Pathology tests for latent mycobacterial infection

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The Medical Services Advisory Committee (MSAC) is an independent committee, which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by Bridie Murphy, Patti Whyte, and Liliana Bulfone from Deakin Health Technology Assessment Group (DHTAG), Deakin Health Economics, Deakin University and an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of the Medical Services Advisory Committee (MSAC). It was edited by Words Editing Services.

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Purpose of Application

An application requesting MBS listing of interferon gamma release assays (IGRAs) for diagnosis of latent tuberculosis infection (LTBI) was received from Douglass Hanly Moir Pathology by the Department of Health and Ageing in October 2009.

IGRAs are whole-blood *in vitro* tests used to diagnose latent infection with *Mycobacterium tuberculosis* (*M. tuberculosis*) by measuring immunological response to *M. tuberculosis*-specific antigens. When whole blood taken from an individual infected with *M. tuberculosis* is mixed with *M. tuberculosis*-specific antigens, effector T-cells that recognise the antigens are stimulated and release interferon-gamma (IFN-γ). The production and subsequent measurement of IFN-γ forms the basis of IGRAs.

In LTBI, *M. tuberculosis* infection is known to be present by evidence of immunological sensitization by mycobacterial proteins, but the individual remains asymptomatic with an absence of clinical signs or symptoms of active TB disease. It is estimated that up to 10% of individuals infected with *M. tuberculosis* may develop active TB disease in their lifetime, most commonly within a few years after exposure.[1]

Identification of individuals with LTBI is an important part of tuberculosis control. Prophylactic treatment reduces the risk that persons with LTBI will progress to active TB disease, particularly those deemed to be at high risk of disease progression, such as immunosuppressed individuals or young children. Accurate diagnosis minimises the unnecessary treatment of persons not infected.

For this report, IGRAs were assessed for use in the following populations:

- healthcare workers;
- recent immigrants from high-incidence countries or those who may have lived in a country with endemic TB;
- people who have had recent contact with someone with active TB disease;
- patients who are immunocompromised or immunosuppressed due to disease or medical treatment.

For the primary outcome of predictive accuracy of IGRAs, limited data for these different populations did not allow for any population-based analyses to be conducted. For the secondary outcome of concordance, population-specific results are provided in Table 17 to Table 24, however no population-based analyses were conducted.

Proposal for public funding

The applicant did not provide a proposed item descriptor.

Current arrangements for public reimbursement

Currently, IGRAs are available for immunosuppressed or immunocompromised patients, reimbursed under MBS item 69471 (test of cell-mediated immunity in blood for the detection of latent tuberculosis in an immunosuppressed or immunocompromised patient). The Schedule fee for this item is provided Table 1. It has been indicated by the Advisory Panel that the Schedule fee for this item is insufficient to recover costs for the laboratories to run the test.

Table 1: Current MBS arrangements

Item number	Item description	Schedule fee	Benefit (75%)	Benefit (85%)
69471	Test of cell-mediated immunity in blood for the detection of latent tuberculosis in an immunosuppressed or immunocompromised patient – 1 test	$35.15	$26.40	$29.90

Source: Medicare Benefits Schedule, September 2011.

Tests are funded for other patient populations as part of state and territory Department of Health TB control units; however, data are not readily available on the use of IGRAs and TSTs within these units.

Background

IGRA tests for LTBI have not been previously considered by MSAC.

Prerequisites to implementation of any funding advice

QuantiFERON®-TB Gold ELISA (single device) was listed on the TGA in May 2004 while QuantiFERON®-TB Gold (QTF-G) and QuantiFERON®-TB Gold In-Tube (QTF-GIT) (device kits) were listed in April 2007. T.SPOT®-TB is not TGA approved. Given the need to include data across the range of IGRAs, the decision was made to include T.SPOT®-TB, which is not TGA-approved but used worldwide.

Consumer Impact Statement

There is a concern that MBS listing of IGRAs may affect the availability of tuberculin skin tests (TSTs), particularly in remote areas. The potential effect on consumers in remote areas was sought. Respondents from the Northern Territory acknowledged the potential benefit of IGRAs, but they also noted numerous logistical issues, particularly for communities that are located considerable distances from pathology laboratories.

Clinical need

Tuberculosis (TB) is an infectious disease caused by bacterial pathogens from the *M. tuberculosis* complex. In Australia, TB is a notifiable disease. The most recent report from the National Notifiable Diseases Surveillance System listed 1,135 active TB notifications, 1,086 of which were new cases in 2007[2]. Untreated TB kills more than 50% of those with active TB disease.

Identification of individuals with LTBI is an important part of TB control because treatment reduces the risk of their progressing to active TB disease, particularly if they are deemed to be at high risk of progression.

It is anticipated that IGRAs will replace the tuberculin skin test (TST), or Mantoux test, for the detection of LTBI. The only effect this substitution will have on the current clinical management algorithm for diagnosis of LTBI is the removal of the need for two-step TST in healthcare workers and other populations (see Figure 2 in the main body of the report).

Comparator

Comparator to the proposed intervention

The appropriate comparator for the assessment of IGRAs for the diagnosis of LTBI in the target populations is the TST. TST is listed on the MBS, having item number 73811 and an item descriptor of "Mantoux test".

Scientific basis of comparison

Assessment of the accuracy of the test is based on 18 studies with longer-term follow-up that allow determination of the progression to active TB, with supportive evidence provided by 119 studies assessing the concordance of IGRAs and TST. Because safety is not an issue with IGRA tests, no literature relevant to safety is available, and there is no literature specifically addressing clinical management.

Comparative safety

Key results

No studies that specifically investigated the safety of IGRAs for the diagnosis of LTBI were identified. IGRAs require patients to undergo venipuncture for collection of blood. It is anticipated that the only safety concerns likely to be associated with this intervention are those associated with venipuncture.

Comparative effectiveness

Key results

Primary effectiveness outcomes/direct evidence

The focus of the assessment of comparative effectiveness is a consideration of whether IGRAs, compared with TST, more accurately predict if patients with LTBI will or will not develop active TB disease. The review of the literature identified a total of 18 studies with follow-up evidence indicating whether patients progressed to active TB in the longer term. All were non-randomised, prospective studies assessing the diagnostic accuracy of IGRAs. Of the 18 studies, six compared QTF-GIT and TST, four compared QTF-G and TST, three compared T.SPOT®.TB and TST, three compared ELISPOT and TST, and two compared QTF-GIT, T.SPOT®.TB and TST.

Meta analyses were conducted to compare the proportions of patients testing positive or negative who then developed active TB within the study periods. Three overall comparisons were made:

i. an assessment of false-negatives, comparing the proportion who develop active TB who had a negative test result;

ii. an assessment of true-positives, comparing the proportion of patients who develop active TB who had a positive test result;

iii. an assessment of overall positives – a comparison of how many patients test positive to either IGRA or TST.

Table 2 provides a summary of results comparing IGRAs and TST. While there are no statistically significant differences in the occurrence of false-negatives or false-positives between IGRAs and TST, the analysis of overall positives demonstrates that significantly fewer patients test positive to IGRA than to TST (OR [odds ratio] = 0.42; 95% CI: 0.31, 0.57). Given that the smaller proportion of patients testing positive with IGRA occurs with no increase in risk of false-negatives, this suggests that IGRA may be a more efficient test for LTBI than TST.

Table 2: Results of meta-analyses comparing IGRAs and TSTs for the development of TB

	QTF-GIT vs. TST OR (95% CI)	QTF-G vs. TST OR (95% CI)	T.SPOT®-TB vs. TST OR (95% CI)	ELISPOT vs. TST OR (95% CI)	Overall OR (95% CI)
False-negatives	0.87 (0.43, 1.77)	0.07 (0.00, 1.26)	0.43 (0.11, 1.73)	0.99 (0.50, 1.96)	0.80 (0.51, 1.27)
True-positives	1.80 (0.89, 3.67)	2.08 (0.38, 11.48)	1.17 (0.60, 2.29)	1.49 (0.54, 4.11)	1.42 (1.02, 1.99)
Overall positives	0.31 (0.18, 0.54)	0.21 (0.04, 1.07)	0.95 (0.25, 0.81)	0.45 (0.25, 0.81)	0.42 (0.31, 0.57)

TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; OR = odds ratio; NR = not reported.

Secondary effectiveness outcomes/indirect evidence - concordance

There is a large body of literature assessing the concordance between IGRAs and TST. A total of 119 studies were identified as relevant, with 63 assessing QTF-GIT and TST, 33 assessing QTF-G and TST, 37 assessing T.SPOT®.TB and TST and 19 assessing ELISPOT and TST. The concordance studies were assessed because they allow for a determination of whether the results from the follow-up studies, summarised in Table 2, are generalisable. Meta-analyses were conducted to assess the agreement between

IGRAs and TST across the different patient populations and by the proportion of the study cohort that was BCG vaccinated.

The overall agreement (concordance) between IGRAs and TST (intention to treat analysis) was lowest in ELISPOT (0.62; 95% CI: 0.55, 0.68), and highest in QTF-GIT (0.69; 95% CI 0.65, 0.73). As would be expected, per-protocol analysis increased agreement overall, with QTF-G and T.SPOT®-TB with the lowest agreement (0.73; 95% CI: 0.63, 0.82 [QTF-G], 0.73; 95% CI: 0.59, 0.85 [T.SPOT®-TB]) and highest agreement in QTF-GIT (0.79; 95% CI 0.76, 0.82). In all IGRAs except T.SPOT®-TB (possibly due to inadequate study range), there was a trend towards greater agreement between IGRA and TST in studies that had a lower proportion of the study cohort that were BCG vaccinated.

As TST is not a perfect reference standard, and is known to be affected by BCG vaccination and environmental mycobacteria, disagreement between IGRAs and TST does not suggest inferiority to TST. The trend towards greater agreement in populations with lower BCG vaccination, or perhaps more importantly, greater disagreement in populations with high BCG vaccination status, suggests that there may be some value of IGRAs over TST in BCG vaccinated populations in reducing the number of false-positives identified.

Impact on patient management and outcomes

The management of patients differs according to whether they test positive or negative. Patients who test positive are managed by active surveillance, and a proportion of these patients will be treated. This treatment has risk of toxicity without proven benefit in patients who are IGRA or TST negative. Patients who test negative are not routinely followed up with active surveillance. As indicated above, IGRA appears to be a more efficient test than TST for identifying patients that will develop active TB: fewer patients test positive with no increase in risk of false-negatives. This means that if IGRA is used in place of TST, there will be fewer patients unnecessarily undergoing active surveillance and perhaps treatment.

It is likely that the potential harm associated with putting patients under active surveillance and requiring a proportion of them to undergo treatment will be small. The main advantage of IGRA vs. TST will be captured as savings due to reduced need for treatment and surveillance of patients.

Other relevant considerations

The National Tuberculosis Advisory Committee (NTAC) has recently released a draft position statement, pending approval by the Communicable Diseases Network Australia (CDNA) on IGRAs for use in the detection of LTBI. NTAC has stated that a review of recent literature on IGRAs indicates that the evidence has not clearly demonstrated that IGRAs are superior to TST. NTAC also noted a continuing absence of cost-effectiveness studies of IGRAs under Australian TB program conditions, and that the long history of use of TST and longitudinal data provides important predictive information that is not yet available with IGRAs. On this basis, NTAC has concluded that TST remains the preferred test for LTBI in most patient groups. NTAC has recommended that IGRA may be used as supplemental tests to improve specificity in screening immunocompetent subjects and also be used in addition to TST in immunocompromised patients at high risk of LTBI.

In addition to the draft NTAC position statement there are three recent publications addressing the use of IGRAs. The first is an updated guideline for the use of IGRAs by the Centers for Disease Control and Prevention (CDC)[3], the second is a short clinical guideline published in 2010 by the National Institute for Health and Clinical Excellence (NICE)[4] in the UK, and the third is guidance published by the European Centre for Disease Prevention and Control (ECDC)[5].

All three organisations have recommended the use of IGRAs, however, the conditions under which they are to be used varies. In all situations in which CDC recommends the use of TST, CDC advises that IGRAs can be used in place of, but not in addition to, TST. NICE, by contrast, recommends the joint use of TST and IGRAs among various patient populations and has estimated that the use of TST and IGRAs in combination is cost-effective, whereas the use of IGRAs alone is not. The ECDC concluded that IGRAs may be used as part of the overall risk assessment to identify individuals (e.g., immunocompromised persons, children, close contacts, and the recently-exposed) for preventive treatment.

Economic evaluation

The applicant did not provide a proposed fee for IGRAs. Advice provided by the Victorian Infectious Disease Reference Laboratory indicated the cost of QTF-GIT is about $48.00. IGRAs also require payment of pathology patient episode initiation fees.

Given the lack of available information regarding cost for IGRAs and longer-term outcomes, a simplified cost comparison has been conducted.

It is assumed that there is no difference in patient outcomes regardless of whether patients are tested for LTBI using IGRA or using TST (i.e., it is assumed that, for patients who have falsely tested positive and put under surveillance [and perhaps prophylactic treatment], the effect on their quality-adjusted survival is negligible). Because the assumption is made that outcomes are no worse if patients are assessed using IGRA rather than TST, then the analysis is reduced to a comparison of costs only (i.e., consideration of implications of false-positives and false-negatives).

Results of the cost comparison indicate that testing for LTBI using IGRAs appears to be cost-saving compared to using TST, with an estimated saving of $35.52 per patient. This may be a conservative estimate because the cost of adverse drug reactions in patients unnecessarily treated with prophylaxis (due to false-positive results) are not included. Sensitivity analyses indicate that the analysis is most sensitive to the extent of difference in proportion of patients testing positive to IGRA compared with proportion testing positive to TST.

Financial/budgetary impacts

An estimate of the number of IGRAs likely to be conducted has not been calculated because of the lack of information available. To derive the number of tests likely to be used, there would have to be an estimate of the proportion of tests that may shift from the public to the private system, as well as an estimate of the number of TSTs conducted. Due to uncertainty regarding these numbers, the current assessment has not formulated an estimate. In addition, the applicant did not provide a proposed fee for IGRAs, and

consequently an assessment of the financial implications of the listing of the test cannot be conducted.

Key issues

Key uncertainties with respect to comparative safety

There is no uncertainty with respect to the evidence and conclusions for safety of IGRAs. Given the nature of the tests, it is not anticipated that they will be associated with any safety issues beyond those associated with collection of blood by venipuncture.

Overall conclusion with respect to comparative safety

It is not expected that there will be a significant difference in safety between the two types of test.

Key uncertainties with respect to comparative clinical effectiveness

While there is considerable evidence available assessing the concordance of IGRAs and TST, the available evidence addressing comparative predictive accuracy for progress to active TB is based on relatively short-term studies. Although there is a statistically significant advantage for IGRAs compared to TST in overall positive test results, this advantage does not occur across all outcomes.

Overall conclusion with respect to comparative clinical effectiveness

The comparison of IGRAs and TST indicates no statistically significant difference between the two tests regarding occurrence of false-negative or true-positive test results. The comparison of overall positive test results indicates that IGRAs may be a more efficient test for LTBI than TST because significantly fewer patients tested positive to IGRA than to TST with no increase in risk of false-negatives. However, the comparison of overall positive results had high heterogeneity ($I^2 = 95\%$) so the results should be interpreted with caution.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of the interferon gramma release assay (IGRA), a test for diagnosing or screening patients for latent tuberculosis infection (LTBI). MSAC evaluates new and existing health technologies and procedures, for which funding is sought under the Medicare Benefits Scheme (MBS), in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's Terms of Reference and membership are presented in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for pathology tests for LTBI.

