children: a screening survey based on skin and blood testing." International Journal of Tuberculosis & Lung Disease 15(9): 1182-1184, i.	No construct validity
91.	Maden, E., et al. (2011). "Evaluation of performance of quantiferon assay and tuberculin skin test in end stage renal disease patients receiving hemodialysis." New Microbiologica 34(4): 351-356.	No construct validity
92.	Maeda, T., et al. (2010). "Usefulness and limitations of QuantiFERON-TB Gold in Japanese rheumatoid arthritis patients: proposal to decrease the lower cutoff level for assessing latent tuberculosis infection." Modern Rheumatology 20(1): 18-23.	Inappropriate proxy for LTBI; definition includes prior active TB
93.	Maeda, T., et al. (2011). "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." Journal of Infection & Chemotherapy 17(6): 842-848.	No construct validity
94.	Mahan, C. S., et al. (2011). "Concordance of a positive tuberculin skin test and an interferon gamma release assay in bacille Calmette-Guerin vaccinated persons." International Journal of Tuberculosis & Lung Disease 15(2): 174-178, i.	Mixed population and/or no subgroup of interest
95.	Mancuso, J. D., et al. (2011). "Cost-effectiveness analysis of	Economic study

	targeted and sequential screening strategies for latent tuberculosis." International Journal of Tuberculosis & Lung Disease 15(9): 1223-1230, i.	
96.	Mandalakas, A. M., et al. (2011). "Can we accurately diagnose tuberculosis infection in children?" Pediatric Infectious Disease Journal 30(9): 817-818.	Letter
97.	Mandalakas, A. M., et al. (2013a). "Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting." Thorax 68(3): 247-255.	Economic study
98.	Mandalakas, A. M. and D. Menzies (2011). "Is screening immigrants for latent tuberculosis cost-effective?" The Lancet Infectious Diseases 11(6): 418-419.	Editorial
99.	Mandalakas, A. M., et al. (2013b). "Detecting tuberculosis infection in HIV-infected children: a study of diagnostic accuracy, confounding and interaction." Pediatric Infectious Disease Journal 32(3): e111-118.	No construct validity; two samples on exposure (HIV+ and HIV-) were lumped
100.	Mariette, X., et al. (2012). "Influence of replacing tuberculin skin test with ex vivo interferon release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy." Annals of the Rheumatic Diseases 71(11): 1783-1790.	No construct validity
101.	Marques, C. D., et al. (2009). "Evaluation of an interferon gamma assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis." Rheumatology International 30(1): 57-62.	Inappropriate proxy for LTBI
102.	Martin, J., et al. (2010). "Comparison of interferon {gamma} release assays and conventional screening tests before tumour necrosis factor {alpha} blockade in patients with inflammatory arthritis." Annals of the Rheumatic Diseases 69(1): 181-185	IGRA vs. IGRA only (no TST)
103.	Martyn-Simmons, C. L., et al. (2013). "Evaluating the use of the interferon- response to Mycobacterium tuberculosis-specific antigens in patients with psoriasis prior to antitumour necrosis factor-alpha therapy: a prospective head-to-head cross-sectional study." British Journal of Dermatology 168(5): 1012-1018	No construct validity
104.	Mendez-Echevarria, A., et al. (2012). "Interferon- release assay for the diagnosis of tuberculosis in children." Archives of Disease in Childhood 97(6): 514-516.	No construct validity; only for IGRA
105.	Milman, N., et al. (2011). "Quantiferon test for tuberculosis screening in sarcoidosis patients." Scandinavian Journal of Infectious Diseases 43(9): 728-735.	IGRA only (no TST)
106.	Minguez, S., et al. (2012). "Interferon-gamma release assays in the detection of latent tuberculosis infection in patients with inflammatory arthritis scheduled for anti-tumour necrosis factor treatment." Clinical Rheumatology 31(5): 785-794.	No construct validity
107.	Molicotti, P., et al. (2012). "Performance of QuantiFERON TB in a student population at low risk of tuberculosis." Journal of Infection in Developing Countries 6(1): 100-101.	Letter
108.	Moran Mendoza, O. (2011). "Interferon- release assays for the diagnosis of latent Mycobacterium tuberculosis infection." European Respiratory Journal 38(5): 1237-1238; author's reply 1238-1239.	Letter
109.	Moyo, S., et al. (2011). "Tuberculin skin test and QuantiFERON assay in young children investigated for tuberculosis in South Africa." International Journal of Tuberculosis & Lung Disease	Active TB

	15(9): 1176-1181, i.	
110.	Mrozek, N., et al. (2011). "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: Revue du Rhumatisme 78(6): 655-656; author reply 656-657.	Letter
111.	Murakami, S., et al. (2009). "Screening of tuberculosis by interferon-gamma assay before biologic therapy for rheumatoid arthritis." Tuberculosis 89(2): 136-141.	Case-control study of test results
112.	Nellore, A. and C. N. Kotton (2013). "Screening strategies for tuberculosis in children with kidney disease: what is cost-effective?" American Journal of Kidney Diseases 61(1): 3-5.	Letter
113.	Nguyen, M. Q. and J. Green-McKenzie (2012). "What are the differences between the tuberculin skin test and the QuantiFERON-TB Gold test?" Journal of Occupational & Environmental Medicine 54(9): 1177-1178.	Editorial
114.	Nkurunungi, G., et al. (2012). "Determining Mycobacterium tuberculosis infection among BCG-immunised Ugandan children by T-SPOT.TB and tuberculin skin testing." PLoS ONE [Electronic Resource] 7(10): e47340.	No construct validity
115.	Ohnishi, T. (2011). "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." Journal of Infection & Chemotherapy 17(6): 849-850.	Letter
116.	Oni, T., et al. (2012). "Smoking, BCG and employment and the risk of tuberculosis infection in HIV-infected persons in South Africa." PLoS ONE [Electronic Resource] 7(10): e47072.	Non-standard or in-house IGRA
117.	Onur, H., et al. (2012). "Comparison of quantiferon test with tuberculin skin test for the detection of tuberculosis infection in children." Inflammation 35(4): 1518-1524.	Inappropriate proxy for LTBI
118.	Ormerod, L. P. (2013). "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 68(3): 201.	Letter
119.	Pareek, M., et al. (2013). "Community-based evaluation of immigrant tuberculosis screening using interferon release assays and tuberculin skin testing: observational study and economic analysis." Thorax 68(3): 230-239.	Economic study
120.	Pattnaik, S., et al. (2012). "Agreement between skin testing and QuantiFERON-TB Gold In-Tube assay (QFT-TB) in detecting latent tuberculosis infection among household contacts in India." Indian Journal of Tuberculosis 59(4): 214-218.	No construct validity
121.	Petrescu, L., et al. (2010). "Tuberculin skin test, interferon-gamma assay, and T cells subpopulations in hemodialysis patients." Journal of Renal Nutrition 20(5 Suppl): S109-117.	No construct validity
122.	Pooran, A., et al. (2010). "Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis." BMC Pulmonary Medicine 10: 7.	Economic study
123.	Qumseya, B. J., et al. (2011). "QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States." Inflammatory Bowel Diseases 17(1): 77-83.	No construct validity

124.	Ramos, J. M., et al. (2012). "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 12: 169.	Inappropriate proxy for LTBI
125.	Riazi, S., et al. (2012). "Rapid diagnosis of Mycobacterium tuberculosis infection in children using interferon-gamma release assays (IGRAs)." Allergy & Asthma Proceedings 33(3): 217-226.	Active TB
126.	Ringrose, J. S., et al. (2011). "Detecting latent tuberculosis infection during anti-tumor necrosis factor therapy." Clinical & Experimental Rheumatology 29(5): 790-794.	No relevant outcomes
127.	Santin, M., et al. (2011). "Detection of latent tuberculosis by the tuberculin skin test and a whole-blood interferon- release assay, and the development of active tuberculosis in HIV-seropositive persons." Diagnostic Microbiology & Infectious Disease 69(1): 59-65.	Mixed population and/or no subgroup of interest for construct validity
128.	Sattah, M. V., et al. (2012). "Interferon-gamma release assay T-SPOT.TB and HIV-related tuberculosis." International Journal of Tuberculosis & Lung Disease 16(2): 281-282.	Letter
129.	Sayarlioglu, H., et al. (2011). "QuantiFERON-TB Gold test for screening latent tuberculosis infection in hemodialysis patients." Tuberkuloz ve Toraks 59(2): 105-110.	No construct validity
130.	Schneider, W. J., et al. (2011). "QuantiFERON-TB testing for latent tuberculosis infection in low-prevalence countries: making the most of an imperfect process." Infection Control & Hospital Epidemiology 32(10): 1055.	Letter
131.	Serrano-Escobedo, C. J., et al. (2013). "Performance of tuberculin skin test compared to QFT-IT to detect latent TB among high-risk contacts in Mexico." Archives of Medical Research 44(3): 242-248.	Mixed population and/or no subgroup of interest
132.	Seshadri, C., et al. (2008). "Low sensitivity of T-cell based detection of tuberculosis among HIV co-infected Tanzanian in-patients." East African Medical Journal 85(9): 442-449.	Old pre-2009 study
133.	Setiawati, L., et al. (2011). "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 Journal of Tropical Medicine & Public Health 42(6): 1460-1468.	No construct validity
134.	Shah, M., et al. (2012). "Programmatic impact of QuantiFERON-TB Gold In-Tube implementation on latent tuberculosis diagnosis and treatment in a public health clinic." PLoS ONE [Electronic Resource] 7(5): e36551.	Mixed population and/or no subgroup of interest
135.	Shanaube, K., et al. (2011). "Risk factors associated with positive QuantiFERON-TB Gold In-Tube and tuberculin skin tests results in Zambia and South Africa." PLoS ONE [Electronic Resource] 6(4): e18206.	Mixed population and/or no subgroup of interest
136.	Shovman, O., et al. (2009). "QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study." International Journal of Tuberculosis & Lung Disease 13(11): 1427-1432.	Included/excluded in CG117
137.	Simsek, H., et al. (2010). "Comparison of tuberculin skin testing and T-SPOT.TB for diagnosis of latent and active tuberculosis." Japanese Journal of Infectious Diseases 63(2): 99-102.	Mixed population and/or no subgroup of interest

138.	Singanayagam, A., et al. (2013). "Evaluation of screening methods for identification of patients with chronic rheumatological disease requiring tuberculosis chemoprophylaxis prior to commencement of TNF-alpha antagonist therapy." Thorax 68(10): 955-961.	Inappropriate proxy for LTBI
139.	Song, Q., et al. (2012a). "Evaluation of a new interferon-gamma release assay and comparison to tuberculin skin test during a tuberculosis outbreak." International Journal of Infectious Diseases 16(7): e522-526.	Non-standard or in-house IGRA
140.	Song, S., et al. (2012b). "Performance of confirmatory interferon- release assays in school TB outbreaks." Chest 141(4): 983-988.	QFT used as confirmatory test on subgroup of TST + patients
141.	Soysal, A., et al. (2012). "Diagnosing latent tuberculosis infection in haemodialysis patients: T-cell based assay (T-SPOT.TB) or tuberculin skin test?" Nephrology Dialysis Transplantation 27(4): 1645-1650.	No construct validity
142.	Starke, J. R. (2012). "Interferon- release assays for the diagnosis of tuberculosis infection in children." Journal of Pediatrics 161(4): 581-582.	Letter
143.	Stefan, D. C., et al. (2010). "Interferon-gamma release assays for the detection of Mycobacterium tuberculosis infection in children with cancer." International Journal of Tuberculosis & Lung Disease 14(6): 689-694.	No construct validity
144.	Steffen, R. E., et al. (2013). "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 [Electronic Resource] 8(4): e59546.	Economic study
145.	Sultan, B., et al. (2013). "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." International Journal of STD & AIDS 24(10): 775-779.	IGRA vs. IGRA only (no TST)
146.	Talati, N. J., et al. (2011). "Diagnosis of latent tuberculosis infection among HIV discordant partners using interferon gamma release assays." BMC Infect Dis 11: 264.	No construct validity
147.	Tannus Silva, D. G., et al. (2012). "Latent tuberculosis in rheumatoid arthritis: evaluating cellular response and high-resolution computed tomography." Archivos de Bronconeumologia 48(5): 144-149.	No construct validity
148.	Tebruegge, M., et al. (2013). "Interferon- release assays for the diagnosis of tuberculosis in children." Archives of Disease in Childhood 98(3): 239-240.	Letter
149.	Theodoropoulos, N., et al. (2012). "Use of the QuantiFERON-TB Gold interferon-gamma release assay for screening transplant candidates: a single-center retrospective study." Transplant Infectious Disease 14(1): 1-8.	IGRA only (historical TST)
150.	Thomas, B., et al. (2011). "Concordance between tuberculin skin test and interferon- assay and interferon- response to mitogen in pediatric tuberculosis contacts." Pediatric Pulmonology 46(12): 1225-1232.	No construct validity
151.	Thomas, T. A., et al. (2010). "Malnutrition and helminth infection affect performance of an interferon gamma-release assay." Pediatrics 126(6): e1522-1529.	No construct validity

152.	Uluk, T., et al. (2013). "Evaluation of an interferon-gamma release assay in children with suspected tuberculosis in Papua New Guinea." Pediatric Infectious Disease Journal 32(2): 187-189.	No construct validity
153.	Wassie, L., et al. (2013). "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 13: 265.	No construct validity
154.	Weinfurter, P., et al. (2011). "Predictors of discordant tuberculin skin test and QuantiFERON-TB Gold In-Tube results in various high-risk groups." International Journal of Tuberculosis & Lung Disease 15(8): 1056-1061.	No construct validity
155.	Wolf, T., et al. (2013). "Tuberculosis skin test, but not interferon--releasing assays is affected by BCG vaccination in HIV patients." Journal of Infection 66(4): 376-380.	No construct validity
156.	Xie, X., et al. (2011). "A T-cell-based enzyme-linked immunospot assay for tuberculosis screening in Chinese patients with rheumatic diseases receiving infliximab therapy." Clinical & Experimental Medicine 11(3): 155-161.	No construct validity
157.	Yilmaz, N., et al. (2012). "Comparison of QuantiFERON-TB Gold test and tuberculin skin test for the identification of latent Mycobacterium tuberculosis infection in lupus patients." Lupus 21(5): 491-495.	No construct validity
158.	Zhao, J., et al. (2011). "Low agreement between the T-SPOT.TB assay and the tuberculin skin test among college students in China." International Journal of Tuberculosis & Lung Disease 15(1): 134-136.	No construct validity
159.	Pareek, M., et al. (2011). "Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis." Lancet Infect Dis 11(6): 435-444.	Economic study
160.	Shah, M., et al. (2012). "QuantiFERON-TB gold in-tube implementation for latent tuberculosis diagnosis in a public health clinic: a cost-effectiveness analysis." BMC Infect Dis 12: 360.	Economic study

Pre-MEDLINE and other databases search results table

N	Study	Reason for exclusion
161.	(2011). "Erratum: Interferon-gamma release assays for diagnosis of latent tuberculosis infection: Evidence in immune-mediated inflammatory disorders (Current Opinion in Rheumatology)." Current Opinion in Rheumatology 23(5): 504.	Letter
162.	(2012). "Society for Adolescent Health and Medicine Annual Meeting: Impact of Trauma on Teens: Building the Safety Net 2012." Journal of Adolescent Health 1).	Irrelevant
163.	(2013). "40th Annual Conference Abstracts, APIC 2013." American Journal of Infection Control 1).Endnote Record ID: 2071 [1,3]	Abstract
164.	(2013). "World Tuberculosis Day Symposium 2012." Tuberculosis 93 (1).	Abstract
165.	Abdel-Nabi, E. A., et al. (2014). "QuantiFERON vs. tuberculin testing in detection of latent tuberculous infection among chronic renal failure patients." Egyptian Journal of Chest Diseases and Tuberculosis 63(1): 161-165.	No construct validity

166.	Abdel-Samea, S. A., et al. (2013). "Comparative study between using QuantiFERON and tuberculin skin test in diagnosis of Mycobacterium tuberculosis infection." Egyptian Journal of Chest Diseases and Tuberculosis 62(1): 137-143	Mixed population and/or no subgroup of interest
167.	Abraham, B. and Jacob, R. (2013). "Monitoring and management of latent tuberculosis in IBD patients on antitnf therapy: A case series." American Journal of Gastroenterology 108: S521-S522.	Abstract
168.	Aggarwal, P. and Aggarwal, D. (2012). "Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy." Obstetrics & Gynecology 120(2 Pt 1): 398; author reply 398.	Letter
169.	Ahmad, M. and Pesola, G. R. (2010). "False-positive QuantiFERON Gold tests." Chest 138 (4).	Abstract
170.	Ahmadinejad, Z., et al. (2010). "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." Clinical Microbiology and Infection 16: S542.	Abstract
171.	Akpaka, P. E., et al. (2010). "Evaluation of cost and methods for detecting latent tuberculosis infection among target individual groups in Trinidad & Tobago." International Journal of Infectious Diseases 14: e148.	Abstract
172.	Alberte-Castineiras, A., et al. (2012). "Discordant QuantiFERON-TB Gold In-Tube and tuberculin skin test results in various high-risk groups." Clinical Microbiology and Infection 18: 548.	Abstract
173.	Andrisani, G., et al. (2010). "Tubercolosis screening in Italian patients affected by inflammatory bowel disease: Comparison of quantiFERON-tb gold versus tuberculin skin test." Digestive and Liver Disease 42: S181-S182.	Abstract
174.	Arias, M., et al. (2011). "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 1): S691.	Abstract
175.	Atanassova, A. and Kotzev, I. (2013). "Screening for tuberculosis in patients candidates for anti-TNF terapy in IBD." Journal of Gastroenterology and Hepatology 28: 141.	Abstract
176.	Awan, S., et al. (2012). "Can Quanti-FERON-TB replace TST (mantoux) as a screening tool prior to (biologics) anti-TNF therapy." Irish Journal of Medical Science 181: S75.	Abstract
177.	Bakir, M., et al. (2009). "Use of T cell-based diagnosis of tuberculosis infection to optimize interpretation of tuberculin skin testing for child tuberculosis contacts." Clinical Infectious Diseases 48(3): 302-312.	Inappropriate proxy for LTBI
178.	Behar, S. M., et al. (2009). "Use of the T-SPOT.TB assay to detect latent tuberculosis infection among rheumatic disease patients on immunosuppressive therapy." Journal of Rheumatology 36(3): 546-551.	Inclusion of TST + patients
179.	Belard, E., et al. (2010). "Effects of corticosteroid treatment on the performance of quantiFERON gold in-tube test in the screening of latent tuberculosis infection." Gastroenterology 1): S523.	Abstract

180.	Bergamini, B. M., et al. (2009). "Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents."	IGRA vs. IGRA only (no TST)
181.	Berry, M. P. R., et al. (2009). "Systems biology approaches characterise the host response to tuberculosis." Thorax 64: A10.	Abstract
182.	Bianchi, L., et al. (2009). "Interferon-gamma release assay improves the diagnosis of tuberculosis in children." Pediatric Infectious Disease Journal 28(6): 510-514.	No construct validity
183.	Blandinieres, A., et al. (2013). "QuantiFERON to diagnose infection by Mycobacterium tuberculosis: performance in infants and older children." Journal of Infection 67(5): 391-398.	No construct validity
184.	Blandinieres, A., et al. (2012). "Deficient IFN-gamma response to Mycobacterium tuberculosis antigens in infants improved since 1 year of age." Immunology 137: 727-728.	Abstract
185.	Borkowska, D., et al. (2011). "Interferon-gamma assays T-SPOT.TB for the diagnosis of latent tuberculosis infection	Mixed population and/or no subgroup of interest
186.	Borra, H., et al. (2009). "Reliability of tuberculosis screening tests in patients receiving tumor necrosis factor antagonist therapy in a united states rheumatology clinic." Arthritis and Rheumatism 60: 137.	Abstract
187.	Bortlik, M., et al. (2009). "Usefulness of the quantiFERON TB gold test in assessing the necessity for TB prophylaxis in IBD patients treated with biologicals." Gastroenterology 1): A197.	Abstract
188.	Bottger, E. C. (2012). "Interferon-gamma Release Assays and the Risk of Developing Active Tuberculosis." American Journal of Respiratory and Critical Care Medicine 185(7): 786-787.	Abstract
189.	Brebner, J., et al. (2010). "Questionable utility of T-SPOT testing in a TB exposure incident on a clinical haematology unit." Thorax 65: A103.	Abstract
190.	Bruzzese, E., et al. (2009). "Gamma interferon release assays for diagnosis of tuberculosis infection in immune-compromised children in a country in which the prevalence of tuberculosis is low." Journal of Clinical Microbiology 47(7): 2355-2357.	Letter
191.	Bua, A., et al. (2012). "Epidemic of tuberculosis in a high school in Northern Sardinia." International Journal of Mycobacteriology 1(3): 161-163.	No relevant outcomes
192.	Bumbacea, D., et al. (2011). "New immunodiagnostic tests for latent and active tuberculosis." Revista Romana De Medicina De Laborator 19(3): 267-278.	Abstract
193.	Buonsenso, D., et al. (2012). "Evaluation of a mathematical model proposed to predict the diagnosis of tuberculosis in children with cervical lymph node enlargement." International Journal of Pediatric Otorhinolaryngology 76(7): 1068-1070.	Letter
194.	Buonsenso, D., et al. (2012). "Pediatric tuberculosis in two tertiary hospitals in Rome: A 20-year retrospective study." Archives of Disease in Childhood 97: A11-A12.	Abstract
195.	Burgos, J. L., et al. (2009). "Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico." International Journal of Tuberculosis and Lung Disease 13(8): 962-968.	Economic study
196.	Cagan Appak, Y., et al. (2013). "Comparison of tuberculin skin testing and in vitro interferon-gamma release assay test for diagnosis of latent tuberculosis in children Journal of Medical	Foreign language (Turkish)

	Sciences 33(6): 1402-1407.	
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366.	Stavri, H. R., et al. (2010). "Prospective Comparison of Two Brands of Tuberculin Skin Tests and Quantiferon-TB Gold in-tube Assay Performances for Tuberculosis Infection in Hospitalized Children." Medica 5(4): 271-276.	Active TB
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369.	Tavast, E., et al. (2009). "IGRA tests perform similarly to TST but cause no adverse reactions: pediatric experience in Finland." BMC Research Notes 2: 9.	Active TB
370.	Tavast, E., et al. (2012). "Immunosuppression Adversely Affects TST but Not IGRAs in Patients with Psoriasis or Inflammatory Musculoskeletal Diseases." International journal of rheumatology 2012: 381929.	Non-standard or in-house IGRA
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372.	Van Zyl-Smit, R. N., et al. (2011). "Immunodiagnosis of latent TB in HIV-infected persons in a high burden setting." American Journal of Respiratory and Critical Care Medicine 183 (1 MeetingAbstracts).	Abstract
373.	Vassilopoulos, D., et al. (2009). "Comparison of two interferon-gamma release assays to tuberculin skin testing for latent tuberculosis screening in rheumatic patients starting anti-TNF treatment." Arthritis and Rheumatism 60: 1907.	Abstract
374.	Velizarova, S. A., et al. (2009). "To what extent T-SPOT.TB could be used in the diagnosis of tuberculosis in children exposed to tb infection?" European Journal of Immunology 39: S217.	Abstract
375.	Vortia, E., et al. (2013). "Use of the quantiferon-TB gold in-tube test for latent tuberculosis screening in children with inflammatory bowel disease treated with infliximab." Gastroenterology 1): S887.	Abstract
376.	Wang, H., et al. (2013). "Clinical value of a whole blood interferon- release assay for the diagnosis of Mycobacterium tuberculosis infection during antitubercular treatment." Experimental and Therapeutic Medicine 6(2): 455-458.	Active TB
377.	Wiwanitkit, V. (2010). "QuantiFERON-TB gold test versus tuberculin skin test." Annals of Thoracic Medicine 5(2): 119.	Abstract

378.	Wollman, J., et al. (2013). "The effect of the severity of psoriasis on screening for latent tuberculosis: A comparison study between psoriasis and rheumatoid arthritis patients." Annals of the Rheumatic Disease 71.	Abstract
379.	Wong, S. H., et al. (2013). "Tuberculosis screening with interferon-gamma release assay in inflammatory bowel disease in a tuberculosis-endemic population." Gastroenterology 1): S418.	Abstract
380.	Yilmaz, N., et al. (2009). "Comparison of quantiferon-tb gold test and tuberculin skin test for identification of latent mycobacterium tuberculosis infection in lupus patients." Arthritis and Rheumatism 60: 286.	Abstract
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Number	Reference	Exclude
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385.	Al-Taweel, T., M. Pai, M. Strohl, T. Bessissow, A. Bitton, E. G. Seidman and W. Afif (2014). "A pilot study of optimal screening for latent tuberculosis in patients with inflammatory bowel disease." Gastroenterology 1): S-582.	Abstract
386.	Arenas Miras, M. D. M., C. Hidalgo-Tenorio, P. Jimenez-Gamiz and J. Jimenez-Alonso (2014). "Diagnosis of latent tuberculosis in patients with systemic lupus erythematosus: T.SPOT.TB versus tuberculin skin test." BioMed Research International 2014(291031).	No construct validity Immunocompromised: concordance information
387.	Arstikyte, I., I. Butrimiene, R. Zablockis and A. Venalis (2014). "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." Scandinavian Journal of Rheumatology 43: 44-45.	Abstract
388.	Belknap, R. and C. L. Daley (2014). "Interferon-gamma release assays." Clinics in Laboratory Medicine 34(2): 337-349.	Review
389.	Bennett, A., J. Ashby, M. Curtiss, N. Pal, T. Wambaa and S. Menzies (2014). "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 69: A209.	Abstract
390.	Calzada-Hernandez, J., A. Noguera Julian, S. Ricart Campos, R. Bou Torrent, E. Iglesias Jimenez, M. I. Gonzalez Fernandez, J.	Abstract

Number	Reference	Exclude
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391.	Chuke, S. O., N. T. Yen, K. F. Laserson, N. H. Phuoc, N. A. Trinh, D. T. Nhung, V. T. Mai, A. D. Qui, H. H. Hai, T. H. Loan le, W. G. Jones, W. C. Whitworth, J. J. Shah, J. A. Painter, G. H. Mazurek and S. A. Maloney (2014). "Tuberculin Skin Tests versus Interferon-Gamma Release Assays in Tuberculosis Screening among Immigrant Visa Applicants." Tuberculosis Research & Treatment Print 2014: 217969.	No construct validity Recently arrived: concordance information
392.	Cruz, A. T. and J. R. Starke (2014). "Relationship Between Tuberculin Skin Test (TST) Size and Interferon Gamma Release Assay (IGRA) Result: When Should Clinicians Obtain IGRAs in Children With Positive TSTs?" Clinical Pediatrics 53(12): 1196-1199.	- No valid construct validity for LTBI (prior TB is not a construct of LTBI) - Study aim was compare the tests in predicting chest X ray result suggesting the presence of MTB
393.	Duman, N., S. Ersoy-Evans, O. Karadag, S. Ascioglu, B. Sener, S. Kiraz and S. Sahin (2014). "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." International Journal of Dermatology 53(10): 1286-1292.	Exclude- no construct validity
394.	Elfrink, F., A. van den Hoek, M. E. Mensen and G. J. B. Sonder (2014). "Screening travellers to high-endemic countries for infection with Mycobacterium tuberculosis using interferon gamma release assay; a prospective study." BMC Infect Dis 14(1).	Repeat testing
395.	Elmahdy, M. M. G. F., S. Helal, M. Yonan and R. Saher (2014). "Tuberculin skin test and Quantiferon test for detection of latent Mycobacterium tuberculosis." International Journal of Infectious Diseases 21: 349.	Abstract
396.	Golovics, P. A., A. Szabo, M. Mandel, A. Gyurcsanyi, K. Kristof, Z. Vegh, A. Mohas, B. Szilagyi, Z. Kurti, B. Csako, L. Kiss, B. Lovasz, K. Gecse and P. Lakatos (2014). "Is the tuberculin skin test alone accurate in moderate-to-severe BCG vaccinated patients with inflammatory bowel disease to test for latent tuberculosis?" Journal of Crohn's and Colitis 8: S144.	Abstract
397.	Islam, S., J. Grinsdale, L. Bristow and J. Higashi (2014). "Tuberculin Skin Test and Quantiferon Performance, and Testing of Populations at Low Risk for Tuberculosis Infection." Clinical Infectious Diseases 59(8).	Letter to the editor
398.	Jenum, S., D. A. Hokey, T. M. Doherty, H. M. S. Grewal, B. Lindtjorn, A. C. Hesseling, A. Jacob, F. L. Jahnsen, J. Kenneth, A. V. Kurpad, R. Macaden, J. Nelson, S. Sumithra, M. Vaz and V. Cardenas (2014). "The frequencies of IFN+IL2+TNFalpha+ 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 [Electronic Resource] 9(7).	Comparing antigens

Number	Reference	Exclude
399.	Julian, A. N., J. A. Lopez, J. Calzada-Hernandez, E. N. Cuadros, M. J. M. Pena and F. J. M. Carpi (2014). "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." Pediatric Rheumatology 12.	Abstract
400.	Marquez, C., G. Chamie, J. Achan, A. F. Luetkemeyer, M. Kyohere, G. Dorsey, M. R. Kamya, E. D. Charlebois and D. V. Havlir (2014). "Tuberculosis Infection in Early Childhood in Uganda and the Influence of HIV Exposure." Topics in Antiviral Medicine 22 (e-1): 47-48.	Abstract
401.	Mathad, J. S., R. Bhosale, S. Kanade, P. Deshpande, V. Kulkarni, N. Nevrekar, V. Mave, N. Suryavanshi, N. Gupte and A. Gupta (2014). "Effect of HIV On Latent TB Screening of Pregnant Women in Pune, India." Topics in Antiviral Medicine 22 (e-1): 425-426.	Abstract
402.	McMullen, S. E., D. A. Pegues, F. S. Shofer, A. C. Sheller and E. B. Wiener (2014). "Performance of quanti FERON-TB gold and tuberculin skin test relative to subjects' risk of exposure to tuberculosis." Clinical Infectious Diseases 58(9): 1260-1266.	Population greater than 18 years
403.	Mendy, A., A. N. Albatineh, E. R. Vieira and J. Gasana (2014). "Higher Specificity of Tuberculin Skin Test Compared With Quantiferon-TB Gold for Detection of Exposure to Mycobacterium tuberculosis." Clinical Infectious Diseases 59(8).	Letter to editor
404.	Nassiri, A. A. and P. Tabarsi (2014). "Re: Interferon-gamma release assay agreement with tuberculin skin test in pretransplant screening for latent tuberculosis in a high-prevalence country." Iranian Journal of Kidney Diseases 8(5): 432-433.	Letter
405.	O'Flynn, E., M. Haroon, M. O. Neill and O. FitzGerald (2014). "Performance and benefits of replacing Mantoux test with Quantiferon in screening for latent TB in patients prior to anti TNF therapy." Irish Journal of Medical Science 183: S105-S105.	Abstract
406.	O'Flynn, E., M. Haroon, M. O'Neill, A. Ahmad and O. FitzGerald (2014). "Performance and benefits of replacing mantoux test with quantiferon in screening for latent TB in patients prior to anti-TNF therapy." Annals of the Rheumatic Diseases 73.	Abstract
407.	Opris, D., D. Mazilu, I. Saulescu and R. Ionescu (2014). "Is tuberculosis screening sufficient for preventing TB reactivation in biologic treated patients?" Annals of the Rheumatic Diseases 73.	Abstract
408.	O'Shea, M. K., T. E. Fletcher, N. J. Beeching, M. Dedicoat, D. Spence, H. McShane, A. F. Cunningham and D. Wilson (2014). "Tuberculin skin testing and treatment modulates interferon-gamma release assay results for latent tuberculosis in migrants." PLoS ONE [Electronic Resource] 9(5).	Military recruits
409.	Panchal, R. K., I. Browne, P. Monk, G. Woltmann and P. Haldar (2014). "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 69(4): 354-362.	No comparison between IGRA and TST
410.	Pease, E., A. Ainley, M. Curtiss, T. Wambaa, J. Ashby, S.	Poster

Number	Reference	Exclude
	Dawson and S. Menzies (2013). "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." International Journal of STD and AIDS 24: 56.	
411.	Prignano, F., A. Bartoloni, F. Bartalesi, A. Gori, F. Ricceri, A. Cavallo, L. Attala and A. Mantella (2014). "Latent tuberculosis infection in psoriasis and other dermatological immunomediated diseases: A combined approach by Quantiferon-TB Gold and tuberculin skin tests." International Journal of Dermatology 53(8): e372-e374.	Letter
412.	Rose, W., I. Kitai, F. Kakkar, S. E. Read, M. A. Behr and A. Bitnun (2014). "Quantiferon Gold-in-tube assay for TB screening in HIV infected children: Influence of quantitative values." BMC Infect Dis 14(1).	Repeat testing, proportion of people had self- read TST results
413.	Sanchez Riera, L., N. Wilson, M. Al Izzi, I. Hussein, S. Nuhaily, N. Qahtani, N. Ibrahim, R. Aneja, T. Khan, S. Gonuguntla, H. Maashari, S. Waheeduddin and M. Al Maini (2014). "Quantiferon-tb more useful than tuberculin skin test for latent tuberculosis screening: A hospital experience." Annals of the Rheumatic Diseases 73.	Abstract
414.	Santoro-Lopes, G. (2014). "Screening for latent tuberculosis infection in low-incidence areas." American Journal of Transplantation 14(7): 1709.	Letter to the editor
415.	Savaj, S., J. Savoj, M. Ranjbar and F. Sabzghabaei (2014). "Interferon-gamma release assay agreement with tuberculin skin test in pretransplant screening for latent tuberculosis in a high-prevalence country." Iranian Journal of Kidney Diseases 8(4): 329-332.	No construct validity
416.	Scholman, T., M. Straub, U. Sester, D. Wagner and M. Sester (2010). "Analysis of agreement between IGRAs and tuberculin skin-testing by the use of PPD as the same antigen." Transplantation 90: 540.	Abstract
417.	Senturk, T., G. Sargin, M. Telli, S. Cildag, I. Akdam and E. Ceylan (2014). "Comparison of diagnostic test for latent Tuberculosis infection." International Journal of Rheumatic Diseases 17: 103.	Abstract
418.	Shokrollahi, M. R., S. Noorbaksh, L. Nasehi and Z. Movahedi (2014). "Diagnosis of latent tuberculosis in individuals with recent exposure: tuberculin skin test versus interferon-gamma release assay." British Journal of Biomedical Science 71(3): 125-126.	Not population of interest
419.	Soare, A., C. Mihai, A. M. Gherghe, R. Dobrota, S. Pintilie, M. Milicescu, I. Ancuta, A. Martin, L. Macovei, C. Ciofu, M. Sasu, V. Stoica and M. Bojinca (2014). "Preventing active tuberculosis in rheumatoid arthritis patients receiving TNF inhibitors: TB screening at baseline is not enough." Annals of the Rheumatic Diseases 73.	Abstract
420.	Sztajnbok, F., N. L. Boechat, S. K. Oliveira, S. B. Ribeiro, M. C. Rodrigues, C. Diniz, F. C. D. N. Sztajnbok and C. C. Sant'Anna (2013). "PReS-FINAL-2054: Latent tuberculosis infection in patients with juvenile idiopathic arthritis undergoing methotrexate therapy: A longitudinal study with TST and ELISPOT." Pediatric Rheumatology 11.	Repeat testing at 3 and 12 months

Number	Reference	Exclude
421.	Sztajnbok, F., N. L. F. Boechat, S. B. Ribeiro, S. K. F. Oliveira, D. C. N. Sztajnbok and C. C. Sant'Anna (2014). "Tuberculin skin test and ELISPOT/T. SPOT.TB in children and adolescents with juvenile idiopathic arthritis." Pediatric Rheumatology 12(1).	Repeat testing at 3 and 12 months
422.	Verhagen, L. M., M. Maes, J. A. Villalba, A. d'Alessandro, L. P. Rodriguez, M. F. Espana, P. W. M. Hermans and J. H. de Waard (2014). "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 14(1).	Repeat testing
423.	Zelinkova, Z., M. Zakuciova, L. Gombosova, E. Veseliny, M. Horakova, P. Lietava, K. Palencikova, B. Kadleckova, M. Gregus, K. Gregusova, I. Pav, T. Hlavaty, T. Koller, J. Toth, M. Hlista, I. Bunganic, J. Zan, I. Mincik and M. Huorka (2014). "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." Journal of Crohn's and Colitis 8: S212.	Abstract
424.	Zelinkova, Z., M. Zakuciova, L. Gombosova, E. Veseliny, M. Horakova, P. Lietava, K. Palencikova, B. Kadleckova, M. Gregus, K. Gregusova, I. Pav, T. Hlavaty, T. Koller, J. Toth, M. Hlista, B. Ivan, J. Zan and M. Huorka (2014). "Screening for latent tuberculosis is effective but does not fully protect against tuberculosis reactivation during antitnf treatment in areas with high background incidence of tuberculosis." Gastroenterology 1): S-585.	Abstract

11.6 Appendix 6. Included studies for clinical effectiveness 2011

Table 53. Studies included for the clinical effectiveness review 2011

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, I., Weldingh, K., Lillebaek, T., Follmann, F., & Andersen, P. 2004[154]	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** was comprised of 40 students from 2 other classes at the school with no connection to the index case	IGRA(QFTG)	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 in to TST in detecting LTBI in young non BCG vaccinated individuals.
Chun, J.K., Kim, C.K., Kim, H.S., Jung, G.Y., Lee, T.J., Kim, K.H., & Kim, D.S. 2008 [155]	Observational conducted in South Korea	Age 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	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Close contacts: Kappa 0.19 for 5mm and 0.529 for 10mm. (B) Kappa 0.378 for 10mm. A significantly higher rate of positive QFTG results was evident for the close contact group. 8/42, 19% as compared with	Not determined	Not reported	Authors found that in children with no exposure to TB, the QFTG was positive in only one of the 65 children, although all of them were positive by the TST at 5mm and 64.6% at 10mm. They also found that there was a significant relationship between higher responses to

			healthy children with no contact history. **4**. **Children with symptoms suggestive of tuberculosis** as a potential cause			the control group 3 subjects 1/65, 1.5% p<0.05. Majority of indeterminate QFTG results were from group 4 who were suffering from medical conditions that could be associated with impaired immune function at the time of testing			mitogen-positive control and increasing age of the children
Connell, T.G., Curtis, N., Ranganathan, S.C., & Buttery, J.P. 2006[156]	Observational study. Australia. Some children born in high prevalence countries 52%	Children less than 18years 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(QFTG) 0.35IU/ml positive response	TST PPD 10 IU of tuberculin. Positive if 15mm in individuals with evidence of prior BCG, > 5mm in TB contacts regardless of BCG and > 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. Victoria Australia	Recommended further studies to clarify predictive values.
Connell, T.G., Ritz, N., Paxton, G.A., Buttery, J.P., Curtis, N., & Ranganathan, S.C. 2008[157]	Observational study. Australia/ Australia and some born in high prevalence countries. 52% BCG vaccinated	96 children from 6months 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	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(QFTG), T-SPOT.TB	TST PPD 10 IU of tuberculin. Positive >10mm in	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	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

		a country of high prevalence of TB.				household contacts, 1 non-household contact and 38 had no known contacts with active TB.			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
Hansted, E., Andriuskevicien e, A., Sakalauskas, R., Kevalas, R., & Sitkauskiene, B. 2009[158]	Observational study done in Lithuania. All participants were BCG vaccinated	10 to 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 this group were free from symptoms. 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 >10mm	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, K., Harada, N., Mori, T., & Sekiya, Y. 2007[160]	Observational prospective. Japan. Japanese students all BCG vaccinated	349 15-16years. Patients were all male and previously BCG vaccinated. They attended the same	Students stratified into two groups those with close contact (sharing of classes with index case; 210)	QFTG. Considered positive when > 0.35 IU/ml	TST (defined standard test dose of tuberculin PPD equivalent to 2.5 tuberculin units). Erythma	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 QFGT showed no signs of	Ministry of Health Labour and Welfare Japan	Partial verification only patients with positive TST were tested with QFTG. Authors suggest that similar positive rates

		high school as a student diagnosed with active tb	and those with limited contact (not attending classes with the index case; 139)		used instead of induration. An erythma of >30mm considered positive for a BCG vaccinated individual		active tb after 3.5 years of follow up		of TST in both strata of exposed groups suggest limited transmission of MTB.
Higuchi, K., Kondo, S., Wada, M., Hayashi, S., Ootsuka, G., Sakamoto, N., & Harada, N. 2009[160]	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 90hours contact. Casual participants: total of less than 18hours	IGRA (QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 3 TU PPD-S	QFTG positivity in close contacts 9.8% as compared with 1.8% in casual contacts p = 0.02. TST(5mm) positivity in close contacts 52.6% as compared with 67.2% (p = 0.078).TST (10mm) 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 years olds as adults. Suggestion of testing contacts three months after the end of exposure as an appropriate and sensitive approach.
Lighter, J., Rigaud, M., Eduardo, R., Peng, C.H., & Pollack, H. 2009[161]	Observational prospective	253 Children below 18 years (Mean age 9) Age stratified as follows <24 mo, 24-59mo, 60mo. 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	QFTG. Considered positive when > 0.35 IU/ml and >25% than nil control value	TST (Mantoux technique). Considered positive with induration of >10mm	Proportion of QFTG 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 QFTG+. **High** 0% of TST –ve and 100%of TST+ case were QFTG+.	Not determined	Pott's memorial foundation and the Thrasher Research Fund	Cut off of 0.35IU/ml not validated especially for very young children who produce on average less interferon gamma than school aged children and adults

			imprisonment, homelessness, or intravenous drug use). **High**(Known direct contact with tuberculosis index case)						
Okada, K., Mao, T.E., Mori, T., Miura, T., Sugiyama, T., Yoshiyama, T., Mitarai, S., Onozaki, I., Harada, N., Saint, S., Kong, K.S., & Chhour, Y.M. 2008[162]	Observational / Japan	They used 161 index cases and 217 contacts 5 years and below.	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(QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 2.5TU 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 odds ratios for positive results for both TST and QFTG. The following covariates were analysed. Gender, 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 QFTG
Tsiouris, S.J., Austin, J., Toro, P., Coetzee, D., Weyer, K.,	Observational/United States/ South Africa	1741 5-15years. Mean age of	Participants grouped according to the status of contact	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Univariate analysis showed the likelihood of having a positive	Not determined	Aeras Global TB vaccine foundation.	IGRA performed well without indeterminate results. The inability to