Background

Intervention name

Interferon gamma release assay (IGRA) for detection of latent tuberculosis infection (LTBI).

The procedure / test

Interferon gamma release assay

Interferon gamma release assays (IGRAs) are whole-blood *in vitro* tests used to diagnose LTBI by measuring immunological response to *Mycobacterium tuberculosis (M. tuberculosis)*-specific antigens. Whole blood taken from an individual infected with *M. tuberculosis* is mixed with *M. tuberculosis*-specific antigens. This stimulates effector T-cells that recognise the antigens and release interferon-gamma (IFN-γ). The production and subsequent measurement of IFN-γ forms the basis of IGRAs.

M. tuberculosis-specific antigens include early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and TB7.7. These antigens are only made by the *M. tuberculosis* complex bacteria and therefore only identify the presence of T-cells that are specific for TB infection. These antigens are absent from all strains of the Bacille Calmette-Guérin (BCG) vaccine for TB and from most non-tuberculosis mycobacteria with the exception of *M. kansasii*, *M. mariunum* and *M. szulagi*. For persons in which such infections rather than TB are suspected, alternative tests should be investigated.

IGRAs include commercially available kit tests as well as in-house assays. Currently, in Australia, QuantiFERON®-TB Gold In-Tube (QTF-GIT) is the only commercial IGRA available. It utilises the enzyme-linked immunosorbent assay (ELISA) and a combination of ESAT-6, CFP-10 and TB7.7 antigens to stimulate IFN-γ production.

T.SPOT®-TB is another commercial IGRA; however, it is not currently available in Australia. It is a version of the enzyme-linked immunosorbent spot assay (ELISPOT) and uses ESAT-6 and CFP-10 antigens to stimulate IFN-γ production.

QuantiFERON®-TB Gold (QTF-G) and QuantiFERON®-TB (QTF) are commercial IGRA kits that were produced by Cellestis Limited (Carnegie, Victoria, Australia) and are no longer marketed in Australia. QTF-G used ESAT-6 and CFP-10 antigens, while QTF used ESAT-6, CFP-10 and human and avian tuberculin PPD (non-specific antigens), to stimulate IFN-γ production. QTF was removed from the Australian market before this assessment's initiation, and therefore was excluded from the report. QTF-G was removed from the Australian market *during* the assessment; consequently, a decision was made to retain the evidence pertaining to QTF-G in the report.

Enzyme-linked immunosorbent assay

The enzyme-linked immunosorbent assay (ELISA) is an *in vitro* biochemical technique that can detect and quantitate the concentration of soluble cytokine in a sample.

The direct (or sandwich) ELISA employs anti-cytokine antibodies, adsorbed onto the walls of a microplate well, to detect the presence of a specific cytokine in a sample. The test samples and a series of standards are added to the wells pre-coated with anti-cytokine antibodies; if the specific cytokine is present in the sample, it will bind to the antibodies attached to the wall of the well. The plate is then rinsed to remove any unbound material and biotinylated antibody (which binds to any bound antigen) is added. The sample is again rinsed to remove any unbound biotinylated antibody. If the antigen is present, a complex will have formed that includes the antibody bound to the well, the antigen, and the biotinylated antibody. An enzyme substrate that reacts with the complex is then added , resulting in a colour change. The optical density (OD) of the sample is then measured and compared to a standard curve, typically a serial dilution of a known concentration solution of the target antibody, to determine the concentration of the antigen.

QuantiFERON®-TB Gold In-Tube

QuantiFERON®-TB Gold In-Tube (Cellestis Limited, Carnegie, Victoria, Australia) detects *in vitro* CMI response to *M. Tuberculosis* by measuring IFN-γ in plasma from whole blood incubated with TB-specific antigens.

QTF-GIT is an in-tube collection system using three specialised blood collection tubes: nil control, TB-antigen, and mitogen control tubes. The TB-antigen tube uses a peptide cocktail, simulating ESAT-6, CFP-10, and TB7.7 proteins, to stimulate T-cells in the heparinised whole blood to release IFN-γ. The tubes are incubated for 16 to 24 hours at 37°C; after which the tubes are centrifuged, the plasma is removed, and the amount of IFN-γ (IU/mL) is measured by ELISA.

Table 3 provides the criteria for the interpretation of QTF-GIT results as recommended by Cellestis Limited, Australia. The manufacturer notes that "diagnosing or excluding tuberculosis disease, and assessing the probability of LTBI, requires a combination of epidemiological, historical, medical, and diagnostic findings that should be taken into account when interpreting QuantiFERON®-TB Gold IT results"[6].

Table 3: Criteria for the interpretation of QuantiFERON®-TB Gold In-Tube results (Cellestis Limited, Australia)

Nil [IU/mL]	TB-antigen minus nil [IU/mL]	Mitogen minus nil [IU/mL][a]	Result	Interpretation
≤ 8.0	< 0.35	≥ 0.5	**Negative**	*M. tuberculosis* infection NOT likely
	≥ 0.35 and < 25% of nil value	≥ 0.5		
	≥ 0.35 and ≥ 25% of nil value	Any	**Positive**[b]	*M. tuberculosis* infection likely
	< 0.35	< 0.5	**Indeterminate**[c]	Results are indeterminate for TB-antigen responsiveness
	≥ 0.35 and < 25% of nil value	< 0.5		
> 8.0[d]	Any	Any		

QTF-GIT = QuantiFERON®-TB Gold In-Tube.

a Reponses to the mitogen positive control (and occasionally TB-antigen) can be commonly outside the range of the microplate reader. This has no impact on test results.

b Where M. tuberculosis infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QuantiFERON®-TB Gold ELISA. If repeat testing of one or both replicates is positive, the individual should be considered test positive.

c Refer to Trouble Shooting section (of package insert) for possible causes.

d In clinical studies, less than 0.25% of subjects had IFN-γ levels > 8.0 IU/mL for the Nil Control.

The mitogen control tube is used as a positive control for correct blood handling and incubation, as well as when there is doubt concerning the individual's immune status and their ability to respond in the test. A low mitogen response (<0.5 IU/mL) and a negative response to TB antigens is an indeterminate result; there may be insufficient lymphocytes, reduced lymphocyte activity due to incorrect specimen handling or filling/mixing of the mitogen tube, or inability of the patient's lymphocytes to generate IFN-γ. The nil control adjusts for background, heterophile antibody effects, or non-specific IFN-γ in blood samples and is subtracted from the IFN-γ level for the TB-antigen and mitogen tubes.

Cellestis Limited, Australia, provides these precautions regarding the use of QTF-GIT:

- A negative QTF-GIT result does not preclude the possibility of TB infection: false-negative results can be due to the stage of infection (e.g., specimen obtained prior to the development of cellular immune response), co-morbid conditions which affect immune functions, incorrect handling of the blood collection tubes following venipuncture, incorrect performance of the assay, or other immunological variables.

- A positive QFT-GIT result should not be the sole or definitive basis for determining infection with *M. tuberculosis*. Incorrect performance of the assay may cause false-positive responses.

- A positive QFT-GIT result should be followed by further medical evaluation and diagnostic evaluation for active TB disease (e.g., AFB [acid fast bacilli] smear and culture, chest x-ray).

- While ESAT-6, CFP-10, and TB7.7 are absent from all BCG strains and most known non-tuberculous mycobacteria, it is possible that a positive result may be due to infection by *M. kansasii*, *M. szulgai*, or *M. marinum*. If such infections are suspected, alternative tests should be investigated.

Storage and transport limitations

The manufacturer states that tubes must be transferred to a 37°C incubator as soon as possible and within 16 hours of blood collection. Blood samples must not be refrigerated or frozen. Tubes must be incubated upright at 37°C for 16 to 24 hours (does not require CO_2 or humidification) and may be held between 2°C and 27°C for up to 3 days prior to centrifugation.

QuantiFERON®-TB Gold

QuantiFERON®-TB Gold (Cellestis Limited, Carnegie, Victoria, Australia) is no longer marketed and has been replaced by QTF-GIT.

QTF-G detected an *in vitro* CMI response to *M. tuberculosis* by measuring IFN-γ in plasma from whole blood incubated with TB-specific antigens ESAT-6 and CFP1-10. Heparinised whole blood is mixed with ESAT-6, CFP-10, mitogen, or nil control antigens and incubated at 37°C for 16-24 hours using a 24-well culture plate. After incubation, plasma is removed from above the sedimented red cells and the amount of IFN-γ quantified by ELISA.

QTF-G ELISA uses microplate wells coated with anti-human IFN-γ murine monoclonal antibody. Anti-human IFN-γ HRP (horseradish peroxidise) conjugate is added to each of the required wells. The kit standard (recombinant human IFN-γ) is used to produce a dilution series of four IFN-γ concentrations to create a standard curve. The plasma samples and each of the standards are then added to the wells containing conjugate. The plate is incubated for 120 ± 5 minutes at room temperature. Wells are washed, and enzyme substrate solution is added to each well and incubated at room temperature for precisely 30 minutes. Enzyme stopping solution is then added to each well. The optical density (OD) of each well is read within five minutes of terminating the reaction. QuantiFERON®-TB Gold analysis software analyses the raw data and calculates test results by generating a standard curve from the OD values and IFN-γ concentration standards (IU/mL), calculating a line of best fit for the standard curve by regression analysis. The IFN-γ concentration (IU/mL) for each of the test plasma samples is determined by reading the IFN-γ concentration from the standard curve for the OD of each sample.

The interpretation of the obtained result, as recommended by Cellestis Limited, Australia, is provided in Table 4. The cut-off for a positive QTF-G result is 0.35 IU/mL above the nil control for either ESAT-6 or CFP-10 stimulated plasma samples - individuals displaying a response to either TB-specific antigen above this cut-off are likely to be infected with *M. tuberculosis*.

Table 4: Interpretation of QuantiFERON®-TB Gold results (Cellestis Limited, Australia)

Mitogen minus nil [IU/mL]	ESAT-6 minus nil and/or CFP-10 minus nil [IU/mL]	Result	Interpretation
≥0.5	≥0.35	Positive	*M. tuberculosis* infection likely
<0.5	≥0.35	Positive	*M. tuberculosis* infection likely
≥0.5	<0.35	Negative	*M. tuberculosis* infection not likely
<0.5	<0.35	Indeterminate	Result not obtained

Mitogen minus nil must be ≥0.5 IU/mL AND/OR either ESAT-6 minus nil or CFP-10 minus nil must be ≥0.35 IU/mL for a subject to have a valid QFT-G result.

The mitogen-stimulated plasma sample serves as a positive control for each individual tested. The nil control adjusts for background, heterophile antibody effects, or non-specific IFN-γ in samples; under most circumstances, the nil control will not generate IFN-γ above 1.0 IU/mL. A positive result to either ESAT-6 or CFP-10 without a response to mitogen is a valid result indicating infection; a low response to mitogen and both ESAT-6 and CFP-10 is deemed 'indeterminate'.

Cellestis Limited, Australia, provides the following precautions regarding the use of QTF-G:

- A negative QTF-G result does not preclude the possibility of TB infection. The specimen may have been obtained prior to development of cellular immune response, sufficient lymphocytes may not be present in the blood sample collected, or handling of the specimen may have affected lymphocyte function.
- A positive QFT-G result should not be the sole or definitive basis for determining infection with *M. tuberculosis*. Incorrect performance of the assay may cause false-positive responses.
- Some specimens may not yield a measureable IFN-γ response, resulting in low IFN-γ readings and an indeterminate test result.

Storage and transport limitations

Blood samples should be transported to the laboratory at ambient temperature (22°C ± 5 °C) and must be incubated with stimulation antigens within 12 hours of collection.

Enzyme-linked immunospot assay (ELISPOT)

The enzyme-linked immunospot (ELISPOT) assay measures the immune response to an antigen by detecting the number of individual cytokine-producing effector T-cells. Cytokine-specific monoclonal antibodies are immobilized on a microtiter plate. The sample is added to the wells, along with a nil and positive control, and incubated. Cytokine released by activated T-cells are captured by the cytokine-specific antibodies pre-coated to the walls of the wells. Cells and other unwanted materials are removed by washing. A conjugated antibody reactive with an epitope of the cytokine is then added and unbound conjugated antibody is removed by rinsing. A soluble substrate is then added, forming an insoluble precipitate (coloured spot) at the reaction site on the well floor. Each spot that develops represents a single reactive cell; thus, the ELISPOT assay provides qualitative and quantitative information.

T.SPOT®-TB

The T.SPOT®-TB (Oxford Immunotec, Oxford, United Kingdom) assay is a commercial version of ELISPOT, specifically used for the diagnosis of TB infection. It counts the number of *M. tuberculosis*-sensitive effector T-cells in a sample of blood. Currently, it is not available in Australia.

A blood sample is collected and centrifuged to separate peripheral blood mononuclear cells (PBMCs) which produce IFN-γ. The sample is washed (to remove any sources of background interfering signal), counted, and diluted so that 250,000 PBMCs are added to each well to maximise sensitivity and ensure that a standardised cell number is used in the assay. This ensures that those who have low T-cell titres due to a weakened immune system (immunocompromised and immunosuppressed individuals) have adequate numbers of cells added to the microtiter wells. PBMCs and specific TB antigens are added to wells pre-coated with antibodies to IFN-γ and incubated for 16 to 20 hours at 37°C in CO_2. The T.SPOT®-TB assay uses ESAT-6 and CFP-10 proteins to challenge the T-cells and stimulate any sensitized T-cells to release IFN-γ. Secreted IFN-γ is captured by the antibodies pre-coated on the membrane, which forms the base of the well, and the cells and other unwanted materials are removed by washing. A second antibody, conjugated to alkaline phosphatase and directed to a different epitope on the IFN-γ molecule, is added to the wells and binds to IFN-γ captured on the membrane surface. The wells are incubated for one hour and any unbound conjugate is removed by washing. A soluble substrate is then added to each well for seven minutes; this is cleaved by bound enzyme to form a spot of insoluble precipitate at the site of the reaction on the well floor. Each spot represents the footprint of an individual T-cell that responded to the TB antigens and secreted IFN-γ. These spots are counted to provide the assay result. Evaluating the number of spots obtained provides a measurement of the abundance of *M. tuberculosis*-sensitive effector T-cells in the peripheral blood.

Four wells are used for each patient sample:

1. A nil control to identify non-specific cell activation
2. TB-specific antigens, panel A (ESAT-6)
3. TB-specific antigens, panel B (CFP-10)
4. A positive control containing phytohaemagglutinin (PHA, a polyclonal activator) to confirm PBMC functionality.

Results interpretation and assay criteria

T.SPOT®-TB results are interpreted by subtracting the spot count in the nil control well from the spot count in each of the panels according to the algorithm:

- The test result is 'positive' if (panel A minus nil control) and/or (panel B minus nil control) ≥ 6 spots.
- The test result is 'negative' if both (panel A minus nil control) and (panel B minus nil control) ≤ 5 spots. This includes values less than zero.

The T.SPOT®-TB assay should be used and interpreted only in the context of the overall clinical picture. A 'positive' result indicates that the sample contains effector T-

cells reactive to *M. tuberculosis*. A 'negative' result indicates that the sample probably does not contain effector T-cells reactive to *M. tuberculosis*.