Stein, Z., & El-Sadr, W.M. 2006[163]			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 increased with increasing age (p = 0.011) as did having a TST > 10mm. Overall agreement increased with increasing cut off of TST 0.52, 0.56 and 0.62 for 5, 10 and 15mm respectively.			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.
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Ly, I.N., Harstad, I., Dyrhol-Riise, A.M., & Heldal, E. 2008[226]	Cross sectional study/Norway/ Determined by presence of scar	14-15 year olds	Factors associated with latent TB investigated include. Origin, gender, exposure to tuberculosis, travel history. Children grouped into western born, second generation and first generation	IGRA(QFTG) 0.35IU/ml positive	TST PPD RT23 (2 tuberculin units were used)	9% of 511 TST positive children were IGRA positive. They determined adjusted Odds ratios 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 to 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

Immunocompromised

Table 54. Studies with immunocompromised patients included in CG117

<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 & 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>Balcells, M.E., Perez, C.M., Chanqueo, L., Lasso, M., Villanueva, M., Espinoza, M., Villarroel, L., & Garcia, P. 2008[165]</td><td>Observational study of individuals from Chile.HIV Positive patients Mean CD4 Count 393/µl (range 100-977) 116 mean age 38.8years (Range 21-71). Older age, history of previous tb disease, previous known exposure to a case of active pulmonary tb, healthcare workers or individuals working with homeless people, residence in prison,</td><td>TST (Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA(QFT)</td><td>Correlation between TST and IGRA results in HIV positive individuals
<table><tr><td></td><td>IGRA+</td><td>IGRA-</td><td>TOT</td></tr><tr><td>TST+</td><td>9</td><td>2</td><td>11</td></tr><tr><td>TST-</td><td>8</td><td>90</td><td>98</td></tr><tr><td></td><td>17</td><td>92</td><td>109</td></tr></table>
They also performed univariate analysis for a positive LTBI test depending on several factors TB risk factors.</td><td>Not determined</td><td>Supported by a grant from the Department of the Pontificia University of Chile. IGRA were supplied at reduced price by Cellestis</td><td>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)</td></tr>
<tr><td>Bartalesi, F., Vicidomini, S., Goletti, D., Fiorelli, C., Fiori, G., Melchiorre, D., Tortoli, E., Mantella, A., Benucci, M., Girardi, E., Cerinic, M.M., & Bartoloni, A. 2009[166]</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 alpha inhibitors. Risk factors associated with LTBI included birth or residence in high prevalence area, close contact with to patients with sputum positive TB.</td><td>TST(5units PPD)</td><td>IGRA(QFT)</td><td>Overall results
<table><tr><td></td><td colspan="3">IGRA</td></tr><tr><td></td><td>+</td><td>-</td><td>Tot</td></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>Tot</td><td>52</td><td>341</td><td>393</td></tr></table>
Also presented Odds ratios adjusting for the association of risk factors for Tb infection and IGRA and TST positivity
<table><tr><td>No of Risks</td><td>IGRA +</td><td>p-val</td><td>TST +</td><td>P-val</td></tr><tr><td></td><td>OR</td><td></td><td>OR</td><td></td></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>

<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 & 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>Cobanoglu, N., Ozcelik, U., Kalyoncu, U., Ozen, S., Kiraz, S., Gurcan, N., Kaplan, M., Dogru, D., Yalcin, E., Pekcan, S., Kose, M., Topaloglu, R., Besbas, N., Bakkaloglu, A., & Kiper, N. 2007 [167]</td><td>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</td><td>TST 0.1ml (5TU) of PPD</td><td>IGRA(QFT)</td><td>Results stratified by age to adjust for supposed BCG effect.
< 25years (57 participants)
Group 1 9/25 Discordant results
All TST+ IGRA –
Group 2 17/32 Discordant results
16 (TST+ IGRA -) 1 (TST- IGRA +)

>25years (40 participants)
Group1 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</td><td>Not determined</td><td>Not recorded</td><td>Authors say study should be accepted as a basis for the design of future studies that will be helpful for physicians to decide whether the IGRA is more sensitive than TST to detect LTBI before the use of TNF α blockers.</td></tr>
<tr><td>Jones, S., de, G.D., Wallach, F.R., Gurtman, A.C., Shi, Q., & Sacks, H. 2007 [168]</td><td>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. United States</td><td>TST 0.1ml (5TU PPD)</td><td>IGRA (QFT)</td><td>Overall concordance between IGRA and TST results
<table><tr><td></td><td colspan="4">IGRA</td></tr><tr><td></td><td>Ind</td><td>-</td><td>+</td><td>Tot</td></tr><tr><td>TST-</td><td>10</td><td>172</td><td>6</td><td>188</td></tr><tr><td>TST+</td><td>0</td><td>8</td><td>5</td><td>13</td></tr><tr><td></td><td>10</td><td>180</td><td>11</td><td>201</td></tr></table>
Ind = Indeterminate</td><td>Not determined</td><td>QuantiFERON kits donated by Cellestis</td><td>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.</td></tr>
</table>

<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 & 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, A.F., Charlebois, E.D., Flores, L.L., Bangsberg, D.R., Deeks, S.G., Martin, J.N., & Havlir, D.V. 2007[169]</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 rehab 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><td></td><td colspan="4">TST</td></tr>
<tr><td>IG</td><td></td><td>+</td><td>-</td><td>TOT</td></tr>
<tr><td></td><td>+</td><td>8</td><td>11</td><td>19</td></tr>
<tr><td></td><td>-</td><td>10</td><td>167</td><td>177</td></tr>
<tr><td></td><td>TOT</td><td>18</td><td>178</td><td>196</td></tr>
</table>
Results were also stratified by CD4 count.
<table>
<tr><td>CD4+</td><td colspan="4">STRATA (cells/mm3)</td></tr>
<tr><td></td><td><100</td><td>100-350</td><td>>350</td><td>tot</td></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>TOT</td><td>31</td><td>111</td><td>152</td><td>294</td></tr>
<tr><td></td><td></td><td></td><td></td><td></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>TOT</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>

<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 & 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>Mandalakas, A.M., Hesseling, A.C., Chegou, N.N., Kirchner, H.L., Zhu, X., Marais, B.J., Black, G.F., Beyers, N., & Walzl, G. 2008[170]</td><td>43 HIV infected participants were enrolled in this study. 23 children and 20 adults. The mean age of adults was 18.7 years where as the mean for children was 4.4years. Study was conducted in South Africa</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA (QFT & T.SPOT))</td><td>Discordant results for TST and IGRAs
<table><tr><td></td><td>TSPOT +
TST -</td><td>TSPOT -
TST +</td></tr><tr><td>All</td><td>29.7</td><td>10.8</td></tr><tr><td>Children</td><td>39.1</td><td>13.0</td></tr><tr><td>Adults</td><td>14.3</td><td>7.1</td></tr></table><table><tr><td></td><td>QFT+
TST -</td><td>QFT-
TST+</td></tr><tr><td>All</td><td>0</td><td>26.9</td></tr><tr><td>Children</td><td>0</td><td>25.0</td></tr><tr><td>Adults</td><td>0</td><td>28.6</td></tr></table></td><td>Not determined</td><td>Funded by Bill and Melinda Gates Foundation</td><td>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.</td></tr>
<tr><td>Manuel, O., Humar, A., Preiksaitis, J., Doucette, K., Shokoples, S., Peleg, A.Y., Cobos, I., & Kumar, D. 2007[171]</td><td>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 tb. Study was conducted in a preliver transplant clinic in Canada</td><td>TST</td><td>IGRA (QFT)</td><td>Overall results
5mm cut off<table><tr><td></td><td>TST+</td><td>TST-</td><td>Total</td></tr><tr><td>IGRA+</td><td>25</td><td>9</td><td>34</td></tr><tr><td>IGRA-</td><td>12</td><td>95</td><td>107</td></tr><tr><td>Total</td><td>37</td><td>104</td><td>141</td></tr></table>10mm cut off<table><tr><td></td><td>TST+</td><td>TST-</td><td>Total</td></tr><tr><td>IGRA+</td><td>18</td><td>16</td><td>34</td></tr><tr><td>IGRA-</td><td>9</td><td>98</td><td>107</td></tr><tr><td>Total</td><td>27</td><td>114</td><td>141</td></tr></table>Indeterminate IGRA result 12/153 = 7.8%</td><td>Not determined</td><td>Test kits provided by Cellestis Ltd</td><td>Authors conclude that study demonstrates that IGRA and TST performed similarly for the diagnosis of LTBI in a population with end stage liver disease.</td></tr>
</table>

<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 & 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>Matulis, G., Juni, P., Villiger, P.M., & Gadola, S.D. 2008[172]</td><td>142 participants of which 126 received immunosuppressive therapy. 50% were female. Anti TNF, DMARDS and corticosteroids were the medicines they received. The mean age was 48years. Study was conducted in a University Hospital in Berne Switzerland.</td><td>TST (2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table><tr><td></td><td>TST+</td><td>TST-</td><td>Un</td><td>tot</td></tr><tr><td>IG+</td><td>10</td><td>5</td><td>2</td><td>17</td></tr><tr><td>IG-</td><td>34</td><td>60</td><td>23</td><td>117</td></tr><tr><td>Ind</td><td>2</td><td>4</td><td>2</td><td>8</td></tr><tr><td>Tot</td><td>46</td><td>69</td><td>27</td><td>142</td></tr></table>Multivariate analysis were presented as Odds ratios
<u>CORTICOSTEROID TREATMENT (YES, NO)</u>
OR IGRA = 1.11(0.30-4.14)
OR TST = 0.74(0.32-1.72)
<u>DMARDS TREATMENT (YES, NO)</u>
OR IGRA = 2.34(0.52-10.6)
OR TST = 0.75(0.32-1.77)
<u>TNFα INHIBITORS</u>
OR IGRA = 0.19 (0.05-0.76)</td><td>Not determined</td><td>Study funded by Swiss commission for Rheumatic Disease and the Swiss National Science Foundation</td><td>They did a multivariate analysis which did not include analysis for the participants which had two or more immunosuppressant medications</td></tr>
</table>

<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 & 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>Piana, F., Ruffo, C.L., Baldan, R., Miotto, P., Ferrarese, M., & Cirillo, D.M. 2007[173]</td><td>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.</td><td>TST 0.1ml (5TU) of Siebert PPD</td><td>IGRA (T-SPOT.TB)</td><td>Overall result
<table>
<tr><td></td><td colspan="5">IGRA</td></tr>
<tr><td></td><td>+</td><td>-</td><td>Ind</td><td>Ins T cell</td><td>Tot</td></tr>
<tr><td>TST+</td><td>21</td><td>3</td><td>0</td><td>0</td><td>24</td></tr>
<tr><td>TST-</td><td>34</td><td>57</td><td>5</td><td>2</td><td>98</td></tr>
<tr><td>No res</td><td>6</td><td>8</td><td>1</td><td>1</td><td>16</td></tr>
<tr><td>Tot</td><td>61</td><td>68</td><td>6</td><td>3</td><td>138</td></tr>
</table>
Ind = Indeterminate
Ins = Insufficient
No res = No result
Results also stratified by pathological WBC count.
Pathological (<4.3x10^3 or>10.8X10^3 WBC.mm^{-3})
IGRA 44.3% +VE TST 14.5% +VE
Non Pathological
IGRA 44.6% +VE TST 25.9+VE</td><td>Not determined</td><td>T-SPOT.TB kits provided by Oxford Immunotech</td><td>It was important to determine whether 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.</td></tr>
</table>

<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 & 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>Ponce de, L.D., Acevedo-Vasquez, E., Alvizuri, S., Gutierrez, C., Cucho, M., Alfaro, J., Perich, R., Sanchez-Torres, A., Pastor, C., Sanchez-Schwartz, C., Medina, M., Gamboa, R., & Ugarte, M. 2008[174]</td><td>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 less than 10mg daily. They also recruited 97 controls</td><td>TST(Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (QFT)</td><td>Overall results showing TST and IGRA results of immunosuppressed patients and controls

RA patients
<table><tr><td></td><td colspan="4">TST</td></tr><tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr><tr><td>+</td><td>21</td><td>24</td><td>45</td></tr><tr><td>-</td><td>6</td><td>50</td><td>56</td></tr><tr><td></td><td>27</td><td>74</td><td>101</td></tr></table>
Control
<table><tr><td></td><td colspan="4">TST</td></tr><tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr><tr><td>+</td><td>50</td><td>5</td><td>55</td></tr><tr><td>-</td><td>11</td><td>27</td><td>38</td></tr><tr><td></td><td>61</td><td>32</td><td>93</td></tr></table>
RA = Rheumatoid arthritis</td><td>Not determined</td><td>Not recorded</td><td>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 more accurate than the TST in RA patients but cannot determine absolute sensitivity of both tests</td></tr>
</table>

<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 & 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, L., Losi, M., D'Amico, R., Luppi, M., Ferrari, A., Mussini, C., Codeluppi, M., Cocchi, S., Prati, F., Paci, V., Meacci, M., Meccugni, B., Rumpianesi, F., Roversi, P., Cerri, S., Luppi, F., Ferrara, G., Latorre, I., Gerunda, G.E., Torelli, G., Esposito, R., & Fabbri, L.M. 2009[175]</td><td>369 participants who were prospectively enrolled into the following immunosuppressed groups. Liver transplantation candidates, Chronically HIV infected patients and patients with hematologic malignancies. Study participants were evaluated in a referral centre in Italy. Only about 3.6% patients were BCG vaccinated.</td><td>TST(5iu PPD)</td><td>IGRA (T-SPOT.TB) & (QFT)</td><td>Overall results
<table>
<tr><td></td><td>LTC</td><td>HIV</td><td>HM</td></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>
LTC Liver Transplantation Candidates
HM Hematologic Malignancies
HIV Human Immunodeficiency Virus

TSP T-SPOT.TB
TSP.I Indeterminate result
QFT.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>
</table>

<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 & 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>Schoepfer, A.M., Flogerzi, B., Fallegger, S., Schaffer, T., Mueller, S., Nicod, L., & Seibold, F. 2008 [176]</td><td>212 participants consisting of 114 crohns disease, 44 ulcerative colitis 10 indeterminate colitis and 44 controls. Study was conducted in Switzerland</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table><tr><td>Diag</td><td>N</td><td>BCG</td><td>Igra+</td><td>Tst+</td></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>Cont</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>
<tr><td>Shovman, O., Anouk, M., Vinnitsky, N., Arad, U., Paran, D., Litinsky, I., Caspi, D., & Elkayam, O. 2009[177]</td><td>Study performed in Israel. 35 rheumatoid arthritis patients and 15 controls</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table><tr><td></td><td colspan="3">TST results as percentage</td></tr><tr><td></td><td>+ve</td><td>-ve</td><td>Anergy</td></tr><tr><td>RA</td><td>45</td><td>17</td><td>37</td></tr><tr><td>Control</td><td>15</td><td>7</td><td>78</td></tr></table><table><tr><td></td><td colspan="3">IGRA results by percentage</td></tr><tr><td></td><td>+ve</td><td>-ve</td><td>ind</td></tr><tr><td>RA</td><td>11.4</td><td>60</td><td>28.6</td></tr><tr><td>Control</td><td>13</td><td>87</td><td>0</td></tr></table>RA = Rheumatoid Arthritis</td><td>Not determined</td><td>Not recorded</td><td>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.</td></tr>
</table>

<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 & 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>Soborg, B., Ruhwald, M., Hetland, M.L., Jacobsen, S., Andersen, A.B., Milman, N., Thomsen, V.O., Jensen, D.V., Koch, A., Wohlfahrt, J., & Ravn, P. 2009[178]</td><td>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 Rheumatology department of the Heart centre in Copenhagen Denmark</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Results presented as risk ratios which determined the associations between factors relevant to TB infection and test reactivity to either IGRA or TST.
<u>CORTICOSTEROID TREATMENT (YES, NO)</u>
RR IGRA = 0.5(0.1-1.6)
RR TST = 0.4(0.1-1.0)
<u>DMARDS TREATMENT (YES, NO)</u>
RR IGRA = 0.7(0.3-1.7)
RR TST = 1.3(0.7-2.3)
<u>CD4 COUNT (<500 >500)</u>
RR IGRA = 1 (0.2-3.2)
RR TST = 1.5(0.7-3.3)
Danish Guideline
<table>
<tr><td></td><td>TST -</td><td>TST+</td></tr>
<tr><td>IGRA-</td><td>180</td><td>36</td></tr>
<tr><td>IGRA +</td><td>9</td><td>9</td></tr>
</table>
US Guideline
<table>
<tr><td></td><td>TST-</td><td>TST+</td></tr>
<tr><td>IGRA-</td><td>159</td><td>57</td></tr>
<tr><td>IGRA+</td><td>9</td><td>9</td></tr>
</table></td><td>Not recorded</td><td>Not recorded</td><td>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.</td></tr>
</table>

<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 & 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>Talati, N.J., Seybold, U., Humphrey, B., Aina, A., Tapia, J., Weinfurter, P., Albalak, R., & Blumberg, H.M. 2009[179]</td><td>336 HIV positive patients of mean age of 42 years. Patients had a past med history of LTBI, diabetes mellitus, chronic renal insufficiency, history of malignancy, anytime smoker and Intravenous drug use. Study done in the US.</td><td>TST 0.1ml (5TU) of Siebert PPD</td><td>IGRA (TSPOT.TB AND QFT)</td><td>Reported a CD4 count of < 200 as associated with an indeterminate result for both IGRAs OR = 3.6(1.9,6.8)</td><td>Not determined</td><td>Partly supported by Centers for Disease Control and Prevention (CDC)</td><td>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</td></tr>
<tr><td>Vassilopoulos, D., Stamoulis, N., Hadziyannis, E., & Archimandritis, A.J. 2008[180]</td><td>Observational study Some were on DMARD and various other immunosuppressive medicines such as steroids.

70 participants with various rheumatic diseases with a mean age 60years. The study was conducted in an Outpatients rheumatology clinic in Athens Greece</td><td>TST (Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (T-SPOT.TB</td><td>Overall results showing discordant and concordant results between tests<table><tr><td></td><td colspan="4">TST</td></tr><tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr><tr><td>+</td><td>12</td><td>4</td><td>16</td></tr><tr><td>-</td><td>15</td><td>39</td><td>54</td></tr><tr><td></td><td>27</td><td>43</td><td>70</td></tr></table></td><td>Not determined</td><td>Not recorded</td><td>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 anti TNF treated rheumatic patients with discordant TST/TSPOT results are needed before recommendations can be made.</td></tr>
</table>

Recent arrivals from countries with a high incidence of TB

Table 55. Studies with people from countries with high tuberculosis prevalence included in CG117

Bibliographic Reference (Ref ID)	Stud 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, D., Lederer, D.J., Gallardo, J.S., Trivedi, S.H., Burzynski, J.N., & Schluger, N.W. 2008[181]	Prospective	123	Not specifically recorded.	United States/ Does not mention countries of origin of immigrants	Patients over 5 years old. 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 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
Diel, R., Loddenkemper, R., Meywald-Walter, K., Niemann, S.,	Observational prospective study.	1794	Incidence of TB in Hamburg, Germany reported to be	Germany/ Noted as 'foreign born' but cases progressin	Close contacts of sputum-smear positive cases with at least 40 hours	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST (Threshold 5mm and 10mm)	Overall kappa statistics 0.276 and 0.119 and 0.616 for	Not determined	No declared sponsor	Specific countries of origin of migrants not mentioned.