A typical result would be expected to have few or no spots in the nil control and > 20 spots in the positive control. A nil control spot count > 10 spots should be considered 'indeterminate' and another sample should be collected from the individual and tested. Where the positive control spot count is < 20 spots, it should be considered 'indeterminate', unless either Panel A or Panel B is 'positive' as described above. Where the higher of panel A and panel B (minus nil control) is 5, 6, or 7 spots, the result may be considered borderline (equivocal). Although equivocal results are valid, they are less reliable than results where the spot count is further from the cut-off, and retesting of the patient using a new sample is recommended. If an equivocal result is obtained on retesting, other diagnostic tests and/or epidemiological information should be used to determine the TB infection status of the patient.

Storage and transport limitations

Blood samples must be assayed within 8 hours of blood collection. The manufacturer suggests using T-Cell *Xtend*™ reagent (Oxford Immunotec, Oxford, United Kingdom) to increase sample storage time to 32 hours. Storage and transport of a sample must be at room temperature (18-25ºC), or 10-25 ºC when the T-Cell *Xtend*™ reagent is used.

Intended purpose

The intended purpose of IGRA is for the diagnosis or screening of patients for LTBI.

Clinical need

Tuberculosis

Tuberculosis (TB) is an infectious bacterial disease caused by pathogens from the *M. tuberculosis* complex (MTBC). It is transmitted primarily by airborne droplet nuclei from individuals with pulmonary or laryngeal TB. The primary manifestation in infected individuals who develop the disease is pulmonary TB, but it can occur in any organ of the body. Symptoms include persistent cough, chest pain, blood-stained sputum, weakness or fatigue, weight loss, loss of appetite, chills, fever, and sweating at night. The World Health Organisation (WHO) guidelines for treatment of TB[7] recommend new patients with pulmonary TB disease receive six months of treatment: two months of isoniazid, rifampicin, ethambutol, and pyrazinamide (intensive phase) followed by four months of isoniazid and rifampicin.

There are a number of closely related bacterial sub-species within MTBC that can cause disease. The most common is *M. tuberculosis* which is the leading cause of death worldwide that can be attributed to a single infectious disease agent. Other species include *M. bovis*, uncommonly transmitted from infected animals to humans, *M. africanum*, pulmonary disease in humans in tropical Africa, and *M. canetti*, a recently described member and a rare cause of disease.

TB is a notifiable disease in Australia. In 2007, the National Notifiable Diseases Surveillance System reported 1,135 active TB notifications, of which 1,086 were new

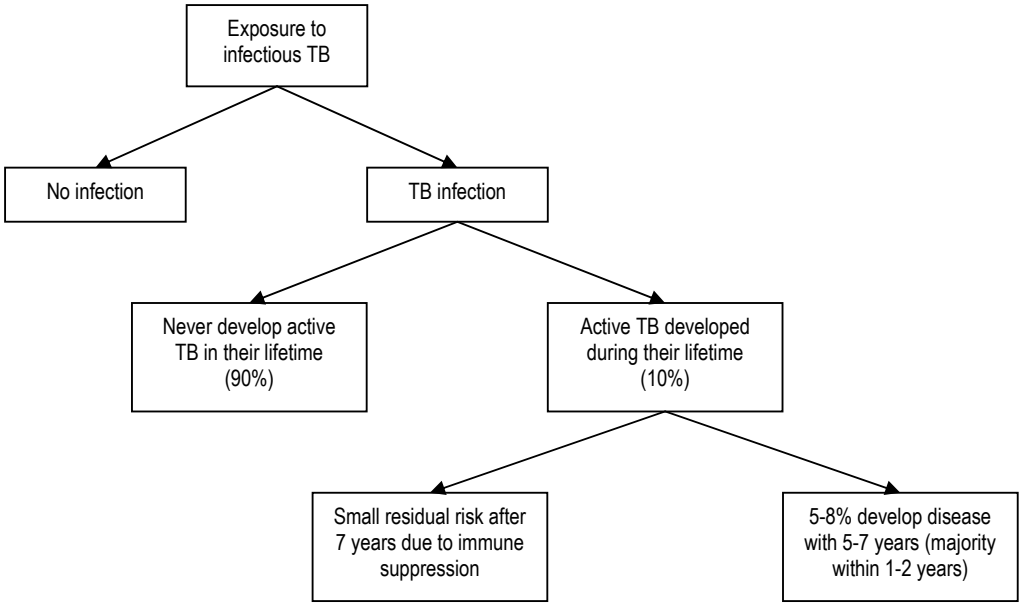
cases[2]. The anatomical site was pulmonary in 694 of cases (61%), 138 of which were pulmonary plus extra-pulmonary disease, and extra-pulmonary only in 441 of cases (39%). Country of birth was reported for 1,111 cases: 86.4% were born overseas (18.3 per 100,000 population [960 cases]), and 13.6% born in Australia (1.0 per 100,000 population [151 cases]).

Latent tuberculosis infection

Not all individuals infected with *M. tuberculosis* have active disease. In LTBI, *M. tuberculosis* infection is present, by evidence of immunological sensitization by mycobacterial proteins, but the individual remains asymptomatic with an absence of clinical signs or symptoms of active TB disease.

It is estimated that up to 10% of individuals infected with *M. tuberculosis* may progress to active TB disease, most commonly within a few years after exposure, although they retain a lifetime risk of disease[1]. The remaining 90% suppress *M. tuberculosis* through their immune system, but have LTBI. The natural progression history of TB infection is shown in Figure 1.

Figure 1: Natural history of TB infection



Adapted from Konstantinos (2010)[8].

The estimate that 10% of people with LTBI will progress to active TB disease in their lifetime may be an overestimate because it is subject to variations in the epidemiology of TB in Australia and it is dependent on associated risk factors. Identification of individuals with LTBI is an important part of tuberculosis control because treatment reduces their risk of progressing to active TB disease, particularly if they are deemed to be at high risk of disease progression. Persons with increased risk of developing active TB include those who have had recent sustained exposure to active TB disease and those who have clinical conditions, such as HIV infection, that are associated with an increased risk of progression of LTBI to active TB (Table 5 and Table 6). The risk of disease

development is increased by immunosuppressive triggers including HIV infection and the use of TNF-inhibitors for other diseases such as rheumatoid arthritis.

Table 5: Incidence of active tuberculosis in persons with a positive tuberculin test, by selected risk factors (adapted from ATS/CDC Statement Committee, 2000)

Risk factor	TB cases/1,000 person years
Recent TB infection	
Infection < 1yr past	12.9
Infection 1-7 yr past	1.6
HIV infection	35.0-162
Injection drug use	
HIV seropositive	76.0
HIV seronegative or unknown	10.0
Silicosis	68
Radiographic findings consistent with prior TB	2.0-13.6
Weight deviation from standard	
Underweight by ≥15%	2.6
Underweight by 10-14%	2.0
Underweight by 5-9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

Source: Adapted from American Thoracic Society and Centres for Disease Control (2000)[9].

Table 6: Relative risk[a] for developing active tuberculosis, by selected clinical conditions (adapted from ATS/CDC Statement Committee, 2000)

Clinical condition	Relative risk
Silicosis	30
Diabetes mellitus	2.0-4.1
Chronic renal failure/hemodialysis	10.0-25.3
Gastrectomy	2-5
Jejunoileal bypass	27-63
Solid organ transplantation	
Renal	37
Cardiac	20-74
Carcinoma of head or neck	16

Source: Adapted from American Thoracic Society and Centres for Disease Control (2000)[9].

a Relative to control population; independent of tuberculin-test status.

Current refugee guidelines recommend all newly-arrived refugees, including children, be assessed for LTBI with either a TST or IGRA within two months of arrival in Australia, with HIV-infected individuals undergoing a two-step TST[10]. Screening for LTBI is also recommended in close contacts of active pulmonary TB cases, those occupationally at TB risk and those travelling to high TB risk countries[11].

Treatment of LTBI is a preventive therapy approach (chemoprophylaxis) to reduce the likelihood of progression to active TB disease. Since the 1950s, standard practice has been isoniazid (INH) for six to nine months on a daily or intermittent basis in an appropriate dose (5-10 mg/kg up to maximum of 300 mg daily as a single dose). The main side effects of INH include hepatotoxicity, peripheral neuropathy, and hypersensitive reactions.

Table 7 provides the pharmaceutical benefits scheme (PBS) cost and prescriber information for INH.

Table 7: PBS cost and prescriber information for INH.

Prescriber code	Item code	Name, manner of administration and form & strength	Max. qty.	No. of repeats	Pack size	Price premium	Dispensed price for max. qty.	Max recordable value for PBS Safety Net	Price to consumer
MP NP	1554T	Isoniazid tablet 100mg	100	2	100	Nil	$11.86	$12.95	Up to $16.87

Source: Pharmaceutical Benefits Scheme, accessed September 2011.

MP = medical practitioner; NP = nurse practitioner; PBS = Pharmaceutical Benefits Scheme.

Existing procedures / tests

BCG vaccination

The BCG vaccine against TB was first used in 1921. In Australia, from 1948, vaccination was targeted at healthcare workers (HCWs), Aboriginal people, and close contacts of active cases, especially children. In the 1950s, the program was expanded to include all Australian school children except those of from New South Wales and the Australian Capital Territory. The program was discontinued in the mid-1980s in favour of a more selected approach, due to the low prevalence of TB in the Australian community[12].

The National Tuberculosis Advisory Committee does not recommend BCG vaccination for general use in the Australian population[12]. It is, however, recommended in the following populations:

- Aboriginal neonates in areas of high incidence of TB (e.g., Northern Territory, Far North Queensland, northern areas of Western Australia and South Australia);
- neonates and children 5 years and under who will be travelling or living in countries or areas with a high prevalence of TB for extended periods;
- neonates born to parents with leprosy or a family history of leprosy.

In addition to these recommendations, BCG vaccination may be considered in the following:

- children over 5 years who will be travelling or living in countries or areas with a high prevalence of TB for extended periods;
- HCWs who may be at high risk of exposure to drug-resistant cases.

Tuberculin skin test

The tuberculin skin test (TST), or Mantoux test, is a diagnostic test used to identify latent *M. tuberculosis* infection. In Australia, tuberculin PPD-S (Human) (Tubersol®) is currently supplied by Sanofi Pasteur Pty Ltd[13].

After a person becomes infected with *M. tuberculosis*, T-lymphocytes proliferate and become sensitized. The sensitization of lymphocytes usually reaches a level adequate to produce a detectable response using TST two to ten weeks after initial infection.

Injection of tuberculin into the skin stimulates sensitized lymphocytes and activates a series of events leading to a delayed-type hypersensitivity (DTH) response, evident after 24 to 48 hours. Lymphocytes are recruited by the immune system to the site of injection where they release lymphokines which induce induration through local vasodilation leading to oedema, fibrin deposition, and recruitment of other types of inflammatory cells to the area. The area of cellular infiltration or induration reflects DTH activity.

An international unit (IU) for tuberculin is a unit of biological activity in a defined amount of standard preparation. In Australia, a standard dose of tuberculin is 10 IU, achieved using an intra-dermal injection of 0.1 mL of 100 IU per mL. In some other countries, the standard dose is 5 IU, however the National Tuberculosis Advisory Council adopted a higher dose in the 1950s to achieve increased specificity of the test.

The test is performed on an area of healthy skin on the left forearm at the junction of the upper and middle thirds. The area is cleaned with acetone, ether, or alcohol, and allowed to dry. A tuberculin syringe with a 26-gauge, 13 mm long intra-dermal needle is used to inject the tuberculin intradermally with the bevel facing upwards to produce a 'bleb' or wheal of 5-8 mm diameter which disappears within one hour. The test is ideally read 48 to 72 hours after injection, using a small ruler to measure the diameter of any area of induration and records the result in millimetres.

Three cut-off diameters, depending on a patients risk group, are recommended for defining a positive reaction to tuberculin (Table 8).

Table 8: Criteria for defining a tuberculin skin testing reaction as positive[a]

Induration	Positive criteria
≥5 mm	People with recent exposure (within 2 years) to tuberculosis + high risk for progression to active disease (e.g., < 5 years of age, HIV infection, other immunosuppressive illness).
≥10 mm	People with recent exposure to tuberculosis, regardless of BCG vaccination; all non-BCG vaccinated people except for those with low lifetime risk for tuberculosis infection and residence in geographical areas where exposure to environment nontuberculous mycobacteriosis is common.
≥15 mm	All people regardless of BCG vaccination status.

Source: Adapted from Konstantinos (2010)[8].

HIV = human immunodeficiency virus; BCG = Bacillus Calmette-Guėrin.

a This refers to the induration produced by intradermal injection of PPD equivalent to 5 units of PPD-S. These criteria are meant as suggestions only. Local tuberculosis control units should be consulted for local guidelines.

Two-step TST

In some persons infected with *M. tuberculosis*, the ability to react to tuberculin may decrease over time. If a TST is conducted years after infection, these persons may have an initial false-negative reaction however, the TST may stimulate the immune system, causing a positive (or 'boosted') reaction to subsequent tests. Thus, a positive reaction to a subsequent test may be misinterpreted as a new infection when in fact it is the result of the boosted reaction to an old infection.

Giving a second TST after an initial negative TST reaction is called two-step testing. Two-step testing is performed as a baseline for pre-employment testing of HCWs and staff of high-risk workplaces, in people who have lowered immunity such as HIV infection or other medical conditions, and in people about to undergo organ donation[14]. This approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection, ensuring that any future positive tests can be interpreted as being caused by a new infection, rather than simply a reaction to an old infection.

If the first test is positive, the person is considered infected. If the first test is negative, a repeat test is given one to two weeks later. If the second test is positive, the person is considered previously infected. If the second test is negative, the person is considered uninfected. A person who is diagnosed as infected by two-step testing, is called a "tuberculin converter".

Cross-reactivity

One of the drawbacks of the TST is that tuberculin is subject to significant cross-reactivity with BCG vaccination and other species of mycobacteria. PPD is a crude mixture of approximately 200 peptides extracted from dead *M. tuberculosis* cells. Many of these proteins have common epitopes to the BCG vaccine and environmental mycobacteria. TST specificity is therefore reduced by the antigenic cross-reactivity of PPD with BCG vaccine and non-tuberculosis mycobacteria.[15]

Usage

Table 9 presents the number of TST services processed by Medicare Australia in the 2010-2011 financial year, reported by State.

Table 9: Number of TST processed by Medicare Australia, 2010–2011 financial year.

Item number	State								Total
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
78311	1,093	4,682	836	89	236	250	59	35	7,280

Source: Medicare Australia, September 2011.

NSW = New South Wales; VIC = Victoria; QLD = Queensland; SA = South Australia; WA = Western Australia; TAS = Tasmania; ACT = Australian Capital Territory; NT = Northern Territory.

Marketing status of technology

QuantiFERON®-TB was originally granted approval to market by the U.S. Food and Drug Administration (FDA) in November 2001. In February 2004 the FDA approved a supplement for the registration of QuantiFERON®-TB Gold, which uses synthetic peptide antigens ESAT-6 and CFP-10 and the removal of the tuberculin purified protein derivative (PPD) and *M. Avium* PPD antigens used in QuantiFERON®-TB. A further supplement was provided to the FDA and approved in October 2007 for a modification of QuantiFERON®-TB Gold to an in-tube collection system.

QuantiFERON®-TB Gold (single device) was registered on the Therapeutic Goods Administration (TGA) in May 2004. QuantiFERON®-TB Gold and QuantiFERON®-TB Gold In-Tube (device kits) were listed on the TGA in April 2007.

Current reimbursement arrangements

The relevant existing tests that are included on the MBS are provided in Table 10. In addition to the Mantoux test (or TST), there is MBS item (69471) which is a test of cell-mediated immunity in blood for the detection of latent tuberculosis in an immunosuppressed or immunocompromised patient. It has been indicated by the Advisory Panel that the Schedule fee for this item is insufficient to recover costs for the laboratories to run the test.

Table 10: Relevant MBS items

Item number	Item description	Schedule fee	Benefit (75%)	Benefit (85%)
73811	Mantoux test	$11.30	$8.50	$9.65
69471	Test of cell-mediated immunity in blood for the detection of latent tuberculosis in an immunosuppressed or immunocompromised patient – 1 test	$35.15	$26.40	$29.90

Source: Medicare Benefits Schedule, September 2011.

Approach to assessment

Objective

To carry out a structured assessment of the following technology: pathology testing for mycobacterial infection, latent or active, based on a consideration of:

- the clinical need for the technology;
- the clinical effectiveness of the technology;
- the safety of the technology;
- economic considerations.

Clinical decision pathway

The following populations were identified as important for the diagnosis or screening for LTBI by IGRAs on the basis of clinical need:

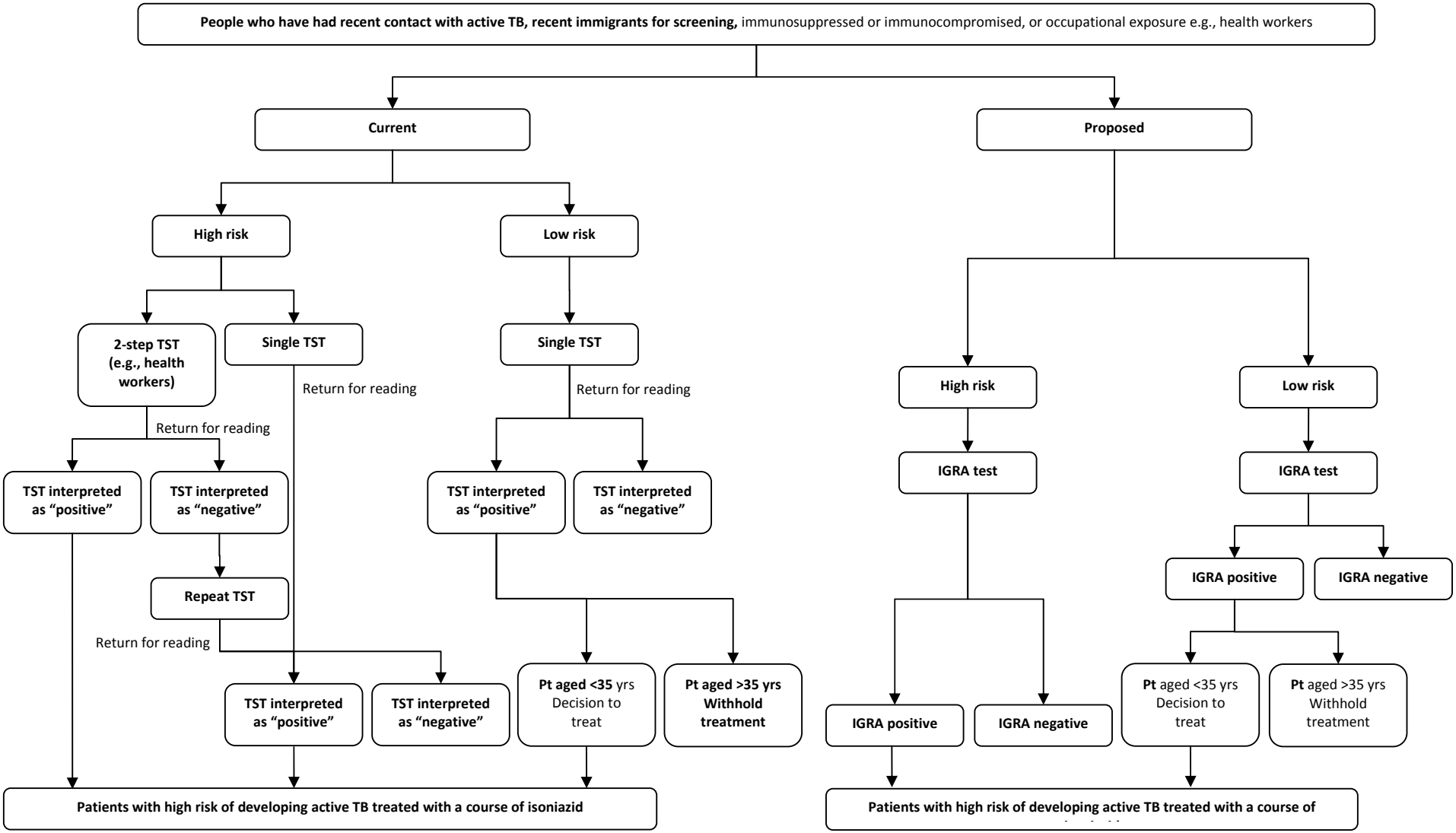
- healthcare workers;
- recent immigrants from high-incidence countries or those who may have lived in a country with endemic TB;
- people who have had recent contact with someone with active TB;
- patients who are immunosuppressed or immunocompromised due to disease or as a result of medical treatment.

Routine screening of travellers from high-incidence countries are not included in this population.

However, due to the limited data available no population-based analyses have been conducted (see Results of Assessment below).

The clinical management algorithm for detection of LTBI is presented in Figure 2, illustrating a scenario where IGRAs are not available (the current scenario) and a scenario where IGRAs are available (the proposed scenario). In the proposed scenario, IGRAs are positioned as a substitute for TST and will alter the clinical management algorithm by removing the need for two-step TST in healthcare workers and other populations.

Figure 2: Clinical management algorithms for the detection of LTBI by TST (current) and IGRAs (proposed)



Comparator

The appropriate comparator for the assessment of IGRAs for the diagnosis of LTBI in the target populations is TST.

The reference standard

The reference standard for the detection of LTBI is TST.

No true reference that provides an absolute diagnosis of LTBI is available; however, TST is the accepted reference standard[16]. As discussed in the section titled 'Existing procedures and tests', the diagnosis of LTBI by TST is subject to false-positives due to cross-reactivity with BCG vaccination and non-tuberculosis mycobacteria.

For the purposes of this assessment, the accuracy of IGRAs for diagnosis LTBI is compared with the results of TST. However, consideration has been given to the potential for IGRAs to overcome the limitations of TST.

Research questions

The research question addressed by this assessment is:

Will patient management that involves the use of IGRA to diagnose LTBI and to guide antibiotic treatment result in an improvement in health outcomes for patients being screened for LTBI or recent infection compared to the use of TST?

To address this research question it was developed into three parts:

i. What is the accuracy of IGRA versus TST in diagnosing LTBI?

ii. In response to information provided by diagnosis of LTBI by IGRA versus TST, will there be a change in the treatment decisions made by clinicians?

iii. As a result of more appropriate treatment decisions, will patients experience improved health outcomes?

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews to inform the assessment of IGRAs for diagnosis of LTBI. Table 11 lists the electronic databases searched and the periods covered by the searches.

Table 11: Electronic databases searched

Database	Period covered
Ovid Medline	1950-August 2010
Embase	to August 2010
Cochrane DSR, ACP Journal Club, DARE, CCTR, HTA and NHSEED	to August 2010

The search terms used included: tuberculosis, TB, latent tuberculosis, latent TB, LTBI, Interferon-gamma, QuantiFERON TB gold, QTF-G, interferon gamma release assay, IGRA, immunoenzyme techniques, enzyme-linked immunosorbent assay, enzyme-linked immunosorbent spot, ELISPOT, ESAT-6, CFP-10, Mantoux, Tuberculin test, tuberculin skin test, TST, tuberculin sensitivity test, pirquet, purified protein derivate, and PPD.

As advised by the Advisory Panel, the Ovid Medline and Embase databases were searched again in October 2011 to identify any additional follow-up studies which reported progression to active TB that had been published since August 2010. Studies which only reported agreement between TST and IGRAs were not included.

Selection criteria

Box 1summarises the selection criteria applied in the electronic searches. The search of the literature was not overly constrained to ensure that all studies that may have investigated the diagnosis of LTBI using IGRAs were located.

Box 1: Selection criteria for included studies

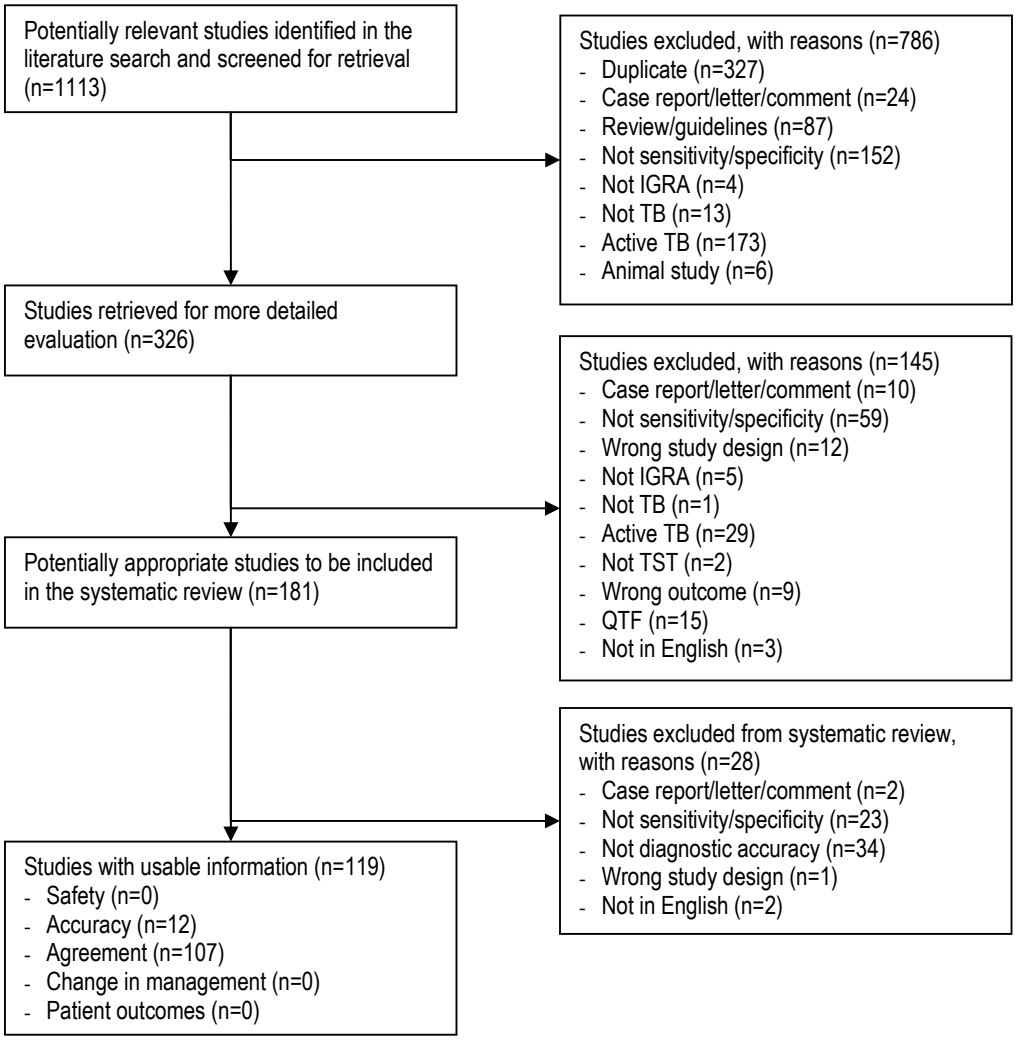
Research question: Will patient management that involves the use of IGRA to diagnose LTBI and to guide antibiotic treatment result in an improvement in health outcomes for patients being screened for LTBI or recent infection compared to the use of TST?		
Selection criteria	**Inclusion**	**Exclusion**
Study design	All study designs	None
Population	Diagnosis or screening for latent tuberculosis	Animal, active TB
Prior tests	Not specified	None
Index test	IGRA	None
Reference standard	TST	Heaf test
Comparator	TST	Heaf test
Outcomes	None specified	None
Publication type	None specified	None

Search results

The publications located by the electronic searches were then assessed to identify those that investigated the accuracy or efficacy of IGRAs in diagnosing LTBI. This process is summarised in Figure 3.

Quorum Flowchart

Figure 3: Summary of the process used to identify and select studies assessing the accuracy or effectiveness of IGRAs in diagnosing patients suspected of LTBI



Adapted from Moher et al (1999)

The search repeated in October 2011 identified an additional 360 studies. From these, six relevant studies with follow-up included.

Studies in which the study population included patients with suspected active TB disease whose results were reported as aggregate data were excluded from the review.

Appraisal of the evidence

Appraisal of the evidence was conducted at 3 stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000).

These dimensions (Table 12) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 12: Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

* See Table 13.

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The "level of evidence" reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see Table 13).

Table 13: Designations of levels of evidence according to type of research question (including table notes) (NHMRC 2008)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Table notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. Population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 14.

Table 14: Grading system used to rank included studies

Validity criteria	Description	Grading System
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed and to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium Q3 poor reference standard poor quality or insufficient information

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000a). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001). Studies of diagnostic accuracy were assessed using the QUADAS quality assessment tool (Whiting 2003).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000b). Studies need to be appropriately to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

For intervention studies it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000b).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

- The evidence base - which includes the number of studies sorted by their methodological quality and relevance to patients;
- The consistency of the study results - whether the better quality studies had results of a similar magnitude and in the same direction (i.e., homogenous or heterogeneous findings);
- The potential clinical impact - appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- The generalisability of the evidence to the target population; and
- The applicability of the evidence - integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 15) (NHMRC 2008).

Table 15: Body of evidence assessment matrix

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Adapted from (NHMRC 2008).

Expert advice

An advisory panel was established to provide guidance to the health technology assessors to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the advisory panel is provided in Appendix B.

Results of assessment

Is it safe?

No studies that specifically investigated the safety of IGRAs for the diagnosis of LTBI were identified. Because IGRAs require patients to undergo venipuncture for collection of blood for testing, it is anticipated that the only safety concerns likely to be associated with this intervention are those associated with venipuncture.

Summary of Safety

No studies were identified that specifically investigated the safety of IGRA for the diagnosis of LTBI. Given the nature of this intervention, it is not anticipated that it will be associated with any safety issues beyond those associated with collection of blood by venipuncture.

Is it effective?

Evidence of comparative effectiveness - results for the primary outcome of interest

The focus of the available literature assessing IGRAs and TST is essentially a consideration of the accuracy of the test – does a patient who was tested for LTBI either develop or not develop active TB? In this case the consideration is not whether there is an improvement in health outcomes for the patient, but whether the test accurately predicts if the patient will or will not progress to active TB disease.

While there is considerable literature assessing the concordance of IGRAs and TST (see below, indirect evidence) the literature looking at whether those who test positive, or negative to either an IGRA or TST then go on to develop active TB is more limited. A total of 18 studies were identified which had follow-up evidence indicating whether patients progressed to active TB in the longer term. Details of these studies are provided in Appendix D and Appendix E.