Bibliographic Reference (Ref ID)	Stud 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, A. 2008[184]			10.8/10[5.]	g to TB documented as from Turkey, Angola	exposure in a closed room. Age range between 0 to 60 years, with most (87.5%) falling between the 16 to 50 range. 28% were migrants from 29 different countries			BCG vaccinated and non BCG respectively. For the concordance the values were 69.2%, 44.2% and 90.7% respectively. Odds Ratio for a positive test if foreign born adjusted for BCG vaccination, Age and exposure time were determined as follows. TST 5mm 5.81 (3.6-9.1), 10mm 5.2 (3.2-8.4), QFT 2.28 (1.3-3.9)			
Diel, R., Nienhaus, A., Lange, C., Meywald-Walter, K.,	Observational prospective study.	311	TB incidence rate in Hamburg 12/100000	Germany/ 25 different countries including	Close contacts of sputum-smear positive cases. Contacts with	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST 5mm = 137/309 TST (28/137	Overall Kappa statistics 0.2 CI(0.14-0.23)	No data	No sponsor	For QFT only Origin is an independent predictor of a positive test result.

Bibliographic Reference (Ref ID)	Stud 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
Forssbohm, M., & Schaberg, T. 2006[183]			. Immigrants from countries with incidence of at least 20/100000	former Soviet Union and Turkey.	less than 40hours contact time were excluded. Mean age 28.5 years Previous BCG vaccination 157 (50.8%) Foreign/German (27.1%/72.9)		Positive by IGRA) 10mm = 64/309 15mm = 25/309	Concordant results 197/309 (63.8%). Positive result 169/172(98.2%) Negative result 28/137 (20.4%) Concordance for 5mm between BCG vacc 38.9% k = 0.08(0.026-0.08). Not vacc 89.5% k = 0.58(0.4-0.68) for 10mm 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(5mm) OR = 5.4, TST(10mm) 7.3 and 4.7 QFT			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.

Bibliographic Reference (Ref ID)	Stud 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
Franken, W.P., Timmermans, J.F., Prins, C., Slootman, E.J., Dreverman, J., Bruins, H., van Dissel, J.T., & Arend, S.M. 2007[185]	Prospective Cross sectional study	909	Range from <10, 10-49,50-99,100-199>200) per 100000	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 10mm and 15mm)	Discordance and concordance between tests. Overall concordance and kappa values were determined to be 82% and 0.19 respectively for 10mm cut off and 92.3% and 0.24 respectively for 15mm TST cut off.	No data		Study not clear with regard to the definition of LTBI.
Janssens, J.P., Roux-Lombard, P., Perneger, T., Metzger, M., Vivien, R., & Rochat, T. 2008[186]	Observational prospective study.	295	TB Incidence $20/10^5$ in Geneva. Incidence in countries from which immigrants originated between (50->100)/10^5	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%) Pulmonary TB 22 (7.5%)	IGRA (ESAT-6,CFP-10,) (T-SPOT.TB)	TST Induration 5mm 173(58.6 %) 10mm 148(50.2 %) 61mm (20.7%)	Overall concordant results showed 60.7% TST 5mm, 63.6% 10mm, 63.9% 15mm.Kappa values were 0.24, 0.27 and 0.19 respectively. BCG Non-vaccinated subjects	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 xray. In the analysis they did not mention if they adjusted for immunocompromised individuals. They were only 6%. The TB incidence of

Bibliographic Reference (Ref ID)	Stud 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
								concordant results were 78.4%, 76.5% and 78.4% respectively while kappa values were 0.47, 0.41 and 0.28 for 5mm, 10mm and 15mm respectively when comparing with IGRA .aOR for Gender, BCG and incidence in country of origin (<50/10^5 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)			Geneva from where they recruited was 20/10^5. They did not use that as the baseline value in calculations.

Bibliographic Reference (Ref ID)	Stud 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
								respectively for TST 5mm. Only incidence in country of origin showed the significant association with a positive result for TST 10mm 2.22 (1.15-4.27) and 3.84 (1.61-9.20) for 50-99/10^5 and >100/10^5 respectively. <50/10^5 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-			

Bibliographic Reference (Ref ID)	Stud 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
								4.15) and 2.62 (1.18-5.82) respectively for two categories of incidence.			
Kik, S.V., Franken, W.P., Arend, S.M., Mensen, M., Cobelens, F.G., Kamphorst, M., van Dissel, J.T., Borgdorff, M.W., & Verver, S. 2009[187]	Observational Retrospective study	821	Not specifically recorded.	Netherlands/ South America, Asia, Sub Saharan Africa	Participants aged above 16 years. Close contacts of sputum smear positive TB patients. Foreign born and second generation immigrants.	IGRA (QGIT, TSPOT.TB) (ESAT-6, CFP-10,TB7.7)	TST (Threshold 5mm 10mmand 15mm)	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 15mm 0.418 for QFT and 0.379 for TSPOT.TB. For 10mm they were 0.198 and 0.190 respectively. Agreement values were 71.3% and	No data	Netherlands Organisation for Health Research and Development	Partial verification was performed on those with TST more than 5mm. 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 don't mention how deduced LTBI

Bibliographic Reference (Ref ID)	Stud 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
								69.9% for QFT and TSPOT.TB respectively for 15mm. For 10mm 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 10mm, p value for trend 0.031. Both QFT and TSPOT.tb also showed a positive result independently associated with continent of birth and age			
Nienhaus, A.,	Observation	1040	Incidence	Germany/	Study	IGRA	TST	Agreement	No data	No sponsor	Although study

Bibliographic Reference (Ref ID)	Stud 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
Schablon, A., & Diel, R. 2008[188]	al Cross sectional/ retrospective		of TB in Germany reported to be < 6/100000 and >20/100000 in countries from where the immigrants originated.	Germany Turkey, Eastern Europe and Africa	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.	(QFTBG) Threshold level 0.35IU/ml Positive result 100/1033	(Threshold 5mm 311/1033(30.1%) 10mm = 191/1033(18.5%) 15mm = 69/1033 (6.7%)	5mm 74.8%, 10mm 84.2%, 15mm 89.8%. Kappa Statistics 5mm (0.26) 10mm (0.37) 15mm (0.33.) BCG vacc. 5mm(0.12) 10mm(0.28) 15mm(0.34) No vacc 5mm(0.5) 10mm(0.54) 15mm(0.3) aOR for positive TST(10mm) 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)		reported	states the population consisted of health persons they have said nothing to rule out symptomless TB by chest Xray. TST at 10mm could possibly be confounded by gender foreign birthplace and BCG vaccination. QFT on 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, E., Cheng, L.,	Cross sectional/	474	TB prevalenc	United States/	Adult inmates above 18	IGRA (ESAT-6 and	TST Induration	Kappa statistics for	Not determined	Health Resources and	On logistic regression African

Bibliographic Reference (Ref ID)	Stud 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
Seale, M.M., Delclos, G.L., Ma, X., Reich, R., Musser, J.M., & Graviss, E.A. 2006[189]	Observational		e in United States <10/10^5 of foreign born the prevalence reported 25-300/10^5	Mexico, Jamaica, Nicaragua, Ecuador, El Salvador, Honduras, The Philippines and Brazil.	years of age. 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	CFP-10)(QFGInTube)	10mm	discordance and concordance between TST and QFGT.Adjusted Odds Ratios calculated to determine which factors including Ethnicity, Old age, foreign birth and prior incarceration were more associated with Discordance.		Services Administration Bureau of health professions Grant. Kits provided by Cellestis	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
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Jeppesen, A.S., Harstad, I., Heier, B.T., & Heldal, E. 2008[164]	Observational Cross sectional/ retrospective	1000	TB incidence rate in Norway 6.3/100000	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)(QFGInTube)	TST (Threshold 6mm) 460/912(50.4%) 10mm 311/921(34.1%) 15mm(15.5%)	Agreement 72% for 6mm 79% 10mm 78% 15mm. Kappa 6mm 0.43(0.37-0.49) 10mm 0.51(0.45-0.57) 15mm 0.39(0.32-0.47) statistics 0.43(0.37-	Not determined		Definite prevalence or incidence not recorded for countries of origin. For QFT, BCG vaccination and gender were not independent predictors of a positive result while country of origin and age group and level of

Bibliographic Reference (Ref ID)	Stud 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
								0.49). aOR continent of origin with Asia as baseline for TST 15mm 3.8 and 3.3 for QFT			exposure independently predicted a positive test. For TST 15mm the variables which independently predicted a positive result were gender, country of origin and level of exposure

11.7 Appendix 7. ClinicalTrials.gov and WHO ICTRP list of excluded studies (N = 31)

Table 56. ClinicalTrials.gov and WHO ICTRP list of excluded studies

Study	Title	Recruitment status	URL	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	Healthcare 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.	Improving Latent Tuberculosis (TB) Diagnosis in Thai Children	Completed	http://ClinicalTrials.gov/show/NCT00947609	
6.	QuantiFERON®-TB Gold In-Tube for the Diagnosis of Tuberculosis Infection in Contact Tracing Study.	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01223534	No subgroup of interest
7.	Quantiferon for Detection of Latent Tuberculosis in Healthcare Workers	Completed	http://ClinicalTrials.gov/show/NCT00797836	Healthcare workers
8.	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
9.	Quantiferon Gold Test for Detecting Tuberculosis (TB) Infection in HIV/AIDS Patients in South Africa	Not recruiting yet	http://ClinicalTrials.gov/show/NCT02119130	Active TB
10.	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

11.	The Role of IGRA in Screening and Monitoring for TB During Anti TNF Therapy in IBD	Recruiting	http://ClinicalTrials.gov/show/NCT02135289	No comparison between IGRAs and TST
12.	Immune Response to Mycobacterium Tuberculosis Infection	Completed	http://ClinicalTrials.gov/show/NCT00257907	Active TB
13.	Performance of IGRAs for TB Infection Diagnosis in Elderly	Recruiting	http://ClinicalTrials.gov/show/NCT01895582	Active TB
14.	Monthly Follow up of Interferon Gamma Releasing Assay (IGRA) Among Health-care Workers Treating Tuberculosis (TB) Patients	Completed	http://ClinicalTrials.gov/show/NCT01121068	Healthcare workers
15.	Vitamin A Supplementation for Modulation of Mycobacterium Tuberculosis Immune Responses in Latent Tuberculosis	Withdrawn	http://ClinicalTrials.gov/show/NCT00558480	Withdrawn
16.	Diagnosis of Latent Tuberculosis(TB) Infection in Health Care Workers Using TST and Whole Blood Interferon-γ Assay	Completed	http://ClinicalTrials.gov/show/NCT00962793	Healthcare workers
17.	Latent Tuberculosis Infection in Bone Marrow Transplant Recipients	Completed	http://ClinicalTrials.gov/show/NCT01021124	No comparison between IGRAs and TST
18.	Conversion Rate of (TST) Tuberculin Skin Test and Quantiferon-TB Gold In Tube Assay in Health Care Workers	Completed	http://ClinicalTrials.gov/show/NCT01376843	Healthcare workers
19.	Determining Risk in Latent Tuberculosis	Terminated	http://ClinicalTrials.gov/show/NCT01571739	Study terminated
20.	Treatment of Latent Tuberculosis Infection With Isoniazid	Completed	http://ClinicalTrials.gov/show/NCT00293228	Focus on the effect of treatment
21.	Effects of Vitamin D Supplementation on Antimycobacterial Immunity	Completed	http://ClinicalTrials.gov/show/NCT00157066	Focus on the effect of treatment
22.	A Phase I/IIa Safety & Immunogenicity of AERAS-456 in HIV-Negative Adults With & Without Latent Tuberculosis Infection (C-035-456)	Recruiting	http://ClinicalTrials.gov/show/NCT01865487	Comparing antigen and placebo
23.	Isoniazid (INH) Treatment Based on ELISPOT Assay	Completed	http://ClinicalTrials.gov/show/NCT01087190	Focus on the effect of treatment
24.	A Safety and Immunogenicity Trial With an Adjuvanted TB Subunit Vaccine (Ag85B-ESAT-6 +	Completed	http://ClinicalTrials.gov/show/NCT01049282	Comparing antigens

	IC31)			
25.	IFN-gamma-releasing Assay Based Approach in Patients With Suspected Tuberculous Peritonitis	Recruiting	NCT02175134	Diagnosis of tuberculous peritonitis
26.	Investigational research (clinical trial) to compare CT-b, which is a new test to diagnose tuberculosis, with 2 standard tests (PPD and QuantiFERON)	Authorised	EUCTR2011-005617-36-ES	Active TB
27.	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	EUCTR2009-017430-49-ES	Not English language
28.	Interferon-Gamma Release Assays in Tuberculosis (TB) - HIV Co-infected Children	Recruiting	NCT00604617	Active TB
29.	Screening for Latent Tuberculosis in Healthcare Workers With Quantiferon-Gold Assay: A Cost-Effectiveness Analysis	Recruiting	NCT00449345	Healthcare workers and Economic analysis
30.	Use TST and QFT-RD1 Test to Monitor the Tuberculous Infection in Patients, Close Contact People and Health Care Workers	Recruiting	NCT00311220	Healthcare workers
31.	Diagnosis of Active Tuberculosis by ELISPOT	Recruiting	NCT00174083	Active TB

11.8 Appendix 8. Included on going trials that compared IGRAs with TST (N = 20)

Table 57. Included on going trials that compared IGRAs with TST

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	Recruiting		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 Hemodialysis Patients	Completed		http://ClinicalTrials.gov/show/NCT00695734
7.	Improving Latent Tuberculosis (TB) Diagnosis in Thai Children	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	Recruiting		http://ClinicalTrials.gov/show/NCT00707317

	Individuals			
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
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	Recruiting		NCT00925249
20.	Quantiferon-TB Gold in the Assessment of Latent TB in Patients Candidate to Treatment or Treated With TNFa	Recruiting		NCT00491933

	Antagonists			

11.9 Appendix 9. Data extraction for included studies

Children

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Peter Auguste

Study details

First author surname year of publication: Adetifa 2010[103]
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 (TSPOT):	NR	71	144	0	215
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	**Same house same room vs. Different house** OR (regression-based; reported) = 15.00 (95% CI:

OR (regression-based; reported) = 4.00 (95% CI: 1.40, 11.40) List of covariates: age, sex, ethnic group	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) = 0.58 (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

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 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

te			
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[104]
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[105]
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) = <u>Adult index case type of TB diagnosis</u> 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) <u>Adult index case smear grade</u> 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) = <u>Adult index case type of TB diagnosis</u> 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) <u>Adult index case smear grade</u> 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[146]
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[106]
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[148]
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[107]
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[149]
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[108] and Rutherford 2012b[109] (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[110]
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[152]
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[111]
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[100]
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				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 +	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[101]
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[102]
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[150]
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[118]
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 [119]
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[120]
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^{o}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[121] **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[122] **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[123]
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[124]
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				**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 +	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[125]
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[126]
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[127]
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[128]
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[129]
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

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 +	11	42	53	TST +	13	10	23
IGRA -	4	63	67	TST -	2	94	96
Indeterminate	1	5	6 (excluded)	Indeterminate	1	6	7 (excluded)
Total	16	110	126	Total	16	110	126

Test performance parameters	
IGRA	**TST**
Sensitivity = 11/15 = 73.33% (95% CI: 48.05, 89.1)	Sensitivity = 13/15 = 86.67% (95% CI: 62.12, 96.26)
Specificity = 63/105 = 60.00% (95% CI: 50.44, 68.86)	Specificity = 94/104 = 90.38% (95% CI: 83.2, 94.69)
PPV = 11/53 = 20.75% (95% CI: 12.00, 33.46)	PPV = 13/23 = 56.52% (95% CI: 36.81, 74.37)
NPV = 63/67 = 94.03% (95% CI: 85.63, 97.65)	NPV = 94/96 = 97.92% (95% CI: 92.72, 99.43)
DOR (for T^+ calculated) = 4.12 (95% CI: 1.23, 13.82)	DOR (for T^+ calculated) = 61.1 (95% CI: 12.03, 310.4)
OR (crude; for T^+ reported) = 4.13 (95% CI: 1.23, 13.82)	OR (crude; for T^+ reported) = 0.61 (95% CI: 0.13, 2.91) -error
OR (regression-based; reported) = 4.62 (95% CI: 1.15, 18.64) List of covariates: NR	OR (regression-based; reported) = 0.40 (95% CI: 0.07. 2.20) -error List of covariates: NR
Other reported measure = NR	Other reported measure = NR
Comparison between tests (IGRA vs. TST)	
Ratio of DORs (for T^+ calculated) = 0.07 (95% CI: 0.02, 0.19)	
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 (≥10mm)**

	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[130]
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[131]
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[132]
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[133]
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[134]
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[135]
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[136]
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[137]
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[138]
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[151]
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
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[140]
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[115]
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[117]
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[112]
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[114] **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[116]
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 [147]
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=0.0% (95% CI: 0.0, 19.79)
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 $_{TST}$ = 0.0
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 = NA
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=0.0% (95% CI: 0.0, 28.20)
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 $_{TST}$ = 0.0
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 = NA
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[113]
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[153]
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=0.00 (95% CI: 0.00, 10.93)	Cumulative Incidence $_{TST-}$ = 0/36=0.00 (95% CI: 0.00, 11.47)
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 (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[143]
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[144]
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[145]
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[141]
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[142] (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% (95% CI: 1.20, 6.40)	Cumulative Incidence $_{TST+}$ = 9/288 = 3.12% (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

11.10 Appendix 10. Included studies and incidence of tuberculosis[227]

Table 58. Included studies and incidence of tuberculosis

Author, country	Category	Estimated rate per 100,000 population
Study in children and adolescents (incidence studies)		
Diel 2011[100] Germany	Low incidence	5.6
Mahomed 2011a[106] South Africa	High incidence	1003
Metin Timur 2014[148] Turkey	Intermediate incidence	22
Noorbakhsh 2011[102] Iran	Intermediate incidence	21
Song 2014[150] South Korea	High incidence	409
Study in children and adolescents (exposure studies)		
Adetifa 2010[103] Gambia	High incidence	284
Cruz 2011[104] US	Low incidence	3.6
Kasambira 2011[105] South Africa	High incidence	1003
Laniado-Laborın 2014[146] Mexico	Intermediate incidence	23
Mahomed 2011b[106] South Africa	High incidence	1003
Pavic 2011[107] Croatia	Low incidence	14
Perez-Porcuna 2014[149] Brazil	Intermediate incidence	46
Rutherford 2012a-b[108, 109] Indonesia	High incidence	185
Talbot 2012[110] US	Low incidence	3.6
Tieu 2014[152] Thailand	High incidence	119
Tsolia 2010[111] Greece	Low incidence	4.5
Study in immunocompromised people (incidence studies)		
Anibarro 2012[115] Spain	Low incidence	14
Chang 2011[117] South Korea	High incidence	409
Elzi 2011[112] Switzerland	Low incidence	6
Kim 2011[114] South Korea	High incidence	409
Lee 2009[116] Taiwan	High incidence	73
Lee 2014[147] South Korea	High incidence	409
Moon 2013[113]	High incidence	409

South Korea		
Sherkat 2014[153] Iran	Intermediate incidence	21
Study in immunocompromised people (exposure studies)		
Ahmadinejad 2013[118] Iran	Intermediate incidence	21
Al Jahdali 2013[119] Saudi Arabia	Low incidence	15
Ates 2009[120] Turkey	Intermediate incidence	22
Casas 2011a[121] Spain	Low incidence	14
Casas 2011b[122] Spain	Low incidence	14
Chkhartishvili 2013[123] Georgia	High incidence	116
Chung 2010a[124] South Korea	High incidence	409
Costantino 2013[125] France	Low incidence	8.2
Hadaya 2013[126] Switzerland	Low incidence	6
Hsia 2012[127] USA	Low incidence	3.6
Kim 2010[128] South Korea	High incidence	409
Kim 2013b[129] South Korea	High incidence	409
Kim 2013c[130] South Korea	High incidence	409
Kleinert 2012[131] Germany	Low incidence	5.6
Laffitte 2009[132] Switzerland	Low incidence	6
Maritsi 2011[133] UK	Low incidence	15
Mutsvangwa 2010[134] Zimbabwe	High incidence	562
Papay, 2011[135] Austria	Low incidence	7.9
Ramos, 2013[136] Spain	Low incidence	14
Seyhan, 2010[137] Turkey	Intermediate incidence	22
Shen, 2012[138] China	High incidence	83
Souza 2014[151] Brazil	Intermediate incidence	46
Takeda, 2011[139] Japan	Low incidence	19
Vassilopoulos, 2011[140] Greece	Low incidence	4.5
Study in recently arrived people from high endemic TB countries (incidence studies)		

Harstad, 2010[141] Norway	Low incidence	7.5
Kik, 2010[142] The Netherlands	Low incidence	6.3
Study in recently arrived people from high endemic countries (exposure studies)		
Lucas, 2010[143] Australia	Low incidence	6.5
Orlando, 2010[144] Italy	Low incidence	6.7
Saracino, 2009[145] Italy	Low incidence	6.7
Low incidence: defined as countries with an incidence of TB below 20 cases per 100,000 population (Mor 2008, Heldal 2008) Intermediate incidence: defined as countries with an incidence of TB more than or 20 but less than 40 cases per 100,000 High incidence: defined as countries with an incidence of TB more than 40 cases per 100,000		