Methods of analysis

The outcomes assessed were test results (positive or negative) and the development of active TB during the follow-up period of the studies (true/false positives/negatives). In some studies, a proportion of patients who tested positive, either to an IGRA or TST, received preventive treatment (chemoprophylaxis), these patients were excluded from the analyses of true/false positives.

To compare the proportions of patients testing positive or negative and then progressing to active TB disease, meta-analyses were conducted when there was sufficient data. The software program RevMan 5 was used to conduct the statistical analyses. Results are presented for the random effects model. Odds ratio (OR) and risk difference (RD) results are provided, with the risk difference results to be applied in the economic evaluation. Heterogeneity was assessed using the I^2 statistic.

An odds ratio is essentially a ratio of the odds of an event (in this case progression to active TB) occurring in one group (e.g., those testing positive to an IGRA) divided by the odds of that event occurring in another group (e.g., those testing positive to TST). As a simple example, if 4 of 10 patients in one group have an event while 6 of 10 in the second group have the event, the odds ratio is calculated as (4/6)/(6/4) = 0.67/1.5 = 0.44.

By contrast, a risk difference describes the difference in risk of an event between the two groups. So for the example above, the risk difference would be -20%, calculated as (4/10)-(6/10) = 0.4-0.6 = -0.2. It should be noted that in the comparisons presented the 'Results' section below, the risk difference results are generally small, given that events did not occur with great frequency.

The odds ratios and risk differences are presented with 95% confidence intervals (CIs). A 95% CI is the range of values within which there is 95% confidence that the true population estimate lies. A detailed discussion of confidence intervals is available in a

paper by Gardner and Altman (1986)[17]. Because confidence intervals are calculated using standard error, the sample size has an indirect effect on the width of a confidence interval, with a smaller sample size leading to wider confidence intervals, which indicates less precision. A result is considered statistically significant if the confidence interval does not cross 1 in the case of odds ratios, or 0 in the case of risk difference.

Three overall comparisons were made for the current analyses:

i. an assessment of false-negatives, comparing the proportion who develop active TB who had a negative test result;

ii. an assessment of false-positives, which was analysed comparing the proportion of patients who were true-positives (i.e., those who tested positive and developed active TB);

iii. an assessment of overall positives – a comparison of how many patients test positive to either IGRAs or TST.

Results are provided for the overall comparisons, for which all available IGRA tests are combined and compared to TST, as well as each individual IGRA test compared to TST.

Of the 18 studies with follow-up data available, six compared QTF-GIT and TST, four compared QTF-G and TST, three compared T.SPOT®.TB and TST, three compared ELISPOT and TST, and two compared QTF-GIT, T.SPOT®.TB and TST.

Results

Table 16 provides the numbers testing positive or negative to IGRA or TST and the proportion who progressed to active TB within the study period, for each study. Results are grouped according to the type of IGRA test. In some studies, the number of patients in the study cohort differs from the number who underwent IGRA or TST. This table also provides the number who were treated for LTBI and therefore excluded from the analyses of true/false positives.

Table 16: Number of cases of active TB that developed in untreated individuals, by test result

Study	Follow up period	n, study cohort	Index test indeterminate or failed, n/N (%)	TST lost to follow up	Index test result						TST result						Total cohort	
					Positive			Negative			Positive			Negative				
					n	n, excluded from follow up	n, progressed to active TB, n/N (%)	n	n, excluded from follow up	n, progressed to active TB, n/N (%)	n	n, excluded from follow-up	n, progressed to active TB (%)	n	n, excluded from follow up	n, progressed to active TB (%)	n, excluded from follow-up	n, progressed to active TB (%)
QTF-GIT																		
Aichelburg et al (2009)[18]	2 yrs	830	47/830 (5.7)	0/42 (0.0)	44	8	3/36 (8.3)	739	1	0/738 (0.0)	31	NR	NR	11	NR	NR	8	3/822 (0.4)
Diel et al (2008)[19]	1 yr	601	0/292 (0.0)[a]	19/620 (3.1)	66	25	6/41 (14.6)	535	0	0/535 (0.0)	243	24	5/219 (2.3)	358	0	1/358 (0.3)	25	6/576 (1.0)
Harstad et al (2010)[20]	23-32 mths	823	NA	NA	246	8	8/238 (3.4)	577	0	0/577 (0.0)	426	11	7/415 (1.7)	396	0	1/395 (0.2)	8	8/815 (1.0)
Kik et al (2010)[35]	2 yrs	339	12/339 (3.5)	11/541 (2.0)	160	0	5/160 (3.1)	149	0	3/149 (2.0)	339	0	9/339 (2.6)	94	0	0/94 (0.0)	0	9/339 (2.6)
Lee et al (2009)[34] ESRD patients	2 yrs	32	2/32 (6.25)	0/32 (0.0)	12	0	1/12 (8.3)	18	0	0/18 (0.0)	18	0	1/18 (5.5)	14	0	1/14 (7.1)	0	2/32 (6.25)
Lee et al (2009)[34] Healthy controls	2 yrs	32	0/32 (0.0)	0/32 (0.0)	4	0	0/4 (0.0)	28	0	0/28 (0.0)	15	0	0/15 (0.0)	17	0	0/17 (0.0)	0	0/32 (0.0)
Mahomed et al (2011)[21]	22-24 mths	2669	NR	NR	2669	0	39/2669 (1.5)	2575	0	13/2575 (0.5)	2894	0	40/2894 (1.4)	2350	0	12/2350 (0.5)	0	52/5244 (1.0)
Ringshausen et al (2009)[22]	2 yrs	144	1/144 (0.7)	0/144 (0.0)	13	NR	0/13 (0.0)	130	NR	0/130 (0.0)	40	NR	0/40 (0.0)	103	NR	0/103 (0.0)	1	0/143 (0.0)
Santin et al (2011)[23]	1-24 mths	135	2/135 (1.5)	0/135 (0.0)	13	NA	NA	120	NA	NA	9	NA	NA	124	NA	NA	12	0/106 (0.0)
QTF-G																		
Higuchi et al (2007)[24]	3.5 yrs	349	0/88 (0.0)	0/349 (0.0)	4	4	0	82	0	NF	95	4	0/91 (0.0)	254	NF	NF	163	0/91 (0.0)
Lee et al (2009)[25]	1 yr	196	0/196 (0.0)	0/196 (0.0)	28	NR	NR	168	NR	NR	101	NR	NR	95	NR	NR	26	0/169 (0.0)
Noorbakhsh et al (2011)[26]	1 yr	59	0/59 (0.0)	0/59 (0.0)	18	0	10/18 (55.5)	41	0	0/41 (0.0)	8	0	3/8 (37.5)	50	0	7/50 (14.0)	10	10/59 (16.9)
Soborg et al (2007)[27]	18 mths	139	0/139 (0.0)	0/139 (0.0)	2	0	0/2 (0.0)	137	0	NF	47	0	0/47 (0.0)	92	0	NF	92	0/47 (0.0)

Study	Follow up period	n, study cohort	Index test indeterminate or failed, n/N (%)	TST lost to follow up	Index test result						TST result						Total cohort	
					Positive			Negative			Positive			Negative				
					n	n, excluded from follow up	n, progressed to active TB, n/N (%)	n	n, excluded from follow up	n, progressed to active TB, n/N (%)	n	n, excluded from follow-up	n, progressed to active TB (%)	n	n, excluded from follow up	n, progressed to active TB (%)	n, excluded from follow-up	n, progressed to active TB (%)
T.SPOT®.TB																		
Kik et al (2010)[35]	2 yrs	339	40/339 (11.8)[b]	11/541 (2.0)[c]	181	0	6/181 (3.3)	118	0	2/118 (1.7)[d]	339	0	9/339 (2.6)	94	0	0/94 (0.0)	0	9/339 (2.6)
Kim et al (2011)[28]	1-2.5 yrs	296	32/296 (10.8)[e]	0/296 (0.0)	89	18	4/71 (5.6)	176	5	0/171 (0.0)	24	24	0	272	0	4/272 (1.5)	24	4/272 (1.5)
Lee et al (2009)[34] ESRD patients	2 yrs	32	0/32 (0.0)	0/32 (0.0)	15	0	0/15 (0.0)	17	0	0/17 (0.0)	18	0	1/18 (5.5)	14	0	1/14 (7.1)	0	2/32 (6.25)
Leung et al (2011)[29]	9-46 mths	331	10/331 (3.0)	19/331 (5.7)	204	53	12/151 (7.9)	104	14	1/90 (1.1)	203	67	9/136 (6.6)	105	0	4/105 (3.8)	67	13/241 (5.4)
Piana et al (2006)[30]	1 yr	138	9/138 (6.5)	16/138 (4.3)	24	0	0/24 (0.0)	91	0	0/91 (0.0)	55	0	0/55 (0.0)	60	0	0/60 (0.0)	0	0/138 (0.0)
ELISPOT																		
Hill et al (2007)[31]	18 mths	655	45/655 (6.8)	52/655 (7.9)	222	0	5/222 (2.2)	335	0	8/335 (2.4)	400	0	3/400 (0.75)	158	0	5/158 (3.2)	0	13/665 (1.9)[f]
Hill et al (2008)[32]	24 mths	2348	NR	NR	649	0	11/649 (1.7)	1087	0	10/1087 (0.9)	843	0	14/843 (1.7)	1387	0	11/1387 (0.8)	0	26/2348 (1.1)
Wu et al (2009)[33]	2 yrs	100	0/100 (0.0)	0/100 (0.0)	21	18[g]	0/3 (0.0)[g]	51	49[g]	0/2 (0.0)[g]	41	36[g]	0/5 (0.0)[g]	59	NF	NF	95[g]	0/5 (0.0)[g]

TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; N= number; NR = not reported; NF = not followed-up; NA = not available; ESRD = end stage renal disease; yr = year; mths = months.

a 292/601 patients were tested using the mitogen control tube.

b One patient with failed phlebotomy, but TST+ developed active TB.

c Patients who did not return for TST to be read were excluded from further testing.

d One additional patient with an indeterminate QTF-GIT and positive TST result progressed to active TB.

e No patients with indeterminate IGRA result progressed to active TB.

f Includes five cases of 'secondary TB' diagnosed recruitment which were not excluded by the study authors.

g Only 5 individuals with a strongly positive TST were followed for 20 months.

As can be seen in Table 16, the proportion of tested patients developing TB is small, and there is variation among the tests and test outcomes as to whether the test accurately predicted the occurrence of TB.

False-negatives

The results of assessment of patients who test negative to IGRA or TST and then progress to active TB is provided in Figure 4 (odds ratio) and

Figure 5 (risk difference). This analysis indicates no statistically significant difference between IGRAs and TST tests in the risk of false-negatives (OR = 0.80; 95% CI: 0.51, 1.27).

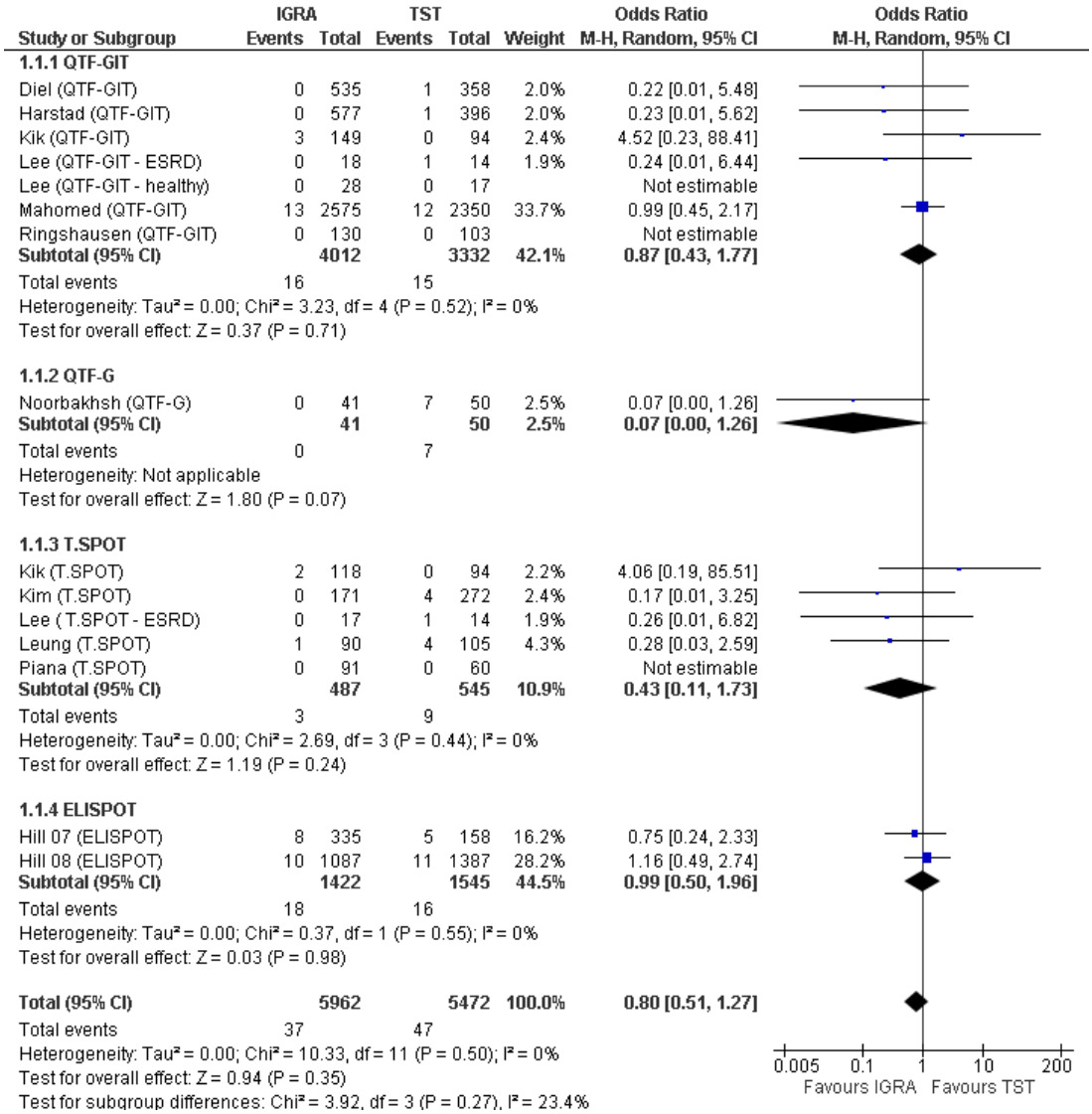


Figure 4: Comparison of IGRAs and TST assessing occurrence of false-negative results – odds ratio

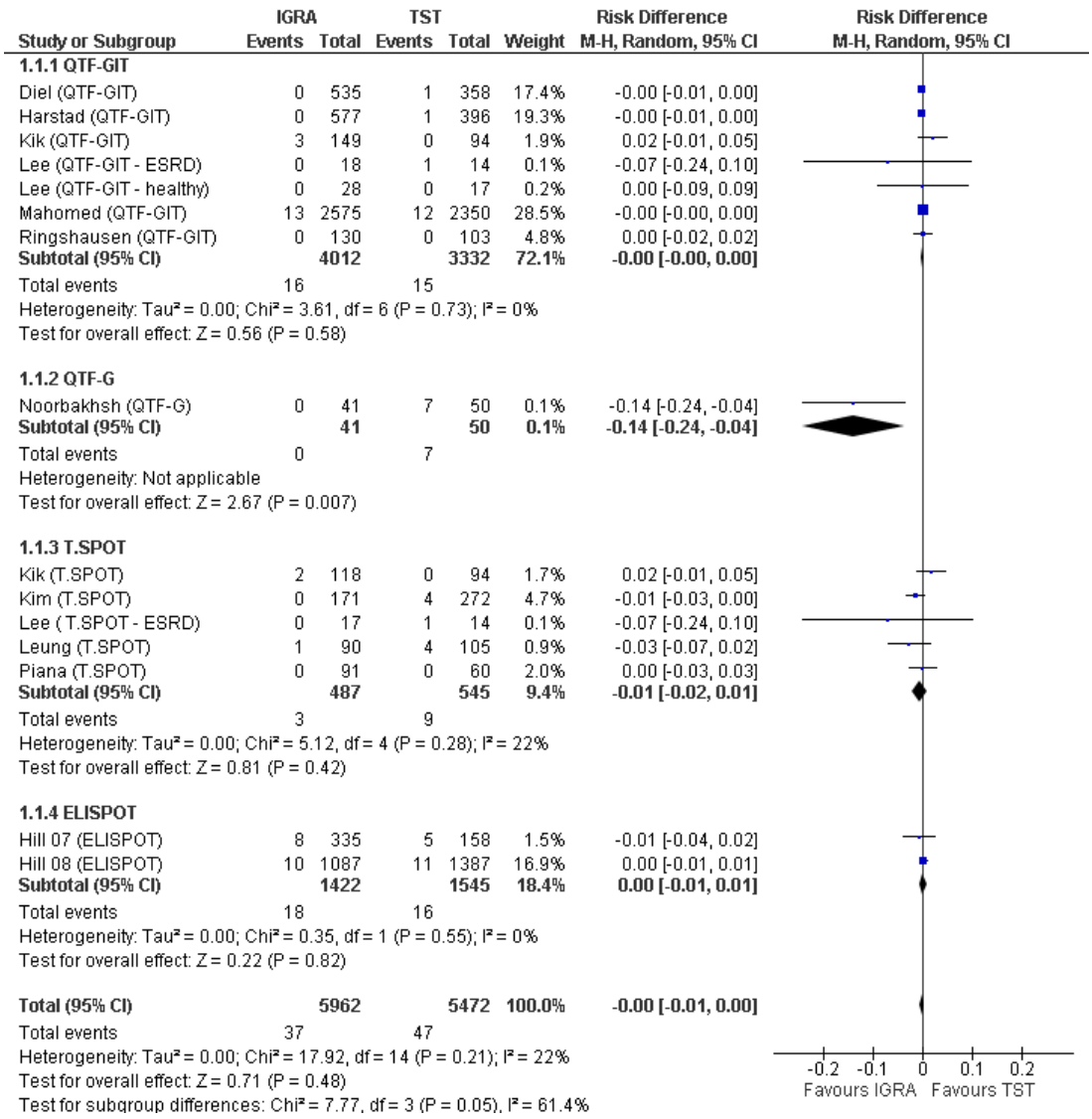


Figure 5: Comparison of IGRAs and TST assessing occurrence of false-negative results - risk difference

True-positives

To assess the effect of true-positives , the analysis compared the true-positive proportions; that is, the proportion of patients who progress to active TB disease after a positive test result. Results are provided in Figure 6 (odds ratio) and Figure 7 (risk difference). There is a statistically significant difference, with the rate of true-positives being significantly higher in patients tested using IGRAs compared with those tested using TST (OR = 1.42; 95% CI: 1.02, 1.99). This suggests that an IGRA can more accurately predict which patients will go on to develop active TB.

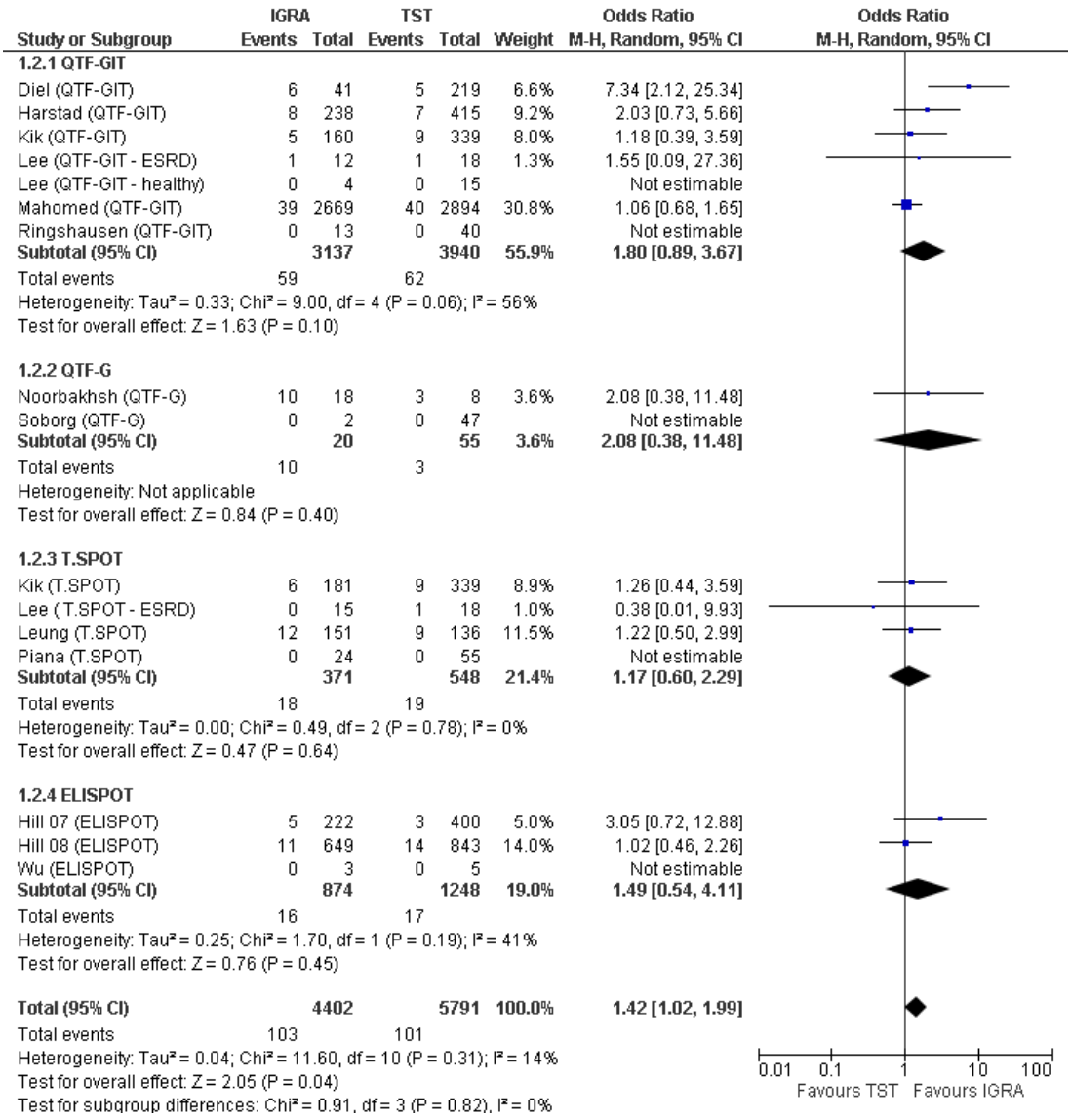


Figure 6: Comparison of IGRAs and TST assessing occurrence of true-positive results - odds ratio

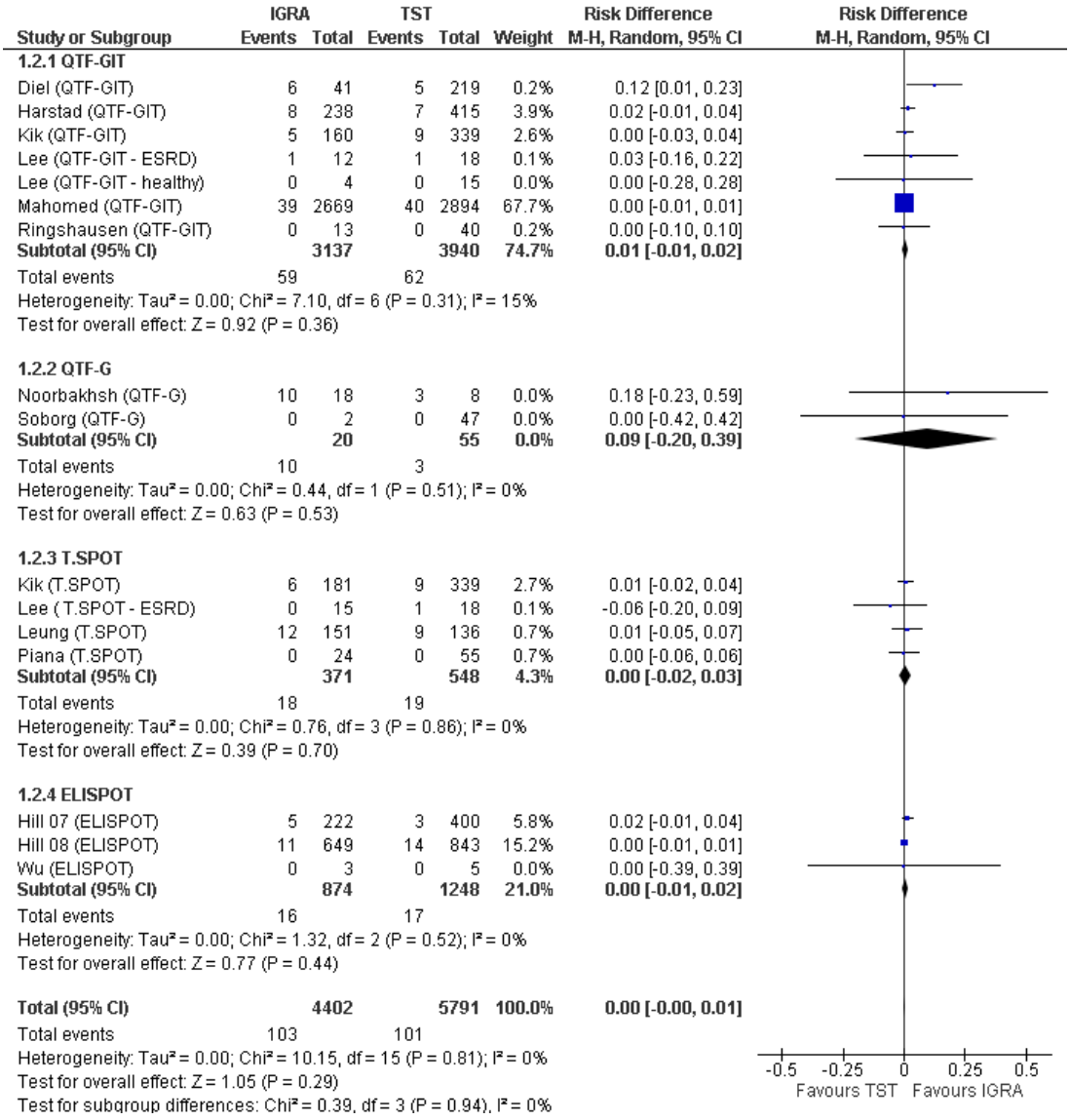


Figure 7: Comparison of IGRAs and TST assessing occurrence of true-positive results - risk difference

Overall positives

Figure 8 provides the results of the comparison between IGRAs and TST for the proportion of patients who test positive. This analysis shows that significantly fewer patients test positive to IGRA than to TST (OR = 0.42; 95% CI: 0.31, 0.57). However, it is notable that this analysis is associated with a significant amount of heterogeneity (I^2 = 95%). Importantly, as shown in Figure 6, the smaller proportion of patients testing positive with IGRA occurs with no increase in risk of false-negatives. This suggests that IGRA may be a more efficient test for LTBI than TST.

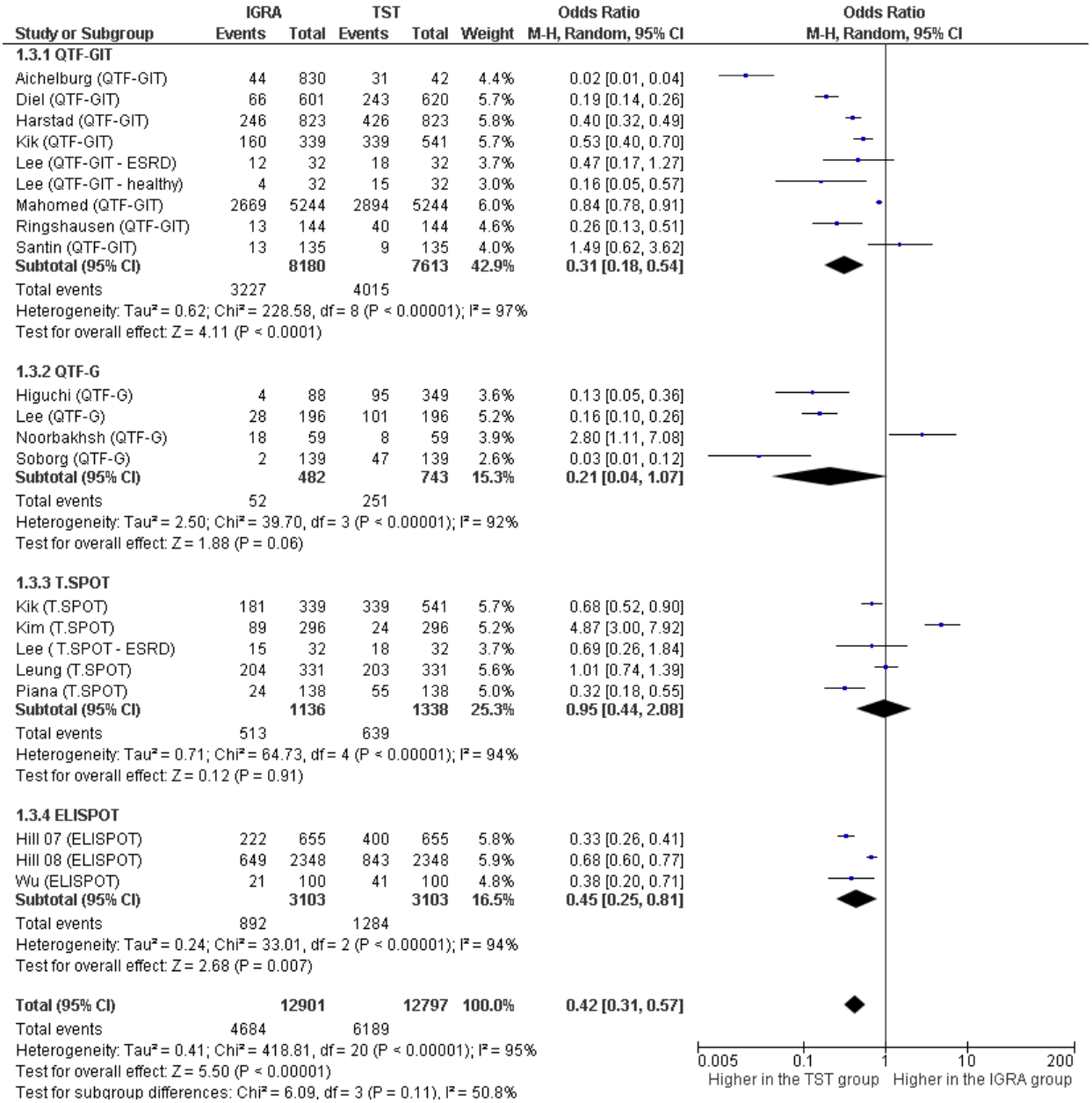


Figure 8: Comparison of IGRAs and TST assessing occurrence of overall positive test results - odds ratio