11.11 Appendix 11. List of excluded studies with reason(s)

Table 59. List of excluded studies from the cost-effectiveness review

Number	Study	Reason(s) for exclusion
1.	Burgos, J. L., et al. (2009). "Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico." International Journal of Tuberculosis and Lung Disease 13(8): 962-968.	No comparator
2.	Deuffic-Burban, S., et al. (2010). "Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection." International Journal of Tuberculosis & Lung Disease 14(4): 471-481.	Close contacts
3.	Diel, R., et al. (2009). "Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany." Respiratory Medicine 103(12): 1838-1853.	Cost analysis
4.	Hardy, A. B., et al. (2010). "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 65(2): 178-180.	No economic model
5.	Iqbal, A. Z., et al. (2014). "Cost-effectiveness of Using QuantiFERON Gold (QFT-G) versus Tuberculin Skin Test (TST) among U.S. and Foreign Born Populations at a Public Health Department Clinic with a Low Prevalence of Tuberculosis." Public Health Nursing 31(2): 144-152.	No economic model
6.	Jit Mark, Stagg Helen R, Aldridge Robert W, White Peter J, Abubakar Ibrahim. 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, L. M. (2010). "IGRAs in public health practice: Economic issues." International Journal of Tuberculosis and Lung Disease 14(6 SUPPL. 1): S60-S63.	Letter to editor
8.	Langley, I., B. Doulla, H. H. Lin, K. Millington and B. Squire (2012). "Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions." Health Care Management Science 15(3): 239-253.	Active TB
9.	Mancuso, J. D., et al. (2011). "Cost-effectiveness analysis of targeted and sequential screening strategies for latent tuberculosis." International Journal of Tuberculosis & Lung Disease 15(9): 1223-1230, i.	Military recruits
10.	Pareek, M., et al. (2011). "Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis." Lancet Infect Dis 11(6): 435-444.	No comparator
11.	Pooran, A., et al. (2010). "Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis." BMC Pulmonary Medicine 10: 7.	Close contacts
12.	Shah, M., et al. (2012). "QuantiFERON-TB gold in-tube implementation for latent tuberculosis diagnosis in a public health clinic: a cost-effectiveness analysis." BMC Infect Dis 12: 360.	TST-positive referrals
13.	Steffen, R. E., et al. (2013). "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 [Electronic Resource] 8(4): e59546.	Immunocompetent close contacts

14.	van der Have M, Oldenburg B, Fidder HH, Belderbos TD, Siersema PD, van Oijen MG. Optimizing screening for tuberculosis and hepatitis B prior to starting tumor necrosis factor-alpha inhibitors in Crohn's disease. Dig Dis Sci. 2014;59(3):554-63.	Intervention not of interest
15.	Verma, G., et al. (2013). "Tuberculosis screening for long-term care: a cost-effectiveness analysis." International Journal of Tuberculosis & Lung Disease 17(9): 1170-1177.	Compared screening strategies (no screening, LTBI screening and active TB screening)

11.12 Appendix 12. Data extraction sheet 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	<u>One-way sensitivity analysis</u> 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 <u>Probabilistic sensitivity analysis</u> 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	<u>One-way sensitivity analysis</u> 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

11.13 Appendix 13. Critical appraisal of the economic evaluation using the CHEERS checklist

Table 60. CHEERS quality assessment checklist for economic evaluation studies

Assessment	Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
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	N/A	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
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

Assessment	Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
Generalizability	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; N/A- Not Applicable; Y- Yes; UNC-Unclear										

11.14 Appendix 14. Critical appraisal of the economic models using an adapted Philips et al., 2004 checklist

Table 61. Philips' quality assessment checklist for studies that include an economic model

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
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	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
	transparent and justified?										
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?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N
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, the duration of treatment 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	N/A	Y	N/A	N/A	N/A
DATA											

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
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?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
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	N/A	Y	N/A	Y	N/A
29.	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	N	N	N	N	N	N	N
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?	N/A	N/A	N/A	N/A	N/A	N/A	UNC	N/A	N/A	N/A

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
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	N/A
39.	Are the utilities incorporated into the model appropriate?	Y	Y	Y	Y	Y	Y	N/A	Y	N/A	N/A
40.	Is the source of utility weights referenced?	Y	Y	Y	Y	Y	Y	N/A	Y	N/A	N/A
41.	Are the methods of derivation for the utility weights justified?	UNC	UNC	UNC	UNC	UNC	Y	N/A	UNC	N/A	N/A
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

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
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
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	N/A	N/A	N/A	N/A	N/A
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	UNC	UNC	UNC	UNC	Y	N/A	N/A	N/A	N/A	N/A
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	N/A	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 sub-groups?	Y	Y	Y	Y	Y	N	Y	N	Y	N/A
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Philips' criteria		Studies									
		Kowada 2010[193]	Kowada 2012[194]	Kowada 2013[195]	Kowada 2014[196]	Laskin et al., 2013[197]	Linas et al., 2011[198]	Mandalakas et al., 2013[200]	NICE CG117[10]	Pareek et al., 2013[76]	Swaminath et al., 2014[199]
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?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	N/A	Y	N	Y	N	Y	N
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

11.15 Appendix 15. Information required to derive diagnostic accuracy of various screening by population

Children

Table 62. Information used to derive sensitivity in the children population

Test	Total tested	Number of positives	Number of positives that developed active TB	Length of follow-up (years)	Source
QFT-G	306	6	0	3	Higuchi et al., 2009
TST (≥ 5mm)	306	200	0		
TST (≥ 10mm)	306	90	0		
QFT-GIT	104	21	6	2 - 4	Diel et al., 2011
TST (≥ 5mm)	104	40	6		
TST (≥ 10mm)	104	40	4		
QFT-GIT	5244	2669	39	3.8	Mahomed et al., 2011a
TST (≥ 5mm)	5244	2894	40		
QFT-G	59	18	10	1	Noorbakhsh et al., 2011
TST (≥ 10mm)	59	8	3		
QFT-GIT	2966	317	11	2	Song et al., 2014
TST (≥ 10mm)	2982	663	13		
TST (≥ 15mm)	2982	231	13		

Table 63. Information used to derive specificity in the children population

Test	Total tested	Number of negatives	Number of negatives that developed active TB	Length of follow-up (years)	Source
QFT-G	306	300	0	3	Higuchi et al., 2009
TST (< 5mm)	306	106	0		
TST (< 10mm)	306	216	0		
QFT-GIT	104	83	0	2 - 4	Diel et al., 2011
TST (< 5mm)	104	64	0		
TST (< 10mm)	104	64	2		

QFT-GIT	5244	2575	13	3.8	Mahomed et al., 2011a
TST (< 5mm)	5244	2350	12		
QFT-G	59	41	0	1	Noorbakhsh et al., 2011
TST (< 10mm)	59	50	7		
QFT-GIT	2966	2649	12	2	Song et al., 2014
TST (< 10mm)	2982	2319	10		
TST (< 15mm)	2982	2751	10		

Immunocompromised

Table 64. Information used to derive sensitivity in the immunocompromised population

Test	Total tested	Number of positives	Number of positives that developed active TB	Length of follow-up (years)	Source
T-SPOT.TB	265	89	4	1.17 (median)	Kim et al., 2011
TST (≥ 5mm)	288	26	1		
QFT-G	30	12	1	2	Lee et al., 2009
T-SPOT.TB	32	15	0		
TST (≥ 10mm)	32	20	1		
QFT-GIT	210	40	1	0.8 (median)	Moon et al., 2013
TST (≥ 5mm)	244	39	0		
QFT-GIT	159	26	3	1.3 (median)	Lee et al., 2014
TST (≥ 10mm)	169	19	0		
TST (≥ 15mm)	169	12	0		
T-SPOT.TB	44	6	1	1.75	Sherkat et al., 2014
TST (≥ 10mm)	44	8	1		

Table 65. Information used to derive specificity in the immunocompromised population

Test	Total tested	Number of negatives	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., 2011
TST (< 5mm)	288	262	3		
QFT-G	30	18	0	2	Lee et al., 2009
T-SPOT.TB	32	17	2		
TST (< 10mm)	32	12	1		
QFT-GIT	210	170	1	0.8 (median)	Moon et al., 2013
TST (< 5mm)	244	205	2		
QFT-GIT	159	133	2	1.3 (median)	Lee et al., 2014
TST (≥ 10mm)	169	150	5		
TST (≥ 15mm)	169	157	5		
T-SPOT.TB	44	38	0	1.75	Sherkat et al., 2014
TST (≥ 10mm)	44	36	0		

Recently arrived

Table 66. Information required to derive sensitivity in the recently arrived population

Test	Total tested	Number of positives	Number of positives that developed active TB	Length of follow-up (years)	Source
QFT-GIT	815	238	8	2.67	Harstad et al., 2010
TST (≥ 6mm)	810	415	8		
QFT-GIT	327	178	5	2	Kik et al., 2010
T-SPOT.TB	299	181	6		
TST (≥ 15mm)	322	184	7		

Table 67. Information required to derive specificity in the recently arrived population

Test	Total tested	Number of negatives	Number of negatives that developed active TB	Length of follow-up (years)	Source
QFT-GIT	815	577	1	2.67	Harstad et al., 2010
TST (≥ 6mm)	810	395	1		
QFT-GIT	327	149	3	2	Kik et al., 2010
T-SPOT.TB	299	118	2		
TST (≥ 15mm)	322	138	1		

11.16 Appendix 16. Illustrative structures for the immunocompromised, recent arrivals from countries with a high incidence of active TB and general population

Immunocompromised or people at risk of immunosuppression

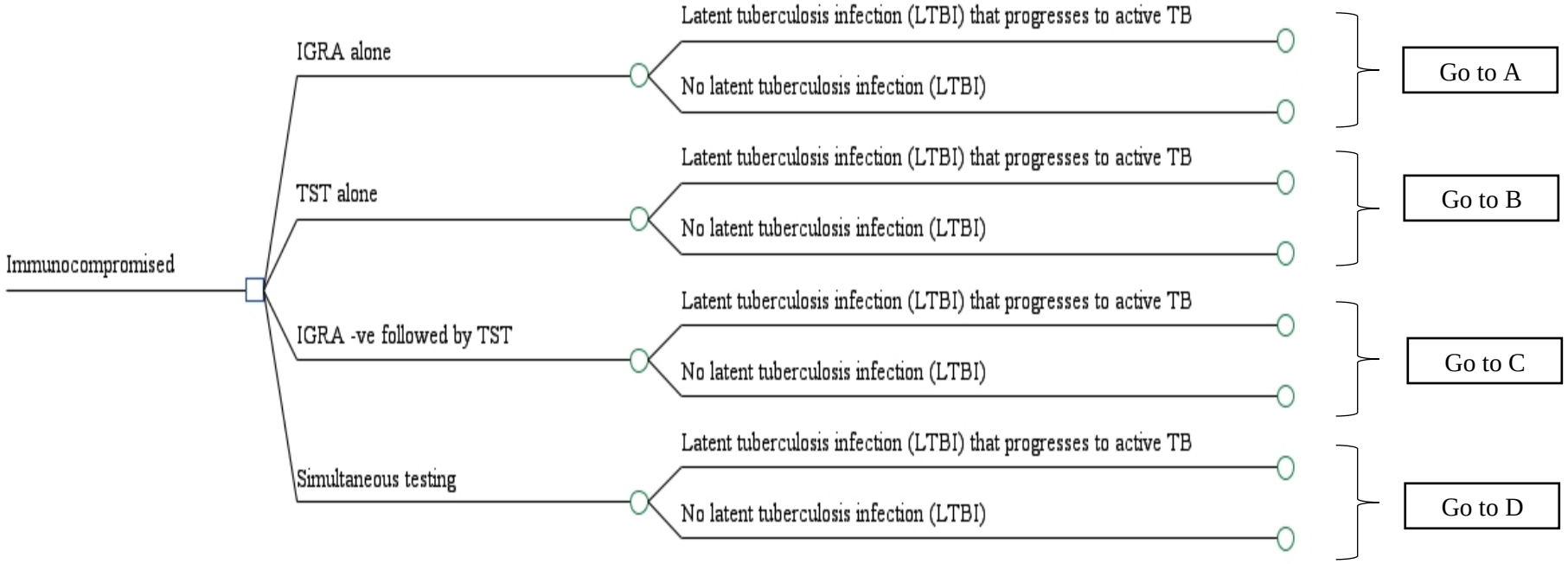

Figure 60. Decision tree pathway for the immunocompromised population

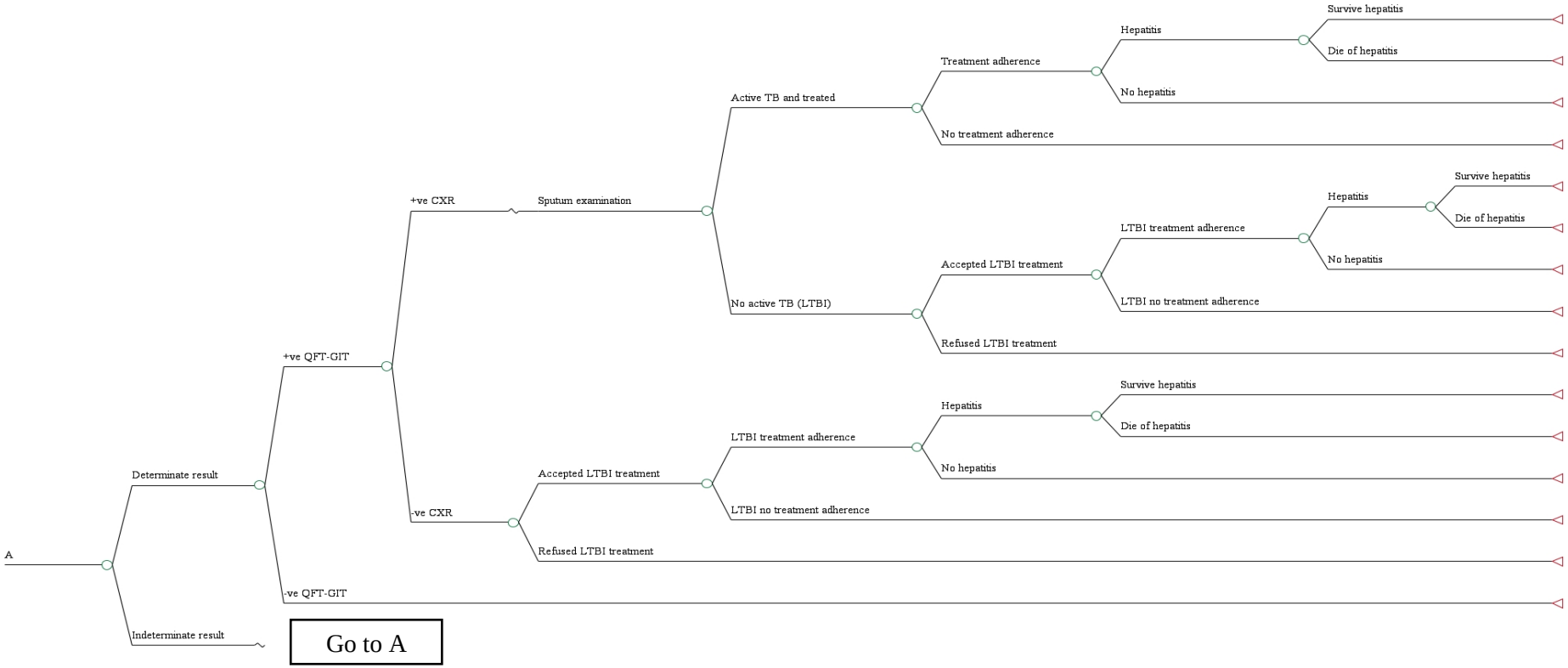

Figure 61. Pathway for the IGRA alone diagnostic strategy in the immunocompromised population

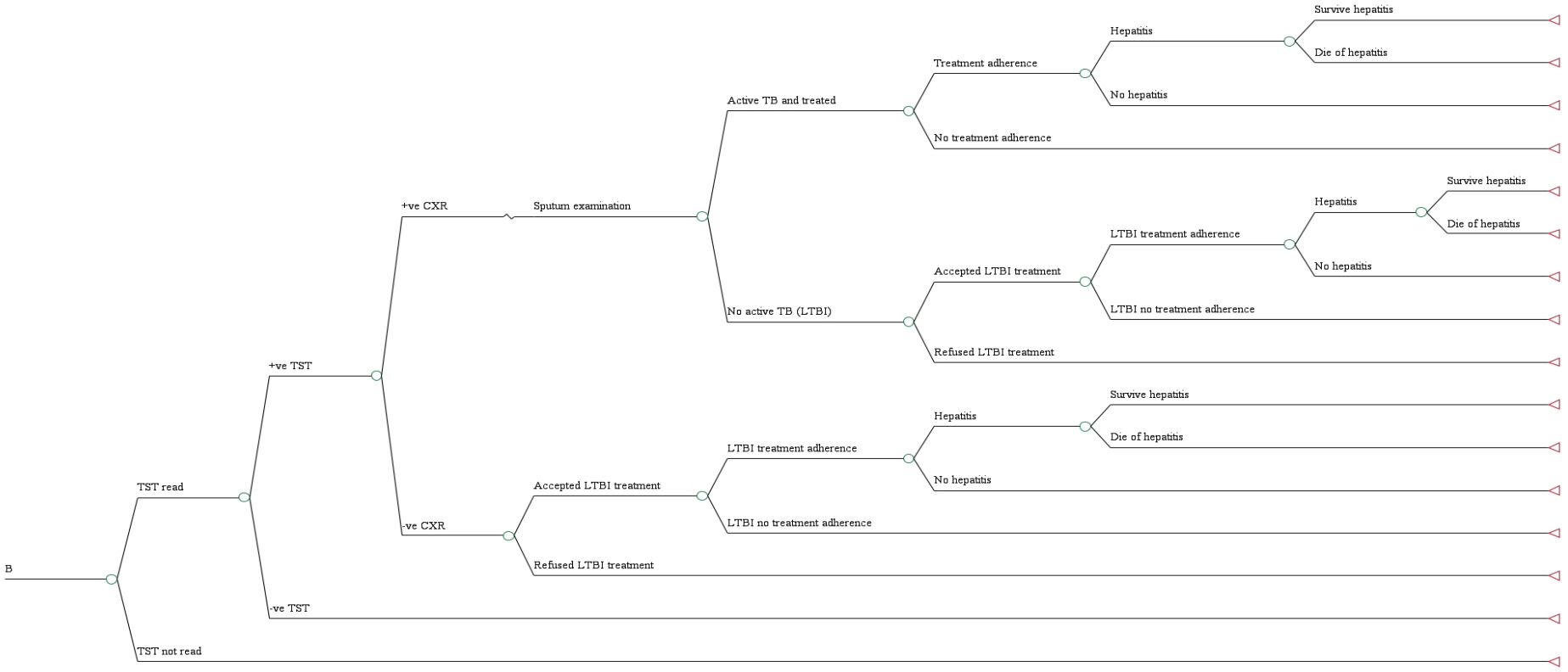

Figure 62. Pathway for the TST alone diagnostic strategy in the immunocompromised population

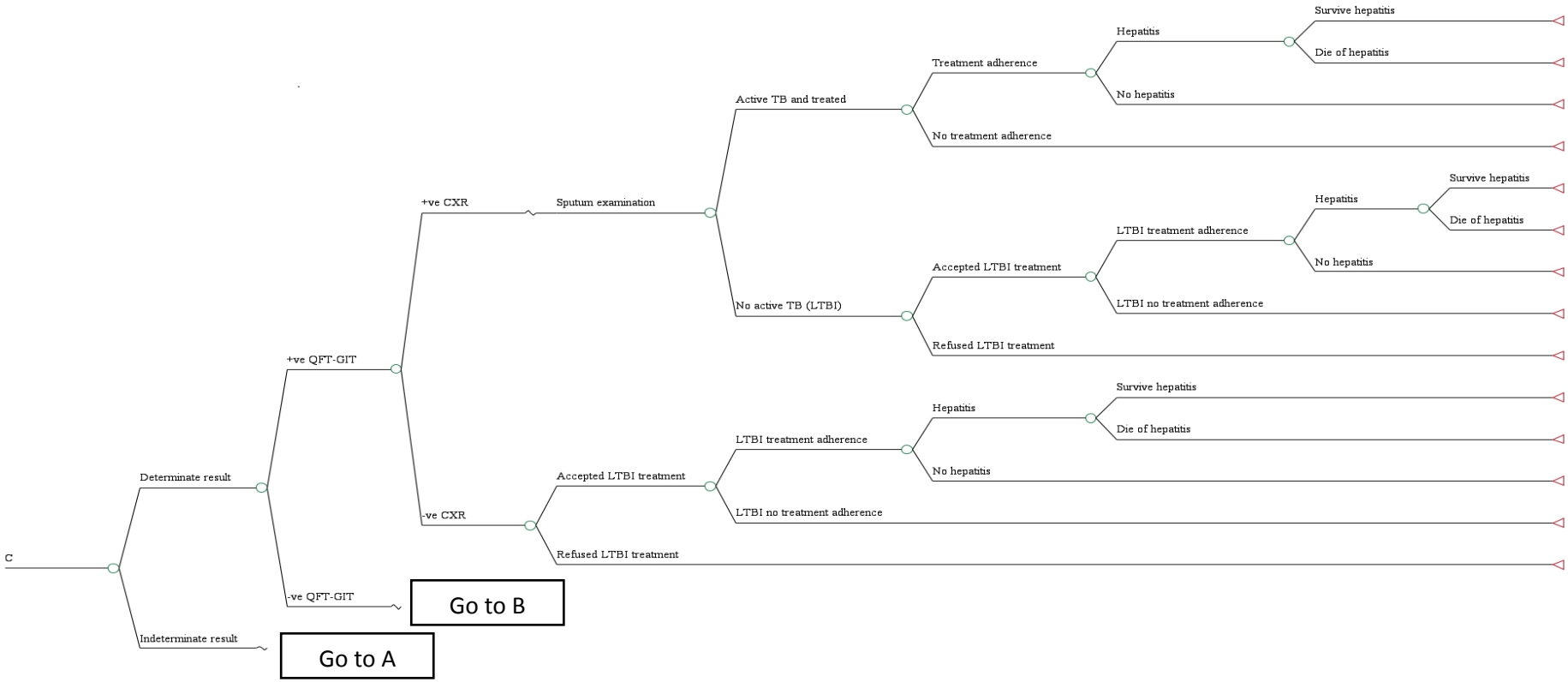

Figure 63. Pathway for the diagnostic strategy IGRA negative followed by TST in the immunocompromised population

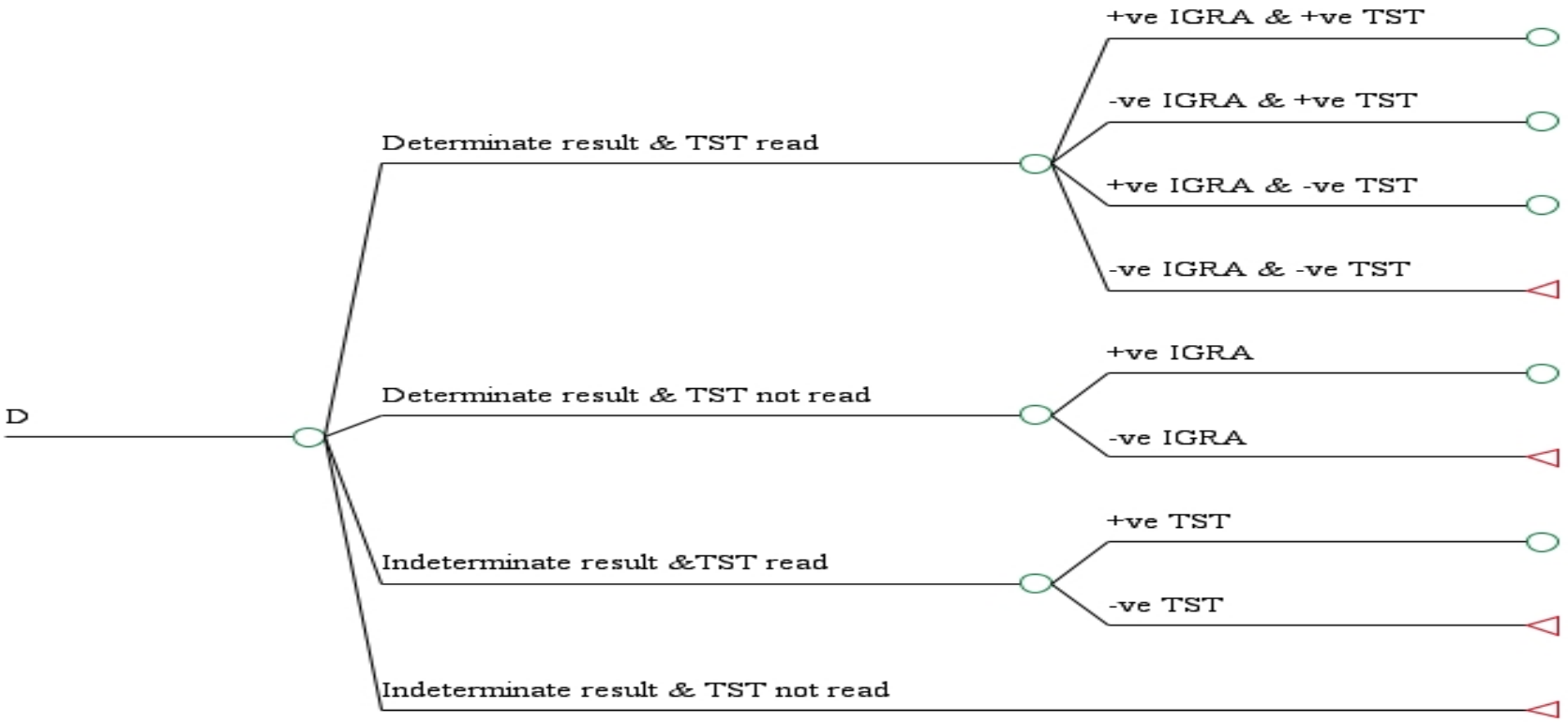

Figure 64. Pathway for the diagnostic strategy IGRA and TST in the immunocompromised population

Recent arrivals from countries with a high incidence of active TB

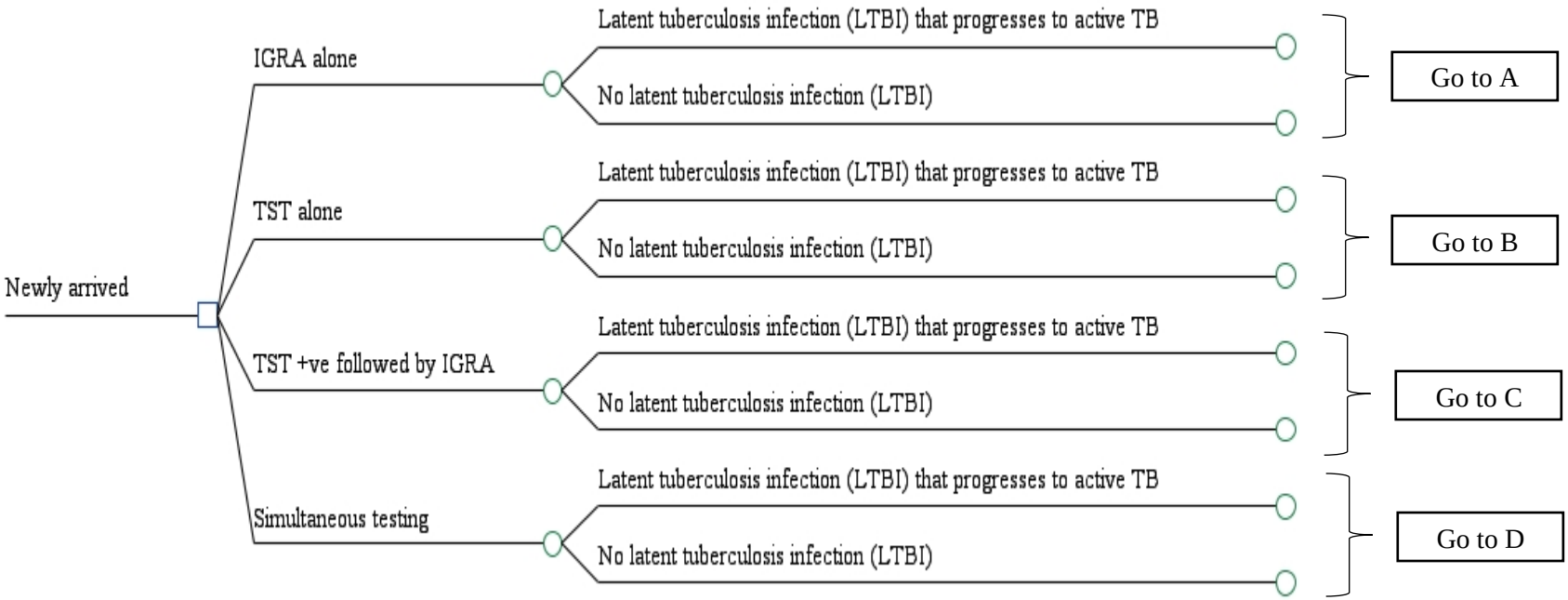

Figure 65. Decision tree structure for recent arrivals from countries with a high incidence of active TB

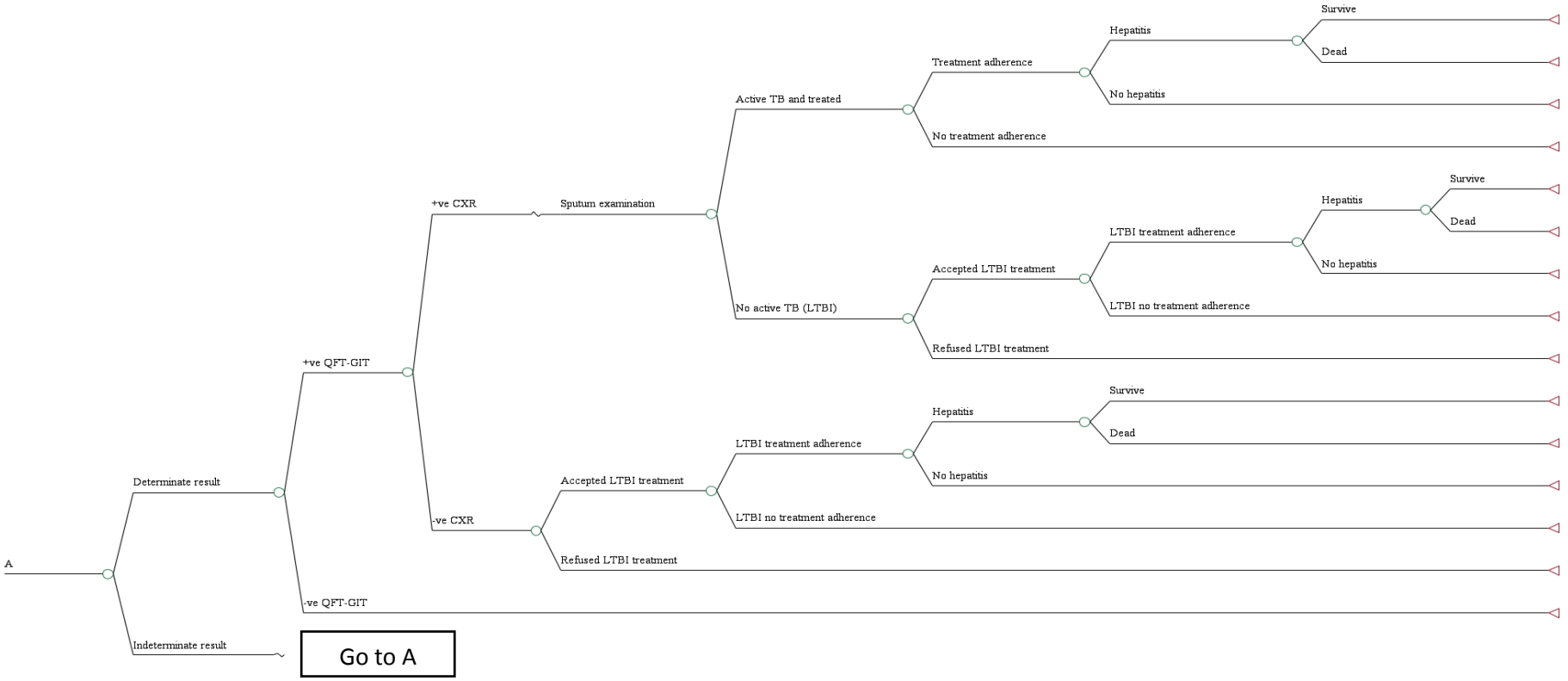

Figure 66. Pathway for IGRA alone diagnostic strategy in recent arrivals population

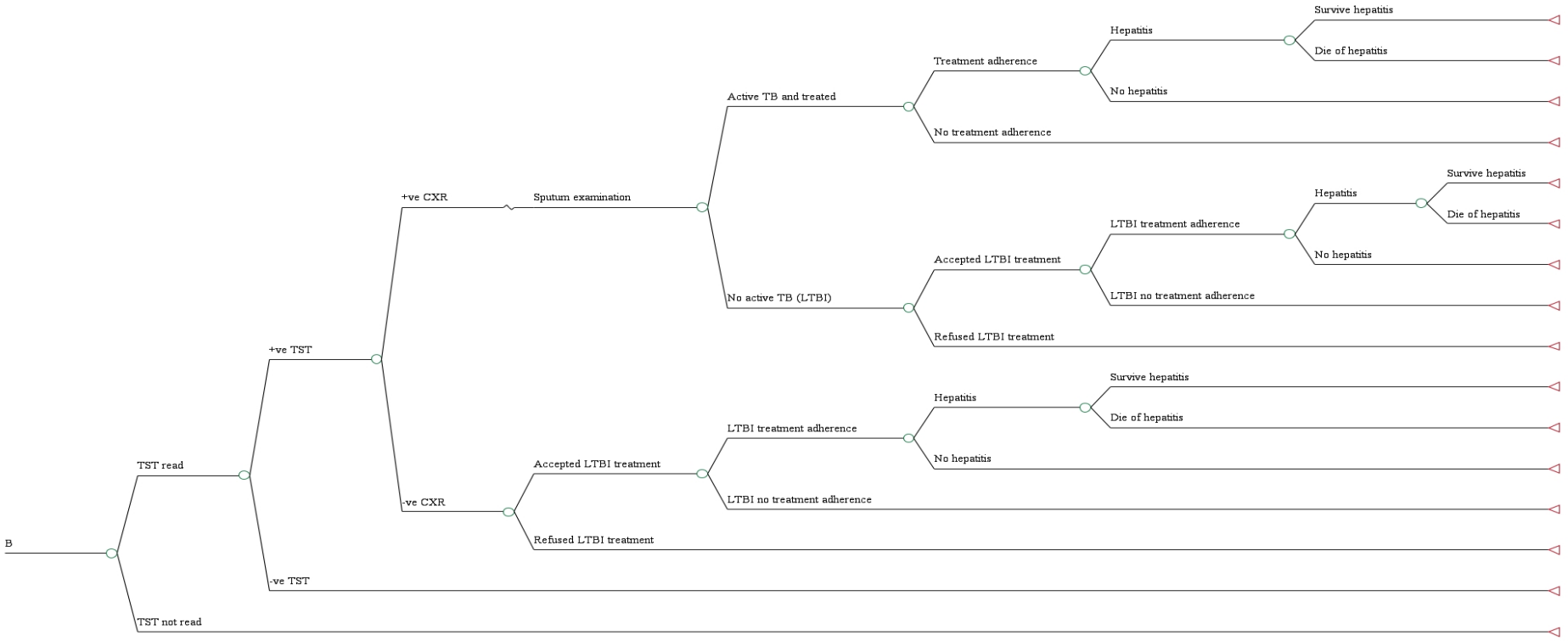

Figure 67. Pathway for the TST alone diagnostic strategy in the recent arrival population

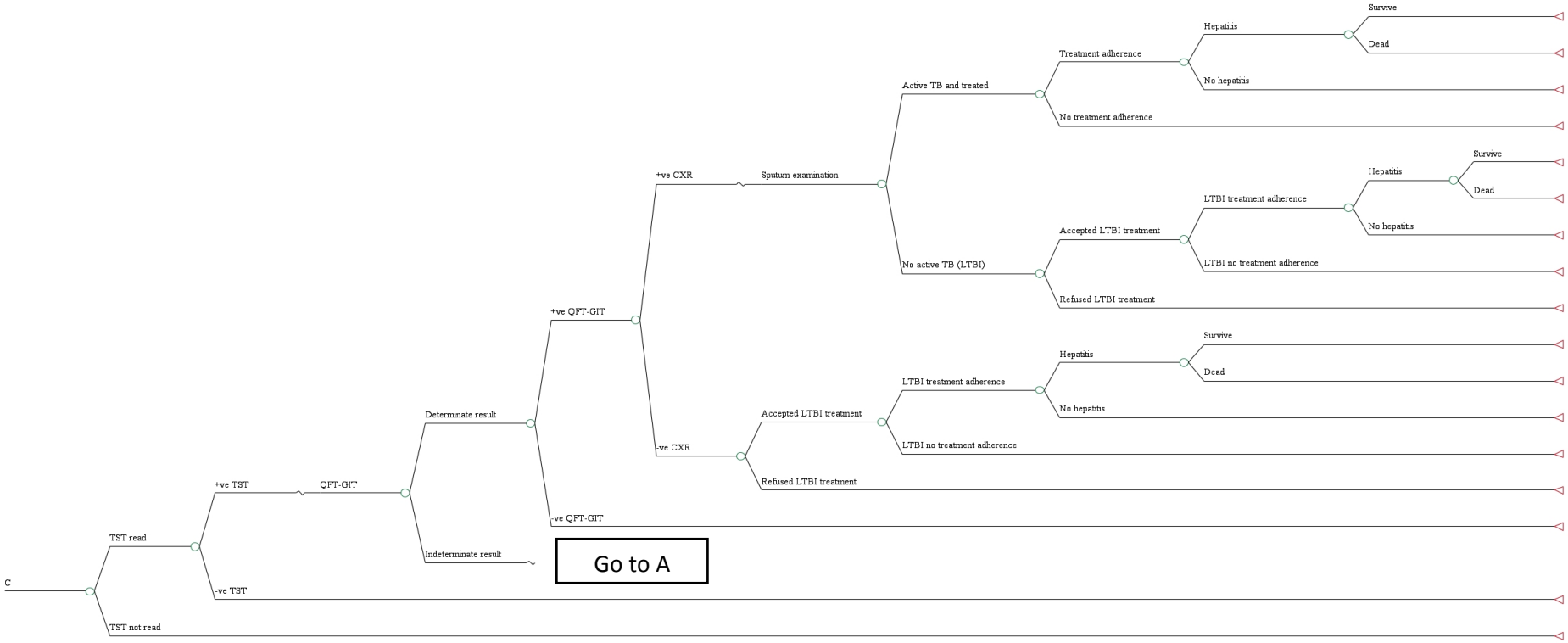

Figure 68. Pathway for the diagnostic strategy TST positive followed by IGRA in the recent arrivals population

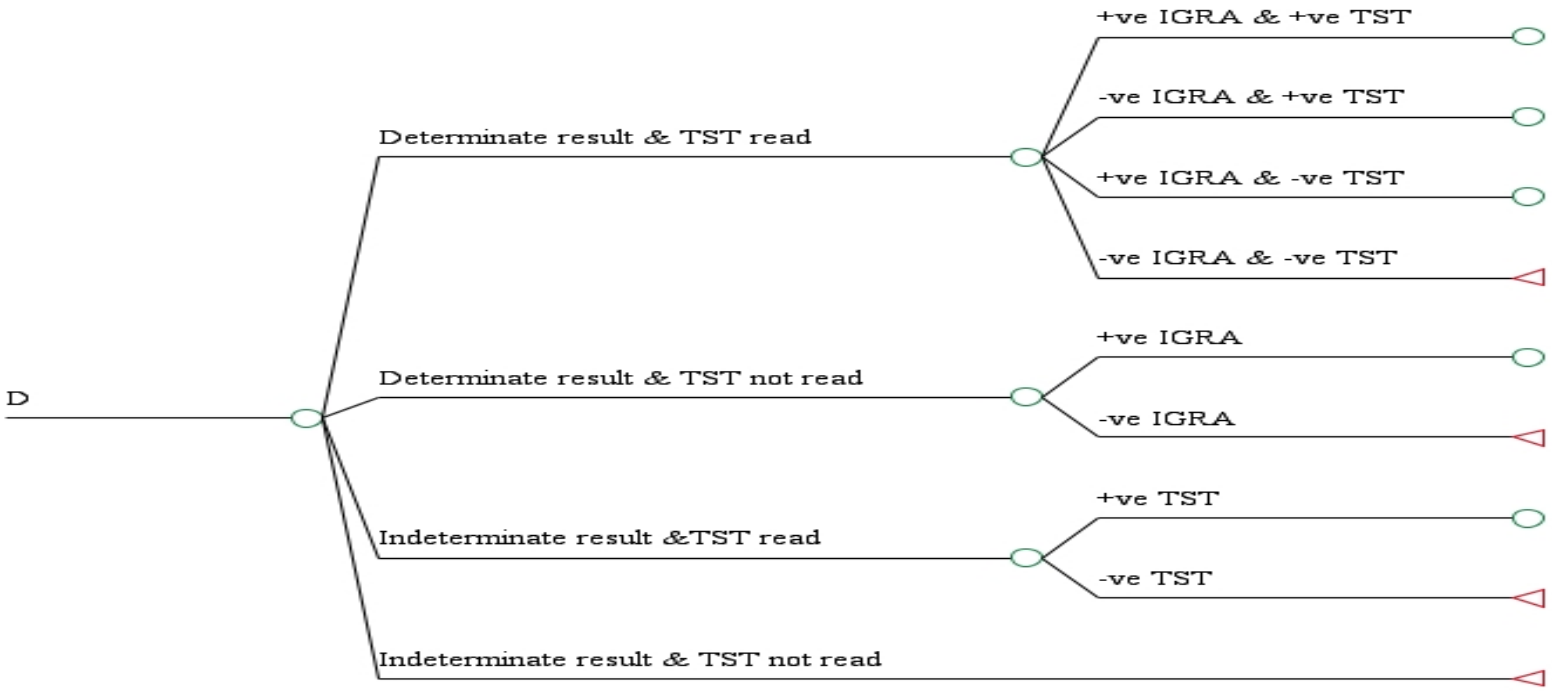

Figure 69. Pathway for the diagnostic strategy of IGRA and TST in the recent arrival population