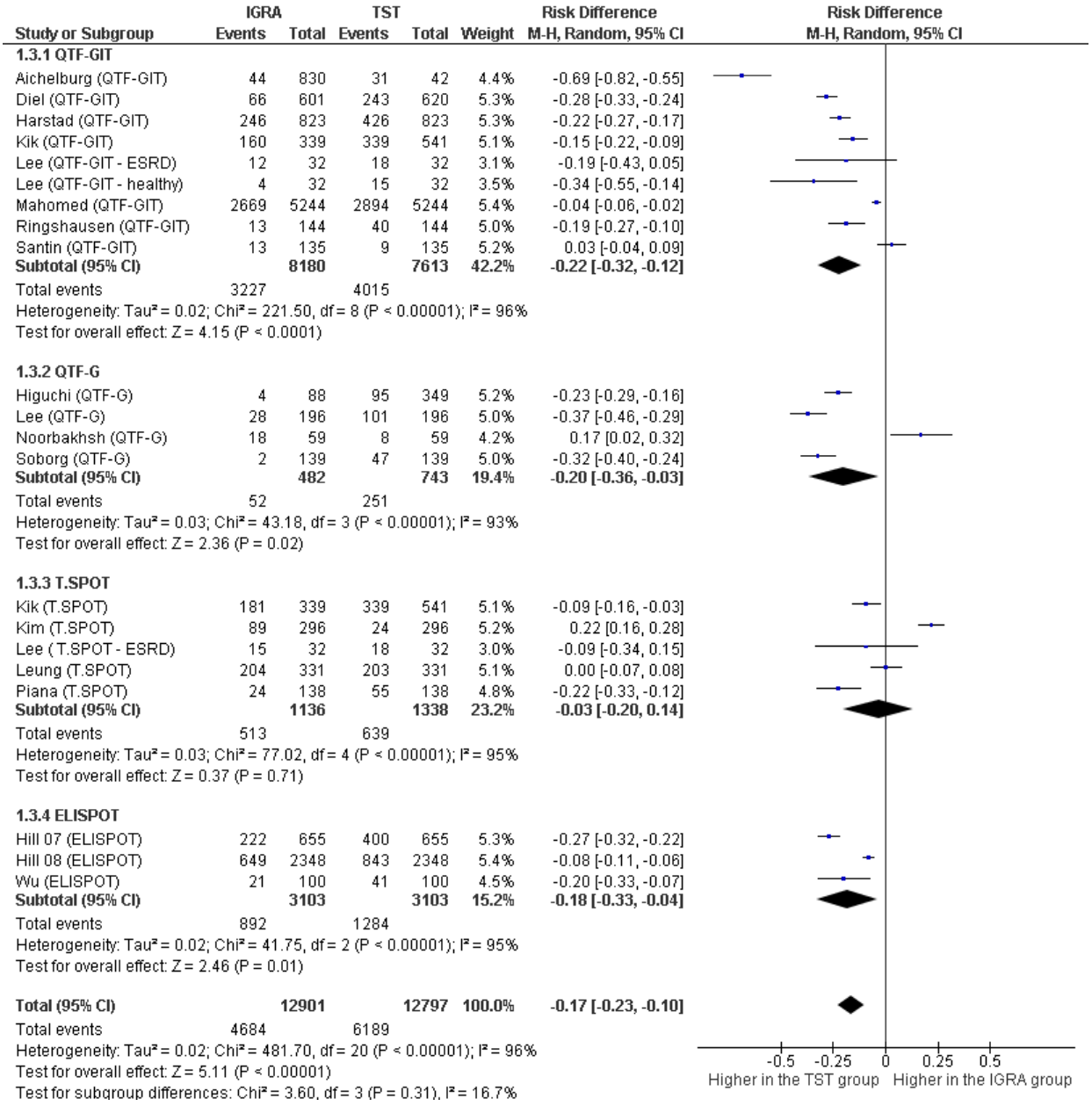


Figure 9: Comparison of IGRAs and TST assessing occurrence of overall positive test results – risk difference

Conclusion

The comparison of IGRAs and TST indicates no statistically significant difference between the two tests regarding occurrence of false-negative test results. However, the rate of true-positives is significantly higher in patients assessed by IGRA, and significantly fewer patients test positive to IGRA compared with TST, with no increase in risk of false-negatives. This suggests that IGRAs may be a more efficient test for LTBI than TST.

Evidence of comparative effectiveness - results for the secondary outcome of interest

Is it accurate? - concordance

There is a large body of literature assessing the concordance between IGRAs and TST. A total of 119 studies were identified as relevant, with 63 assessing QTF-GIT and TST, 33 assessing QTF-G and TST, 37 assessing T.SPOT®.TB and TST and 19 assessing ELISPOT and TST. Some studies assessed the concordance between two IGRAs and TST simultaneously. Details of the included studies are reported in Appendix E.

These studies are of interest because they allow for a determination of whether the results from the follow-up studies, presented above in 'Evidence of comparative effectiveness - results for the primary outcome of interest', are generalisable.

Methods of analysis

Overall agreement between IGRAs and TST for the individual studies are provided as proportions. For studies that included the Kappa statistic, that result is also provided. Meta-analyses were conducted to assess the agreement between IGRAs and TST across the different patient populations and by the proportion of the study cohort that was BCG vaccinated.

Studies that reported follow-up and are included in the ' Evidence of comparative effectiveness - results for the primary outcome of interest' section above are highlighted in the tables and the forest plots in blue.

Results

<u>QuantiFERON®- TB Gold In-tube</u>

A total of 63 studies were identified which reported the agreement between QTF-GIT and TST. Table 17 and Table 18 report the individual study results for the agreement between QTF-GIT and TST (intention to treat [ITT]) and QTF-GIT and TST (per protocol [PP]), respectively.

Forest plots for the meta-analyses of overall agreement are presented in Figure 10 to Figure 13.

Table 17: Agreement of QTF-GIT and TST (ITT)

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Balcells et al (2008)[38] **HIV positive**	116	96/109 (88.1)	2/116 (1.7)	6/116 (5.2)	9/116 (7.7)	90/116 (77.6)	2/116 (1.7)	8/116 (6.9)	99/116 (85.3)
Bartalesi et al (2009)[39] **Rheumatic disease pts**	398	16/393 (4.1)	5/398 (1.2)	0/398 (0.0)	39/398 (9.8)	306/398 (76.9)	13/398 (3.3)	35/398 (8.8)	345/398 (87.8)
Chen et al (2008) **RA patients**	35	35/35 (100)	2/35 (5.7)	0/35 (0.0)	5/35 (14.3)	15/35 (42.8)	1/35 (2.8)	12/35 (34.3)	20/35 (60.0)
Cobanoglu et al (2007)[42] **Pts receiving TNF-α blockers**	68	68/68 (100)	7/68 (10.3)	0/68 (0.0)	8/68 (11.8)	23/68 (33.8)	1/68 (1.5)	29/68 (42.6)	31/68 (45.6)
Cobanoglu et al (2007)[42] **Pts receiving TNF-α blockers - control group**	38	38/38 (100)	2/38 (5.3)	0/38 (0.0)	0/38 (0.0)	23/38 (60.5)	1/38 (2.6)	12/38 (31.6)	23/38 (60.5)
Hoffmann et al (2010)[49] **HD patients**	39	18/39 (46.1)	2/39 (5.1)	6/39 (15.4)[a]	2/39 (5.1)	22/39 (56.4)	7/39 (17.9)	1/39 (2.6)	24/39 (61.5)
Luetkemeyer et al (2007)[56] **HIV positive**	294	18/294 (6.0)	15/294 (5.1)	89/294 (30.3)	8/294 (2.7)	167/294 (56.8)	11/294 (3.7)	10/294 (3.4)	175/294 (59.5)
Ponce de Leon et al (2008)[64] **RA patients**	106	81/101 (80.2)	2/106 (1.9)	3/106 (2.8)[b]	21/106 (19.8)	50/106 (47.2)	24/106 (22.6)	6/106 (5.7)	71/106 (67.0)
Ponce de Leon et al (2008)[64] **RA patients – control group**	97	75/93 (80.6)	0/97 (0.0)	4/97 (4.1)[b]	50/97 (51.5)	27/97 (27.6)	5/97 (5.1)	11/97 (11.3)	77/97 (79.4)
Schoepher et al (2008)[67] **IBD**	168	118/168 (70.2)	5/168 (3)	0/168 (0.0)	2/168 (1.2)	NR	12/168 (7.1)	NR	K=-0.0297
Schoepher et al (2008)[67] **IBD – control group**	44	33/44 (75.0)	0/44 (0.0))	0/44 (0.0)	3/44 (6.8	NR	1/44 (2.3)	NR	K=0.1302
Seyhan et al (2010)[68 a] **HD patients**	100	72/100 (72)	0/100 (0.0)	0/100 (0.0)	21/100 (21)	44/100 (44)	22/100 (22)	13/100 (13)	65/100 (65) [K=0.26]
Talati et al (2009)[119] **HIV positive**	336	25/336 (7.4)	6/336 (1.8)	58/336 (17.3)	2/336 (0.6)	259/336 (77.1)	7/336 (2.1)	5/336 (1.5)	261/336 (77.7) [K=0.23, 95% CI (-0.05, 0.51)]
Contact cases									

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Adetifa et al (2007)**Error! Bookmark not defined.**	194[c]	92/194 (47.4)	7/194 (3.6)	NA	69/194 (35.6)	57/194 (29.4)	33/194 (17.0)	16/194 (8.2)	126/194 (64.9)
Adetifa et al (2010)[108] **Children**	285	173/285 (60.7)	0/256 (0.0)	36/285 (12.6)	43/256 (17.0)	129/215 (50.4)	29/256 (11.3)	14/256 (5.5)	172/256 (67.2)
Diel et al (2006)[44]	311	157/309 (50.8)	0/311 (0.0)	2/311 (0.6)	28/309 (9.1)	169/309 (54.7)	3/309 (1)	109/309 (35.3)	197/309 (63.8) [K=0.20, 95% CI 0.14–0.23]
Diel et al (2008)[19]	601	278/601 (46.2)	0/601 (0.0)	19/620 (3.1)	62/601 (10.3)	354/601 (58.9)	181/601 (30.1)	4/601 (0.7)	416/601 (69.2) [k=0.276]
Dominguez et al (2008)[114] **Contact tracing**	270	128/270 (47.4)	1/270 (0.4)	0/270 (0.0)	NR	NR	NR	NR	151/270 (55.9) [k=0.29, SE 0.040]
Dominguez et al (2008)[114] **Screening**	314	136/314 (43.3)	0/314 (0.0)	0/314 (0.0)	NR	NR	NR	NR	179/314 (57.0) [k=0.25, SE 0.035]
Lee et al (2010)[52]	214	135/201 (67.2)	11/214 (5.1)	22/214 (10.3)	97/214 (45.3)	48/214 (22.4)	11/214 (5.1)	29/214 (13.5)	145/214 (67.7)
Petrucci et al (2008)[63] **Children (Brazil)**	113	113/113 (100)	1/113 (0.9)	2/113 (1.8)	33/113 (29.2)	63/113 (55.7)	12/113 (10.6)	2/113 (1.8)	96/113 (84.9)
Petrucci et al (2008)[63] **Children (Nepal)**	146	137/146 (94)	5/146 (3.4)	4/146 (2.7)	65/146 (44.5)	58/146 (39.7)	5/146 (3.4)	9/137 (6.2)	123/137 (84.2)
Recent immigrants									
Baker et al (2009)[37]	198	NR	0/198 (0.0)	3/198 (1.5) [c]	85/198 (42.9)	67/198 (33.8)	20/198 (10.1)	23/198 (11.6)	152/198 (76.8)
Kik et al (2010)[35]	339	274/339 (80.8)	12/339 (3.5)	11/541 (2.0)	160/339 (47.2)	NA	NA	167 (49.3)	NA
Orlando et al (2010)[61]	1130	72/1130 (6.37)	15/1130 (1.3)[d]	231/1130 (20.4)[e]	-	-	69/1130 (6.1)	193/1130 (17.1)	625/1130 (55.3)
Saracino et al (2009)[66]	449[f]	NR	0/452 (0.0)	169/452 (37.4)	49/449 (10.9)[f]	149/449 (33.2)[f]	58/449 (12.9)[f]	23/449 (5.1)[f]	198/449 (44.1)[f]
Winje et al (2008a)[71]	1000	658/904 (72.8)	82/1000 (8.2)	5/1000 (0.5)	232/1000 (23.2)	420/1000 (42.0)	32/1000 (3.2)	228/1000 (22.8)	652/1000 (65.2)
Children									
Bianchi et al (2009)[40]	320	172/320 (53.7)	2/320 (0.6)	0/320 (0.0)	22/320 (6.9)	251/320 (78.4)	23/320 (7.2)	22/320 (6.9)	273/320 (85.3)
Chun et al (2008)[41] **Close contacts**	42	42/42 (100)	0/42 (0.0)	0/42 (0.0)	8/42 (19.0)	16/42 (38.1)	0/42 (0.0)	18/42 (42.8)	24/42 (57.1) [K=0.19; p<0.05]
Chun et al (2008)[41] **Casual contacts**	29	29/29 (100)	2/29 (6.9)	0/29 (0.0)	2/29 (6.9)	11/29 (37.9)	0/29 (0.0)	14/29 (48.3)	13/29 (44.8) [K=0.38, p<0.01]
Chun et al (2008)[41] **TST+ but no contact history**	65	65/65 (100)	0/65 (0.0)	0/65 (0.0)	1/65 (1.5)	NA	NA	64/65 (98.5)	NA