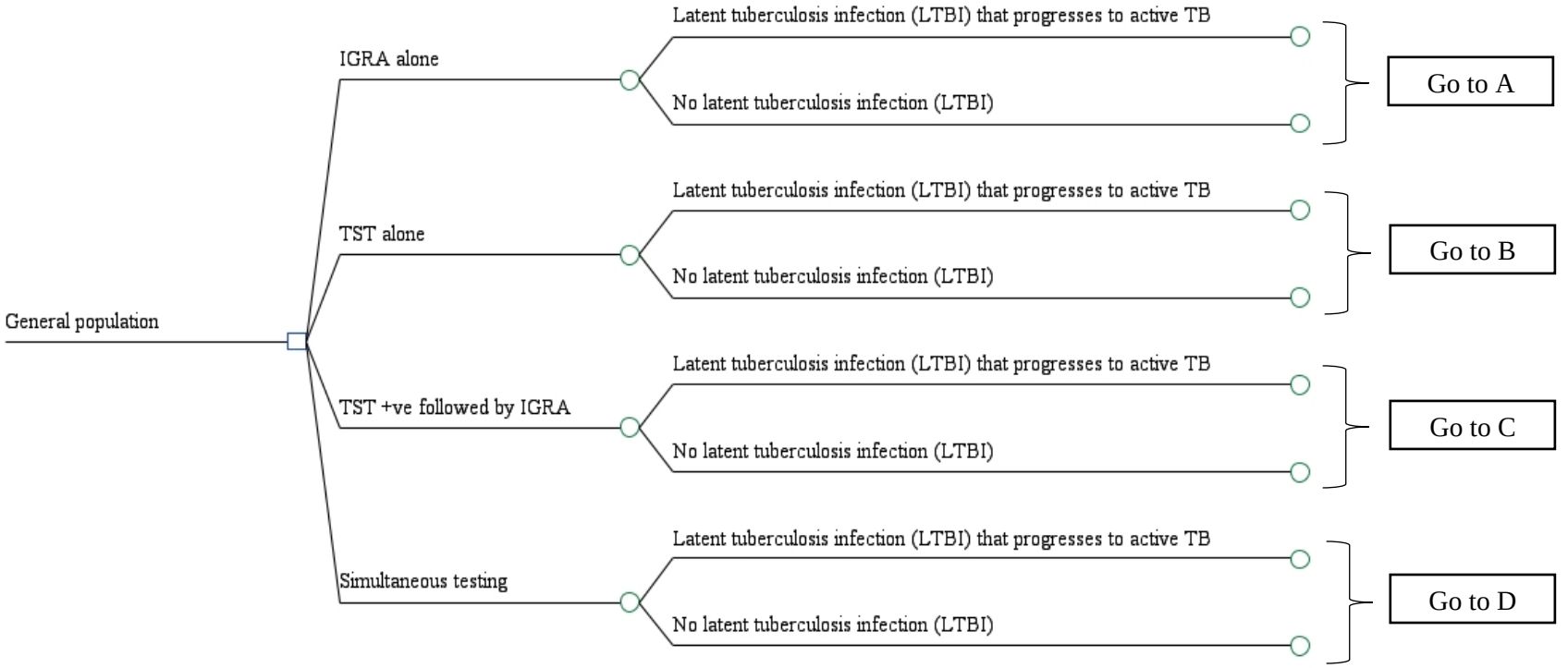

Figure 70. Decision tree structure for general population

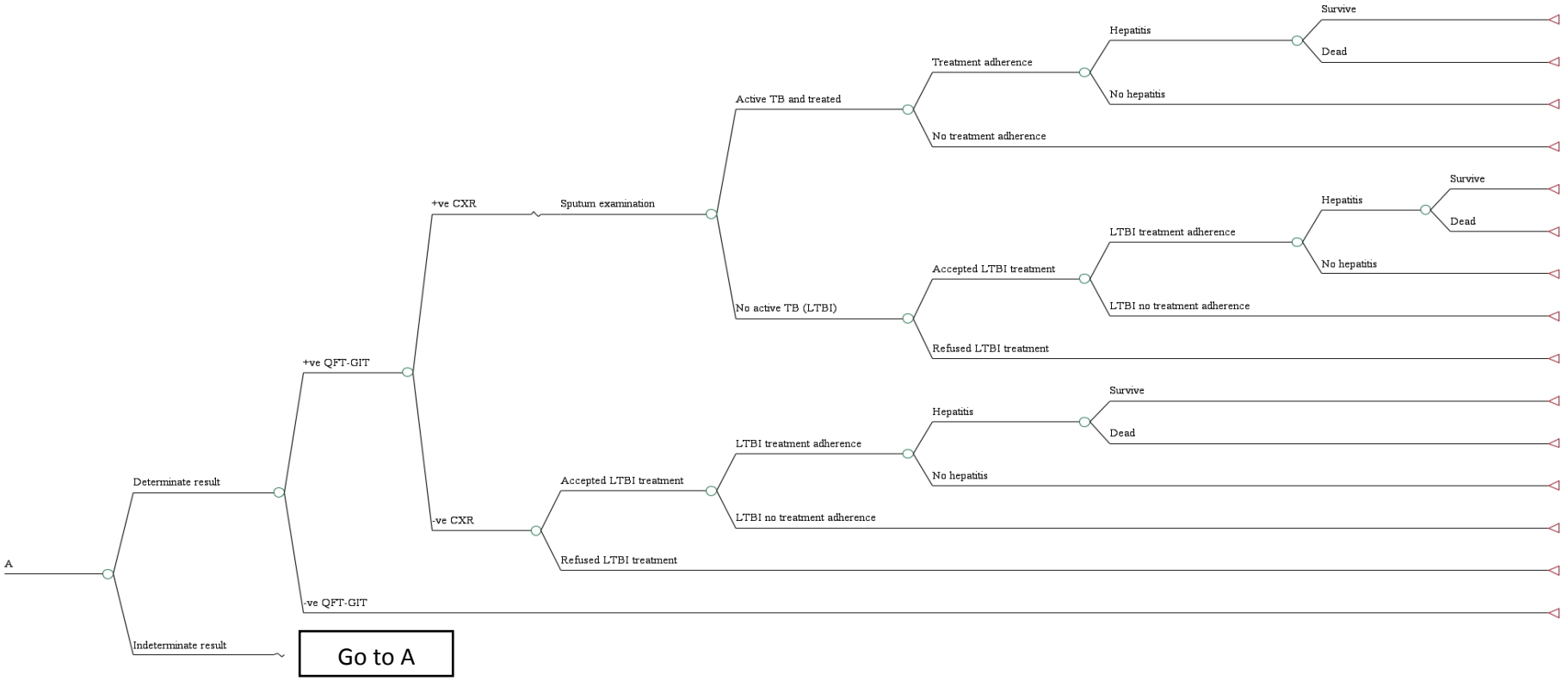

Figure 71. Pathway for the diagnostic strategy of IGRA alone in the general population

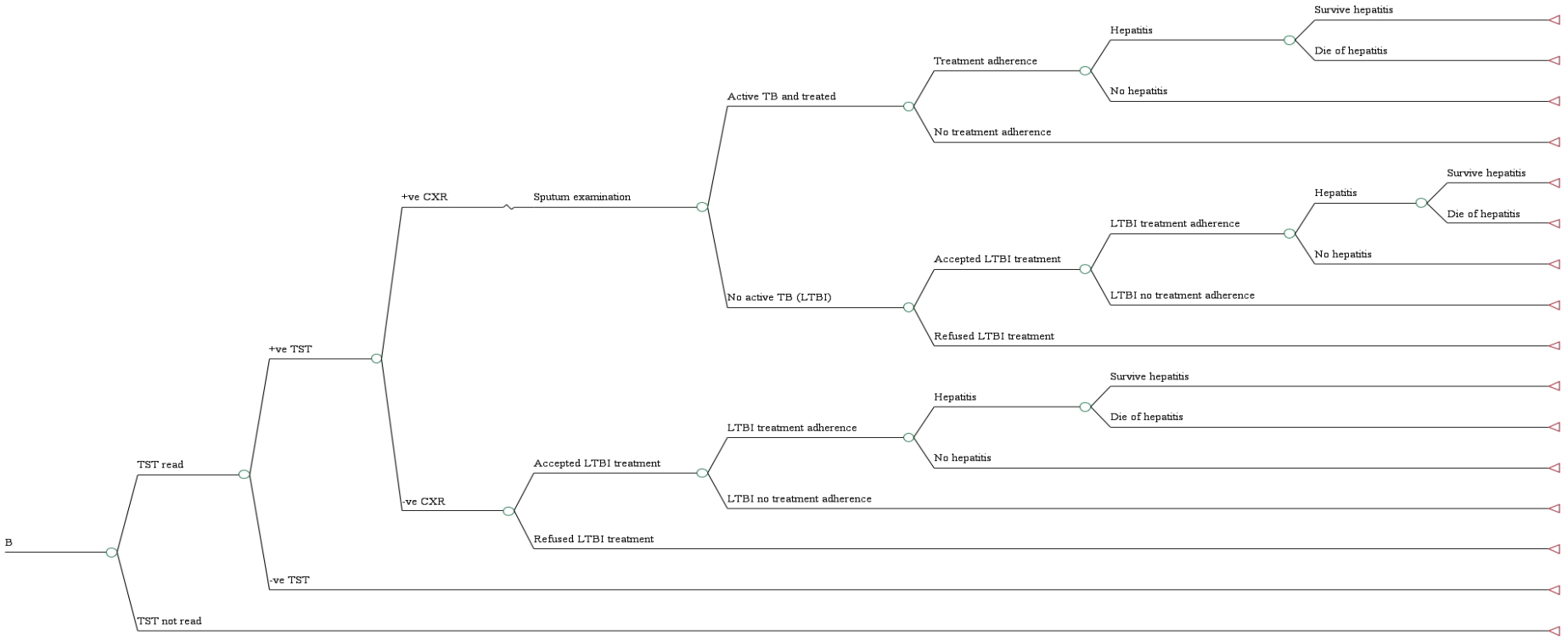

Figure 72. Pathway for the diagnostic strategy of TST alone in the general population

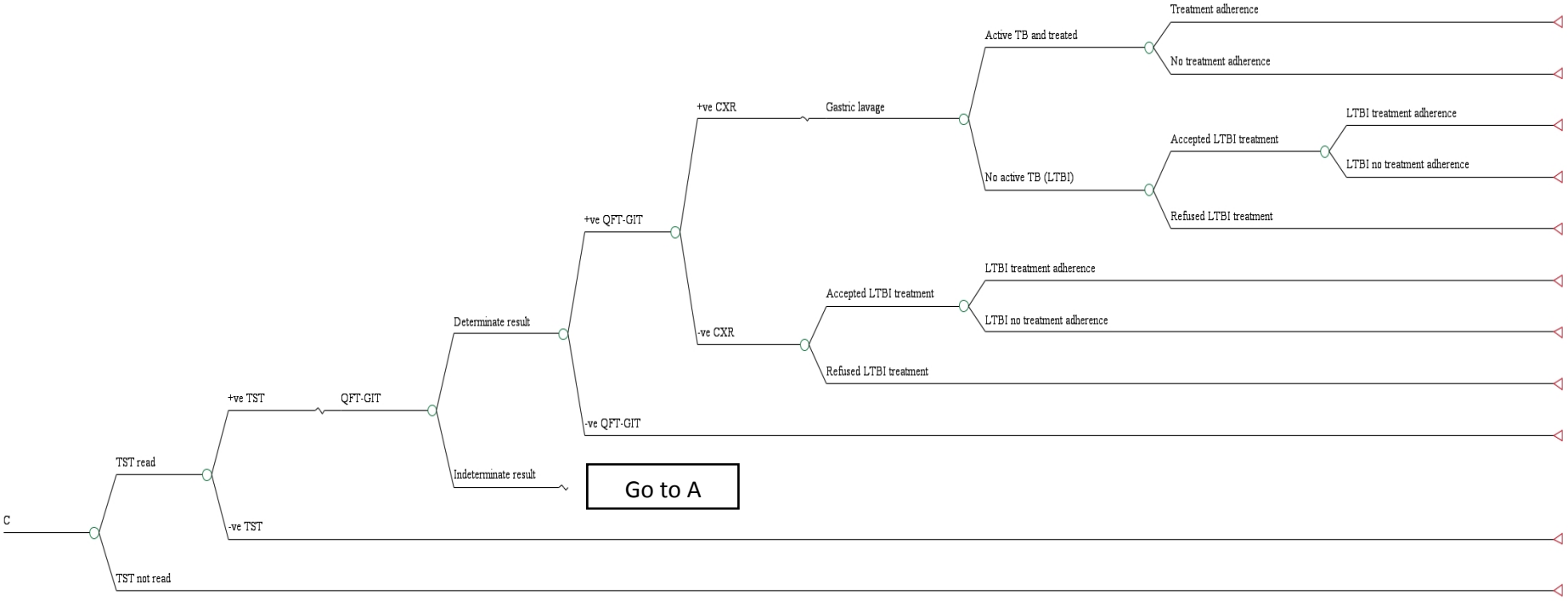

Figure 73. Pathway for the diagnostic strategy of TST +ve followed by IGRA in the general population

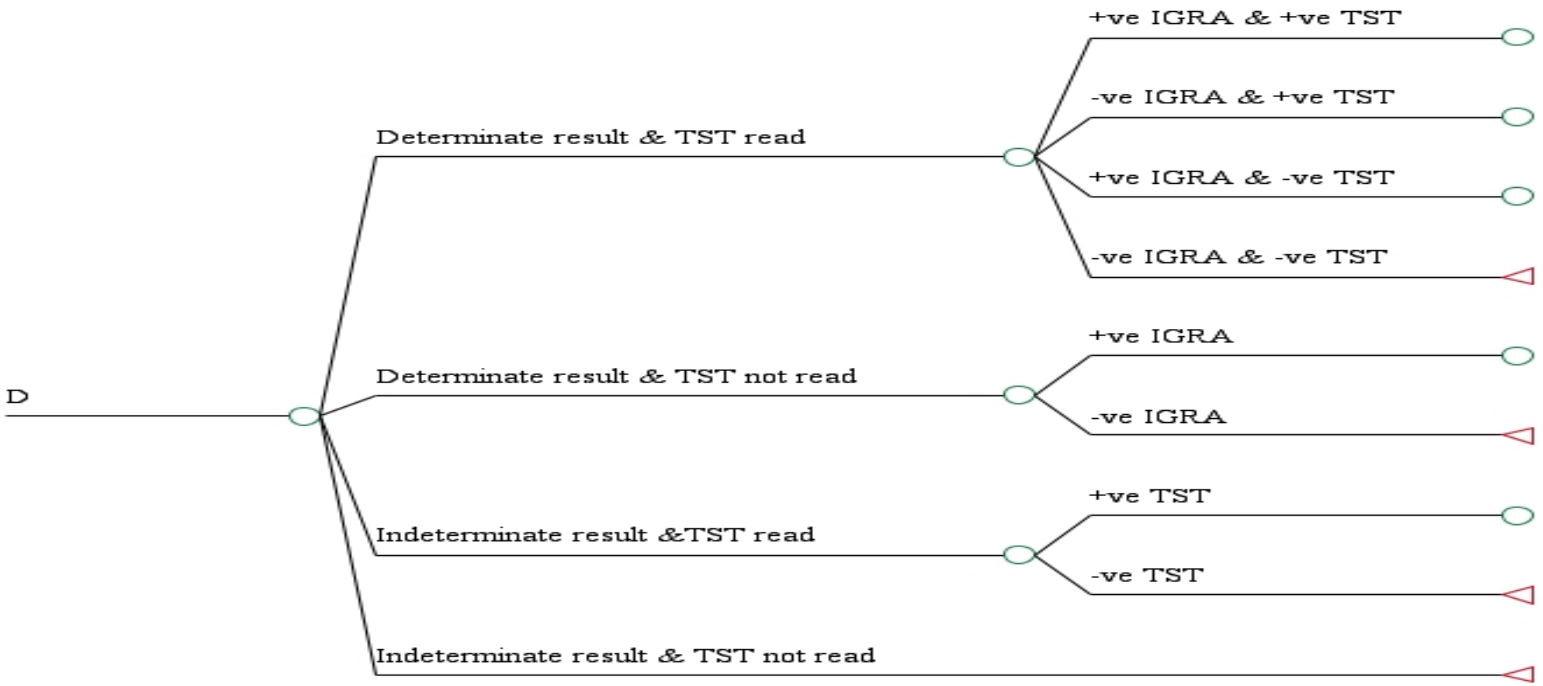

Figure 74. Pathway for the diagnostic strategy of IGRA and TST in the general population

11.17 Appendix 17. Resources used to derive unit cost for the treatment of LTBI and TB and model input parameters

Table 68. 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 FBC, LFTs and outpatient visits NHS reference costs 2012/13[207] Curtis 2013[210]
Liver function tests	4	DAPS08-phlebotomy	£4	
Outpatient visits	2 visits	Weighted average of all outpatient procedures	£135	
Nurse contact (in-clinic)[1]	3 visits	15 minutes	£12.25	Assumption and consultation with clinical expert; Curtis 2013[210]
Drug treatment				
Isoniazid (6H)	18pks (28 tab 100mg per pack)	Six months of Isoniazid[2]	£19.24	NHS electronic drug tariff
Estimated cost for treatment of LTBI per person				**£677.07 (6H)**

[1]We assumed a nurse specialist employed on the NHS scale agenda for change Band 6 point 27 would require 15 minutes of contact time with an LTBI patient
[2]Based on people requiring 300mg daily for six months.
[3]People who refuse treatment are informed and advised. We assumed 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

Table 69. Treatment for tuberculosis

Resource use	Quantity	Description	Unit costs (£,2013)	Source
Investigations				
Chest x-ray	3	DAPF- direct access plain film	28	NHS reference costs 2012/13[207]
Sputum examination	6	DAPS07- microbiology	7	
Full blood count	2	DAPS08- phlebotomy	4	
Liver function tests	8	DAPS08- phlebotomy	4	
Inpatient stay	7.28 days	DZ14E- Pulmonary, Pleural or Other Tuberculosis, with CC Score 0-1	492	Bothamley et al. (2002)[209]
Outpatient visits	8 visits	Weighted average of all outpatient procedures	135	
Drug treatment				
Ethambutol	6pks	(1200mg daily for two months)	256.44	BNF 2013-14[228]
Pyrazinamide	8pks	(2g daily for two months)	250.80	BNF 2013-14[228]
Rifinah (300/150)	6pks	Two tablets daily for six months	126.12	BNF 2013-14[228]
Estimated cost for treatment of active TB per person				**£5461.12**

Table 70. Model input parameters required for the immunocompromised population

Variable	Base-case value	Range for SA	PSA Distribution	Reference(s)
Probabilities				
Prevalence of LTBI	0.0222	0.0152 – 0.0306	#	
Sensitivity TST (≥5mm)	0.3242	0.1119 – 0.5848	#	
Specificity TST (<5mm)	0.7422	0.7288-0.7557	#	
Sensitivity TST (≥10mm)	0.1682	0.0252-0.3899	#	
Specificity TST (>10mm)	0.8397	0.7899-0.8831	#	Derived from our clinically effectiveness study
Sensitivity QFT-GIT	0.5548	0.2473-0.8373	#	
Specificity QFT-GIT	0.8227	0.8052-0.8396	#	
Sensitivity T-SPOT.TB	0.6665	0.3517-0.9144	#	
Specificity T-SPOT.TB	0.6846	0.6346-0.7331	#	
Sensitivity of TST conditional on -ve QFT-GIT (LTBI arm)	0.2775	0.0121-0.7989	Not varied	
Specificity of TST conditional on -ve QFT-GIT (No LTBI arm)	0.4465	0.3909-0.4993	Not varied	
Sensitivity of TST conditional on +ve QFT-GIT (LTBI arm)	0.4206	0.0023-0.3891	Not varied	
Specificity of TST conditional on +ve 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. (2013)[197]
Determinate T-SPOT.TB	0.97	-	Beta(873,27)	Derived from Laskin et al. (2013)[197]
Probability of TST read	0.9400	0.6 – 1.00	Beta(164,10.5)	Pareek et al. (2013)[76]
Probability of initial active TB	0.00001	-	Not varied	Laskin et al. (2013)[197]
TB treatment adherence	1.0000	-	Not varied	Pareek et al. (2013)[76]
Accepting LTBI treatment	0.9400	0.50 – 1.00	Beta(141,9)	CG117 (2011)[10]
Adherence to LTBI treatment	0.8000	0.50 – 0.90	Beta(41,10)	Kowada (2013)[195]
INH hepatitis after TB treatment	0.0040	0.001 - 0.010	Beta(2.7,664)	Assumption
INH hepatitis after LTBI treatment	0.0040	0.001 - 0.010	Beta(2.7,664)	Laskin et al. (2013)[197]
Death from INH hepatitis	0.00002	0.00001-0.0001	Beta(0.5,25125)	Pooran et al., (2010)[206]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	-	Lognormal (-1.065,0.842)	White and Jit (2015)[212]
Average number of secondary cases from one index case	0.2	0.1-0.3	Lognormal (-1.609,0.354)	Pareek et al. (2011)[6]
Average delay from infection to activation	2.88	-	Lognormal (1.058,0.333)	Okuonghae et al. (2013)[213]

Variable	Base-case value	Range for SA	PSA Distribution	Reference(s)
Annualised reactivation rate from resolved TB	0.013	0.004-0.025	Beta(7,513)	Oxlade et al. (2011)[214]
Case fatality rate for active TB (0-4 years)	0.0477	-	Beta(628,12543)	Croft et al. (2008)[215]
Case fatality rate for active TB (5-14 years)	0.0034	-	Beta(1,290)	Croft et al. (2008)[215]
Case fatality rate for active TB (15-44 years)	0.0018	-	Beta(1,564)	Croft et al. (2008)[215]
Case fatality rate for active TB (45-64 years)	0.0476	-	Beta(125,2500)	Croft et al. (2008)[215]
Case fatality rate for active TB (65+ years)	0.1755	-	Beta(413,1940)	Croft et al. (2008)[215]
Resource use and costs				
TST	17.48		Not varied	Pooran et al. (2010)[206]
QFT-GIT	48.73		Not varied	Pooran et al. (2010)[206]
T-SPOT.TB	59.57		Not varied	Pooran et al. (2010)[206]
Chest x-ray	35.00		Not varied	NHS costs 2012/13[207]
Sputum examination	7.00		Not varied	NHS costs 2012/13[207]
Adherence to active TB treatment	5461.12		Gamma(10.41,524.6)	Bothamley et al. (2002)[209]
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 drug tariff (2014)[208]
Cost of non-adherence to LTBI treatment	112.85		Uniform(85.24,140.41)	Assumption
Treatment of INH-induced hepatitis	389.51		Gamma(7.13,55.64)	Pareek et al. (2013)[76]
Utility decrements				
Active TB (whilst on treatment)	0.15[†]	Not reported	Gamma(11.2,0.0134)	Derived from Kowada (2012)[194]
Treatment for LTBI	0.0010	Not reported	Uniform(0,0.002)	
Other				
Discount rate per annum (costs and QALYs)	3.5%			

BNF, British National Formulary; IGRA, Interferon-gamma release assay; INH, Isoniazid; LTBI, Latent tuberculosis infection; QFT-G, QuantiFERON Gold; QFT-GIT, QuantiFERON Gold-In-Tube; SA, Sensitivity analysis; TB, tuberculosis; TST, Tuberculin skin test;

* Management of LTBI in children includes drug treatment alone

[†] QALY decrement for people being treated for active TB

[#] Calculated from posterior distributions generated by Markov Chain Monte Carlo (MCMC)

Table 71. Model input parameters required for the recent arrivals population

Variable	Base-case value	Range for SA	PSA Distribution	Reference(s)
Probabilities				
Prevalence of LTBI	0.0237	0.0150-0.0345	#	Derived from our clinically effectiveness study
Sensitivity TST (≥5mm)	0.9356	0.7786-0.9977	#	
Specificity TST (<5mm)	0.5011	0.4790-0.5229	#	
Sensitivity QFT-GIT	0.5915	0.3584-0.8172	#	
Specificity QFT-GIT	0.7929	0.7780-0.8073	#	
Sensitivity T-SPOT.TB	0.7001	0.3978-0.9242	#	
Specificity T-SPOT.TB	0.3992	0.3439-0.4554	#	
Sensitivity of QFT-GIT conditional on +ve TST (LTBI arm)	0.6009	0.3465-0.8514	#	
Specificity of QFT-GIT conditional on +ve TST (No LTBI arm)	0.6102	0.5775-0.6421	#	
Sensitivity of QFT-GIT conditional on -ve TST (LTBI arm)	0.4807	0.0225-0.9724	#	
Specificity of QFT-GIT conditional on -ve TST (No LTBI arm)	0.9746	0.9555-0.9893	#	
Sensitivity of CXR for diagnosing active TB	0.7800	Not reported	Not varied	Kumar et al. (2005)[211]
Specificity of CXR for diagnosing active TB	0.5100	Not reported	Not varied	Kumar et al. (2005)[211]
Determinate QFT-GIT	0.97	-	Beta(873,27)	Derived from Laskin et al. (2013)[197]
Determinate T-SPOT.TB	0.97	-	Beta(873,27)	Derived from Laskin et al. (2013)[197]
Probability of TST read	0.9400	0.6 – 1.00	Beta(164,10.5)	Pareek et al. (2013)[76]
Probability of initial active TB	0.00001	-	Not varied	Laskin et al. (2013)[197]
TB treatment adherence	1.0000	-	Not varied	Pareek et al. (2013)[76]
Accepting LTBI treatment	0.9400	0.50 – 1.00	Beta(141,9)	CG117 (2011)[10]
Adherence to LTBI treatment	0.8000	0.50 – 0.90	Beta(41,10)	Kowada (2013)[195]
INH hepatitis after TB treatment	0.0040	0.001 - 0.010	Beta(2.7,664)	Assumption
INH hepatitis after LTBI treatment	0.0040	0.001 - 0.010	Beta(2.7,664)	Laskin et al. (2013)[197]
Death from INH hepatitis	0.00002	0.00001-0.0001	Beta(0.5,25125)	Pooran et al. (2010)[206]
Transmission model parameters				
Proportion still infected post LTBI treatment	0.345	-	Lognormal (-1.065,0.842)	White and Jit (2015)[212]
Average number of secondary	0.2	0.1-0.3	Lognormal	Pareek et al.

Variable	Base-case value	Range for SA	PSA Distribution	Reference(s)
cases from one index case			(-1.609,0.354)	(2011)[6]
Average delay from infection to activation	2.88	-	Lognormal (1.058,0.333)	Okuonghae et al. (2013)[213]
Annualised reactivation rate from resolved TB	0.013	0.004-0.025	Beta(7,513)	Oxlade et al. (2011)[214]
Case fatality rate for active TB (0-4 years)	0.0477	-	Beta(628,12543)	Croft et al. (2008)[215]
Case fatality rate for active TB (5-14 years)	0.0034	-	Beta(1,290)	Croft et al. (2008)[215]
Case fatality rate for active TB (15-44 years)	0.0018	-	Beta(1,564)	Croft et al. (2008)[215]
Case fatality rate for active TB (45-64 years)	0.0476	-	Beta(125,2500)	Croft et al. (2008)[215]
Case fatality rate for active TB (65+ years)	0.1755	-	Beta(413,1940)	Croft et al. (2008)[215]
Resource use and costs				
TST	17.48		N/A	Pooran et al. (2010)[206]
QFT-GIT	48.73		N/A	Pooran et al. (2010)[206]
T-SPOT.TB	59.57		N/A	Pooran et al. (2010)[206]
Chest x-ray	35.00		N/A	NHS costs 2012/13[207]
Sputum examination	7.00		N/A	NHS costs 2012/13[207]
Cost of adherence to active TB treatment	5461.12		Gamma(10.41,524.6)	Bothamley et al. (2002)[209]
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 drug tariff 2014[208]
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. (2013)[76]
Utility decrements				
Active TB (whilst on treatment)	0.15[†]	Not reported	Gamma(11.2,0.0134)	Derived from Kowada (2012)[194]
Treatment for LTBI	0.001	Not reported	Uniform(0,0.002)	
Other				
Discount rate per annum (costs and QALYs)	3.5%			

BNF, British National Formulary; IGRA, Interferon-gamma release assay; INH, Isoniazid; LTBI, Latent tuberculosis infection; N/A, Not applicable; QFT-G, QuantiFERON Gold; QFT-GIT, QuantiFERON Gold-In-Tube; SA, Sensitivity analysis; TB, tuberculosis; TST, Tuberculin skin test;

[†] QALY decrement for people being treated for active TB

Calculated from posterior distributions generated by Markov Chain Monte Carlo (MCMC)

11.18 Appendix 18. WinBUGS code

In this Appendix we report on the WinBUGS code used in the evidence synthesis for the children population. The WinBUGS codes used for the immunocompromised and recently arrived populations are very similar, but using different sample data. Table 72 shows the variables with descriptions used in the models.

Table 72. 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
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

Children

```
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(84,84,73,84,84,84,306,306,306,306,306,306,104,104,104,10
4,104,104,5244,5244,5244,5244,5244,5244,59,59,59,59,59,59,69,69,69,69,69,69,204,204,204,204,20
4,204,195,195,195,195,195,195,184,184,184,184,184,184,1073,1073,1073,1073,1073,1073,104,104,1
04,104,104,104,50,50,50,50,50,50,2982,2966,2982,2982,2982,2982),.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,
NA),
rplusTST10=c(38,200,40,2894,NA,42,NA,NA,84,645,27,NA,NA),rplusTST10=c(NA,90,40,NA,8,N
A,115,47,NA,NA,NA,32,663),rplusTST15=c(NA,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,N
A,NA,NA,NA,NA,NA,13),ATBnegTST10=c(NA,0,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA),ATBneg
TST10IT=c(NA,NA,0,13,NA,NA,NA,NA,NA,NA,NA,NA,12),ATBnegTSPOTTB=c(NA,NA,NA,N
A,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),rnegTST10TST
10IT=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 appears 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.

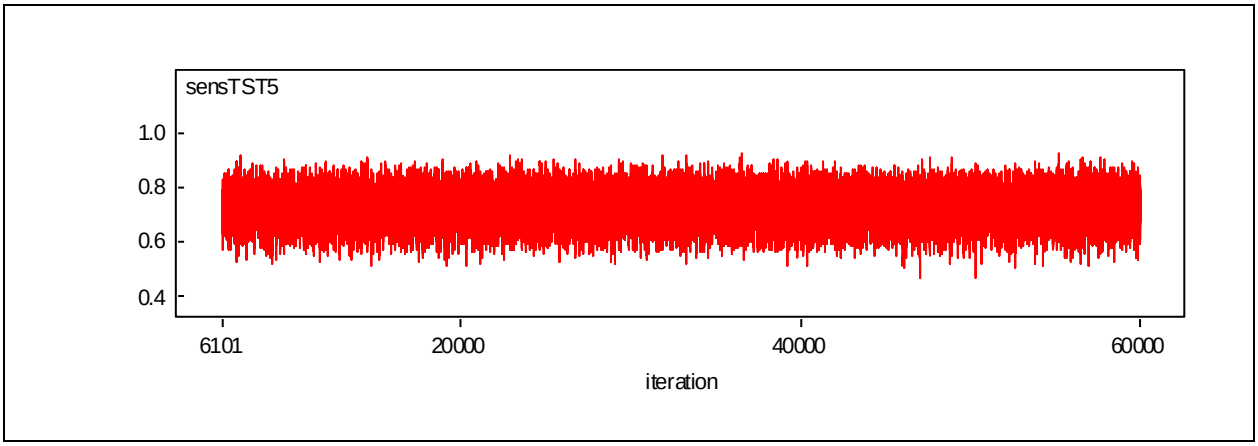

Figure 75. Sample traces of chains for sensitivity of TST (≥ 5mm) where convergence/mixing looks reasonable

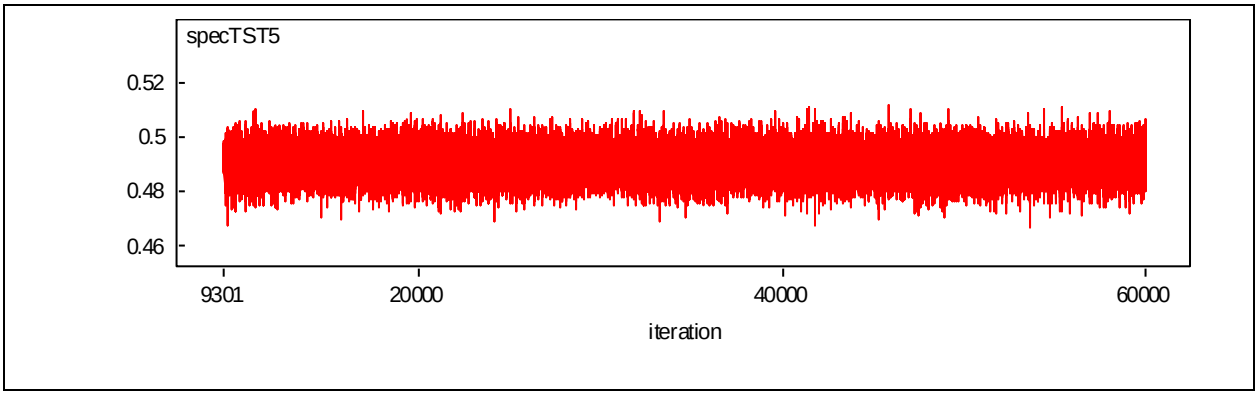

Figure 76. Sample traces of chains for specificity of TST (< 5mm) where convergence/mixing looks reasonable

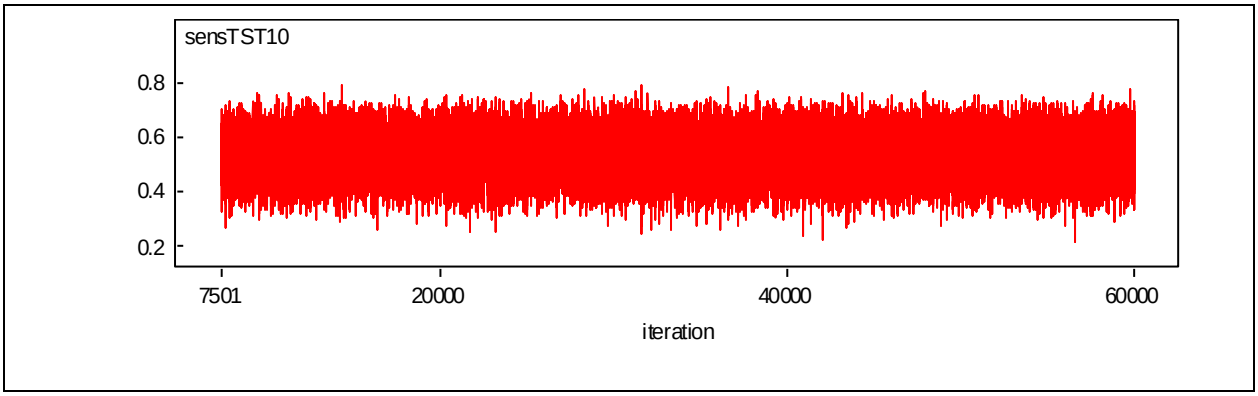

Figure 77. Sample traces of chains for sensitivity of TST (≥ 10mm)

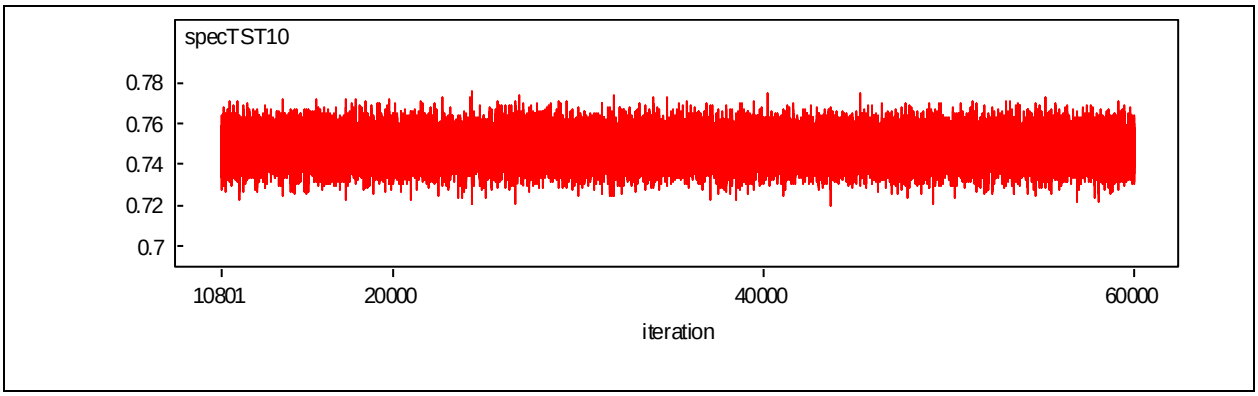

Figure 78. Sample traces of chains for specificity of TST (< 10mm)

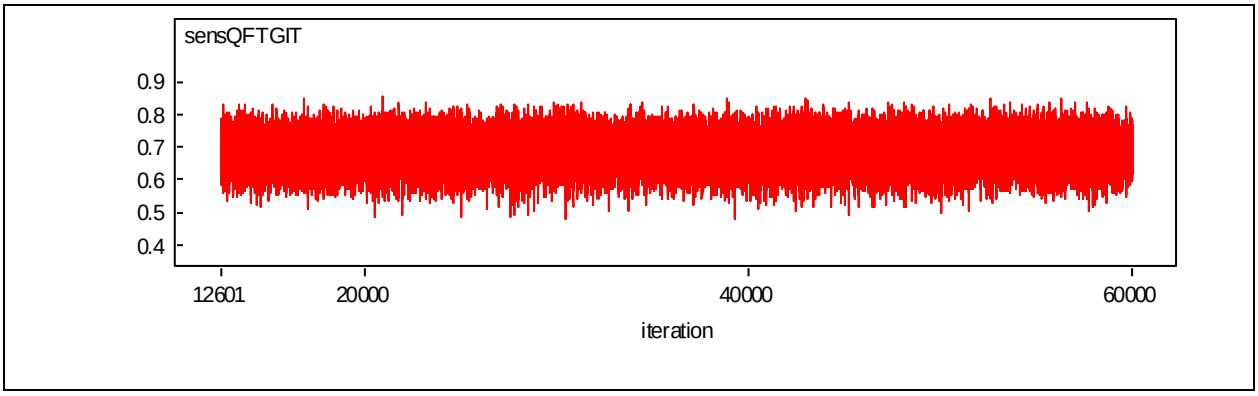

Figure 79. Sample traces of chains for sensitivity of QFT-GIT

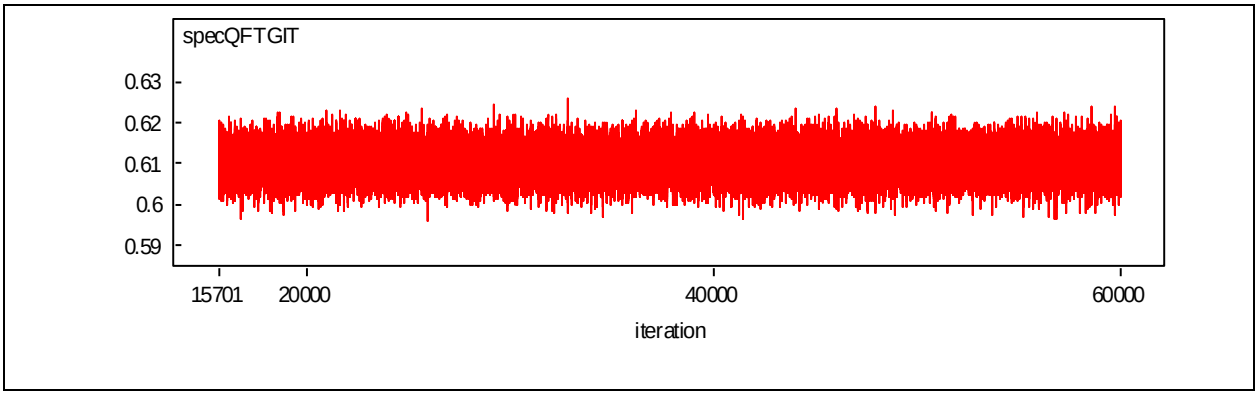

Figure 80. Sample traces of chains for specificity of QFT-GIT