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Connell et al (2008)[113]	91	48/87 (55)	3/91 (3.2)	4/91 (4.4)	18/91 (19.8)	44/91 (48.3)	2/91 (2.2)	20/91 (22.0)	62/91 (68.1)
Dogra et al (2006)[45]	105	86/105 (82.0)	0/105 (0.0)	0/105 (0.0)	8/105 (7.6)	92/105 (87.6)	3/105 (2.8)	2/105 (1.9)	100/105 (95.2) [K=0.73, 95% CI 0.53-0.92]
Grare et al (2010)[48]	44	20/44 (45.4)	5/44 (11.4)	7/44 (15.9)	5/44 (11.4)	22/44 (50.0)	0/44 (0.0)	10/44 (22.7)	27/44 (61.4)
Lighter et al (2009)[55]	207	74/207 (36)	3/207 (1.4)	0/207 (0.0)	27/207 (13.0)	85/207 (41.1)	4/207 (1.9)	88/207 (42.5)	112/207 (54.1)
Nakaoka et al (2006)[58] **Low risk**	129	187/207 (90)	9/129	8/129	6/129 (4.6)	91/129 (70.5)	4/129 (3.1)	12/129 (9.3)	84/129 (65.1)
Nakaoka et al (2006)[58] **High risk**	78	187/207 (90)	5/78	0/78 (0.0)	34/78 (43.6)	15/78 (19.2)	15/78 (19.2)	2/78 (2.6)	49/78 (62.8)
Stefan et al (2010)[118c]	34	(99)[f]	5/34 (14.7)	0/34 (0.0)	1/34 (2.9)	24/34 (70.6)	2/34 (5.9)	2/34 (5.9)	25/34 (73.5)
Tsiouris et al (2006)[69]	221	115/184 (72.3)	37/221 (16.7)[g]	0/221 (0.0)	51/221 (23.1)	94/221 (42.5)	10/221 (4.5)	29/221 (13.1)	145/221 (65.6)
Winje et al (2008b)[72]	519	236/511 (46.2)	16/519 (3.1)[h]	NA	44/519 (8.5)	NA	NA	467/519 (90.0)	NA
Healthcare workers									
Alvarez-Leon et al (2009)[36]	134	37/134 (35.1)	3/134 (2.2)	8/134 (6.0)	5/134 (3.7)	111/134 (82.8)	3/134 (2.2)	4/134 (3.0)	116/134 (86.6)
Casas et al (2009)[112]	147	23/147 (15.6)	2/147 (1.4)	0/147 (0.0)	42/147 (28.6)	43/147 (29.2)	1/147 (0.7)	59/147 (40.1)	85/147 (57.8)
Casas et al (2009)[112**] **Previously TST positive**	95	19/95 (20.0)	2/95 (2.1)	0/95 (0.0)	34/95 (35.8)	NA	NA	59/95 (62.1)	NA
Casas et al (2009)[112**] **No previous positive TST**	52	4/52 (7.7)	0/52 (0.0)	0/52 (0.0)	8/52 (15.4)	43/52 (82.7)	1/52 (1.9)	0/52 (0.0)	51/52 (98.1)
Cummings et al (2009)[43]	182	NR	10/182 (5)	0/182 (0.0)	0/182 (0)	165/182 (90.6)	3/182 (1.6)	4/182 (2.2)	165/182 (90.6)
Fox et al (2009)[46]	100	37/100 (37.0)	9/100 (9.0)	0/100 (0.0)	9/100 (9.0)	52/100 (52.0)	8/100 (8.0)	22/100 (22.0)	61/100 (61.0) [K=0.19]
Kariminia et al (2009)[50] **Low risk group**	166	166/166 (100)	10/166 (6.0)	0/166 (0.0)	6/166 (3.6)	76/166 (45.8)	5/166 (3.0)	69/166 (41.6)	82/166 (49.4)
Kariminia et al (2009)[50] **High risk group**	20	20/20 (100)	0/20 (0.0)	0/20 (0.0)	3/20 (15)	10/20 (50)	0/20 (0)	7/20 (35)	13/20 (63.2) [95% CI 42/84, k=0.28]
Lien et al (2009)[54**] **One step ≥10 mm**	288[a]	112/300 (37.3)	33/288 (11.4)	0/288 (0.0)	114/288 (39.6)	71/288 (24.6)	21/288 (7.3)	49/288 (17.0)	185/288 (64.2)
Lien et al (2009)[54] **Two step ≥10 mm**	288[a]	112/300 (37.3)	33/288 (11.4)	0/288 (0.0)	119/288 (41.3)	62/288 (21.5)	16/288 (5.5)	58/288 (20.1)	181/288 (62.8)
Mirtskhulava et al (2008)[57]	270	206/265 (77.7)	0/270 (0.0)	5/270 (1.8)	133/270 (49.2)	62/270 (23.0)	26/270 (9.6)	44/270 (16.3)	195/270 (72.2)

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Nienhaus et al (2008)[59]	261	98/261 (37.5)	0/261 (0.0)	0/261 (0.0)	15/261 (5.7)	188/261 (72.0)	10/261 (3.8)	48/261 (18.4)	203/261 (77.7) [k=0.24, *p*=0.001] [correlation 0.27, *p*=0.001]
Pai et al (2005)[62]	726	514/726 (71)	1/725 (0.1)	5/725 (0.7)	226/726 (31.1)	359/726 (49.4)	62/726 (8.5)	72/726 (9.9)	585/726 (80.6)
Ringshausen et al (2009)[22]	144	73/143 (51.0)	1/144 (0.7)	0/144 (0.0)	7/144 (4.9)	97/144 (67.4)	6/144 (4.2)	33/144 (22.9)	104/144 (72.2)
Zhao et al (2009)[73]	40	NR	0/40 (0.0)	0/40 (0.0)	10/40 (25.0)	20/40 (50.0)	0/40 (0.0)	10/40 (25.0)	30/40 (75) (k=0.5, 95% CI 0.268-0.732)
Military personnel									
Franken et al (2007)[47]	746	108/909 (11.9)	0/746 (0.0)	70/746 (9.4)	19/746 (2.5)	535/746 (71.7)	2/746 (0.3)	120/746 (16.1)	554/746 (74.3)
Franken et al (2007)[47**] **≥15 mm**	746	108/909 (11.9)	0/746 (0.0)	70/746 (9.4)	10/746 (1.3)	614/746 (82.3)	11/746 (1.5)	41/746 (5.5)	624/746 (83.6)
Katsenos et al (2010)[51]	129	129/129 (100)	0/129 (0.0)	0/129 (0.0)	11/129 (8.5)	31/129 (24.0)	2/129 (1.5)	85/129 (65.9)	42/129 (32.5)
Mixed population studies									
Leyten et al (2007)**Error! Bookmark not defined.** **TST conversion during contact tracing and controls**	40	16/40 (40.0)	0/40 (0.0)	0/40 (0.0)	NR	NR	NR	NR	(58) [k=0.28]
Nienhaus et al (2008b)[60] **Contact cases and HCWS**	1040	448/1033 (43.4)	7/1040 (0.7)	0/1040 (0.0)	66/1040 (6.3)	808/1040 (77.7)	34/1040 (3.3)	125/1040 (12.0)	874/1040 (84.0)
Healthy individuals									
Mahomed et al (2006)[107]	364	289/358 (80.7)	5/364 (1.4)	1/364 (0.3)	189/364 (51.9)	57/364 (15.6)	12/364 (3.3)	100/364 (27.5)	246/364 (67.6)

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR= not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a Includes five patients who refused TST .

b Includes one patient with hypersensitivity to PDD.

c Only patients with valid results for both QTF-GIT and ELISPOT were reported.

d Includes 2/1030 participants who refused venipuncture.

e Includes one patient in which a TST was not performed.

f Estimated from neonatal vaccination coverage

g Thirty seven patients had unsuccessful phlebotomy.

h Among 58 children with a positive first QTF analysis, 16 (28%) had a negative result on the confirmatory analysis of the same plasma sample and the result was considered non-conclusive. Eight of them submitted a new blood sample for QTF testing and are included in the study group based on the second test result; the remaining eight were excluded from analysis.

Table 18: Agreement of QTF-GIT and TST (PP)

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Aichelburg et al (2009)[18] **HIV positive**	42	NR	47/830 (5.6)	0/42 (0.0)	31/42 (73.8)	NA	11/42 (26.2)	NA	NA
Balcells et al (2008)[38] **HIV positive**	116	96/109 (88.1)	2/116 (1.7)	6/116 (5.2)	9/109 (8.2)	90/109 (82.6)	2/109 (1.8)	8/109 (7.3)	99/109 (90.8) [k=0.59; 95% CI 0.411-0.775]
Luetkemeyer et al (2007)[56] **HIV positive**	294	18/294 (6.0)	15/294 (5.1)	89/294 (30.3)	8/196 (4.1)	167/196 (85.2)	11/196 (5.6)	10/196 (5.1)	175/196 (89.3) [k=0.37, p≤0.001]
Cobanoglu et al (2007)[42] **Pts receiving TNF-α blockers** **Total cohort**	68	68/68 (100)	7/68 (10.3)	0/68 (0.0)	8/61 (13.1)	23/61 (37.7)	1/61 (1.6)	29/61 (47.5)	31/61 (50.8)
Cobaoglu et al (2007)[42**] **Pts receiving TNF-α blockers** **Age <25 years**	NA	NR	NA	-	1/32 (3.1)	14/32 (43.7)	1/32 (3.1)	16/32 (50.0)	15/32 (46.9) [k=-0.07]
Cobanoglu et al (2007)[42**] **Pts receiving TNF-α blockers** **Age ≥25 years**	NA	NR	NA	-	7/29 (24.1)	9/29 (31.0)	0/29 (0.0)	13/29 (44.8)	16/29 (55.2) [k=0.25]
Cobanoglu et al (2007)[42] **Controls - total cohort**	38	38/38 (100)	2/38 (5.3)	0/38 (0.0)	0/36 (0.0)	23/36 (63.9)	1/36 (2.8)	12/36 (33.3)	23/36 (63.9)
Cobanoglu et al (2007)[42**] **Controls - age <25 years**	NA	NR	NA	-	0/25 (0.0)	16/25 (64.0)	0/25 (0.0)	9/25 (36.0)	16/25 (64.0) (k=0.00)
Cobanoglu et al (2007)[42**] **Controls - age ≥25 years**	NA	NR	NA	-	0/11 (0.0)	7/11 (63.6)	1/11 (9.1)	3/11 (27.3)	7/11 (63.6) (k=-0.158)
Ponce de Leon et al (2008)[64] **RA patients**	106	81/101 (80.2)	2/106 (1.9)	3/106 (2.8)	21/101 (20.8)	50/101 (49.5)	24/101 (23.8)	6/101 (5.9)	71/101 (70.3) (k=0.374)
Ponce de Leon et al (2008)[64] **Controls**	97	75/93 (80.6)	0/97 (0.0)	4/97 (4.1)	50/93 (53.8)	27/93 (29.0)	5/93 (5.4)	11/93 (11.8)	77/93 (82.8) (k=0.635)

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Bocchino et al (2008)[110] **Inflammatory disease pts undergoing screening before anti-TNF**	69	2 /69 (2.8)	2/69 (2.8)	0/69 (0.0)	14/66 (21.2)[b]	39/66 (59.1)[a]	9/66 (13.6)[a]	2/66 (3.0)[a]	53/66 (80.5)[b] [p<0.0001, k=0.26]
Bartalesi et al (2009)[39] **Rheumatic disease pts**	398	16/393 (4.1)	5/398 (1.2)	0/398 (0.0)	39/393 (10)	306/393 (77.8)	13/393 (3.3)	35/393 (8.9)	345/393 (87.8) [k=0.55; p<0.0001; 95% CI 0.44–0.66]
Hoffman et al (2010)[49] **HD patients - ≥10 mm**	39	18/39 (46.1)	2/39 (5.1)	6/39 (15.4)[b]	2/32 (6)	22/32 (69)	7/32 (22)	1/32 (3)	24/32 (75)
Hoffman et al (2010)[49]** **HD patients - ≥5 mm**	39	18/39 (46.1)	2/39 (5.1)	6/39 (15.4)[b]	5/32 (16)	21/32 (63)	4/32 (12)	2/32 (6)	26/32 (81)
Triverio et al (2009)[120] **HD patients with ESRD**	62	14/62 (23)	5/62 (8)	0/62 (0)	NR	NR	NR	NR	[k=0.16; *P*=0.116]
Lee et al (2010b)[53]** **HD patients- one step TST**	93	(64.8)	10/93 (10.8)	3/93 (3.2)	NR	NR	NR	NR	63/93 (67.5) [k=0.28, 95% CI 0.06-0.50]
Lee et al (2010b)[53] **HD patients - two step TST**	93	(64.8)	10/93 (10.8)	3/93 (3.2)	NR	NR	NR	NR	54/93 (57.8) [k=0.16, 95% CI -0.07-0.39]
Richeldi et al (2009)[116] **LTC group**	108[c]	4/120 (3.3)	NR	NR	NR	NR	NR	4/108 (3.7)	(85.2) [k=0.57; SE 0.09][g]
Richeldi et al (2009)[116] **HIV group**	109[c]	7/116 (6.0)	NR	NR	NR	NR	NR	3/109 (2.8)	(95.4) [k=0.52; SE 0.10] [g]
Richeldi et al (2009)[116] **HM group**	89[c]	1/95 (1.1)	NR	NR	NR	NR	NR	0/89 (0.0)	(91.0) [k=0.65; SE 0.10] [g]
Bruzzese et al (2009)[111] **Children (RA/nodose panarteritis/liver transplantation)**	80	0/80 (0.0)	(20.0)	0/80 (0.0)	NR	NR	NR	NR	K=-0.016 [p=0.89]
Contact cases									
Diel et al (2006)[44]	311	157/309 (50.8)	0/311 (0.0)	2/311 (0.6)	28/309 (9.1)	169/309 (54.7)	3/309 (1)	109/309 (35.3)	197/309 (63.8) [k =0.20, 95% CI 0.14–0.23]
Lee et al (2010)[52a]	214	135/201 (67.2)	11/214 (5.1)	22/214 (10.3)	97/185 (52.4)	48/185 (25.9)	11/185 (5.9)	29/185 (15.7)	145/185 (78.3) [k=0.55, p<0.001]
Petrucci et al (2008)[63] **Children (Brazil)**	113	113/113 (100)	1/113 (0.9)	2/113 (1.8)	33/110 (30.0)	63/110 (57.3)	12/110 (10.9)	2/110 (1.8)	96/110 (87.3) [k=0.73]

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Petrucci et al (2008)[63] **Children (Nepal)**	146	137/146 (94)	5/146 (3.4)	4/146 (2.7)	65/137 (47.4)	58/137 (42.3)	5/137 (3.6)	9/137 (6.6)	123/137 (89.8) [k=0.80]
Adetifa et al (2010)[108] **Children**	285	173/285 (60.7)	0/256 (0.0)	36/285 (12.6)	43/215 (20.0)	129/215 (60.0)	29/215 (13.5)	14/215 (6.5)	172/215 (79.8) [k=0.52 (0.40-0.66), P<0.0001)
Arend et al (2006)[109]	785	0/785 (0.0)	NA[d]	27/865[e] (3.1)	68/785 (8.7)	611/785 (77.8)	13/785 (1.6)	93/785 (11.8)	679/785 (86.5) [OR 34.4 (95% CI 18.3-64.7), k=0.49]
Adetifa et al (2007)**Error! Bookmark not defined.**	194[g]	92/194 (47.4)	7/194 (3.6)	NA	69/175 (39.4)	57/175 (32.6)	33/175 (18.8)	16/175 (9.1)	126/175 (72.0)
Recent immigrants									
Saracino et al (2009)**[66]**	452	NR	0/452 (0.0)	169/452 (37.4)	49/279 (17.6)	149/279 (53.4)	58/279 (20.8)	23/279 (8.2)	198/279 (70.9)[a] [k=0.35]
Baker et al (2009)**[37]**	198	NR	0/198 (0.0)	3/198 (1.5)	85/195 (44)	67/195 (34)	20/195 (10)	23/195 (12)	152/195 (78) [k=0.56, 95% CI 0.44-0.67]
Orlando et al (2010)**[61]**	1130	56/887 (6.31)	15/1130 (1.3)[g]	231/1130 (20.4)[h]	NR	NR	69/887 (7.8)	193/887 (21.76)	625/887 (70.46) [k=0.38, 95% CI 67.32-73.43]
Winje et al (2008a)**[71]**	1000	658/912 (72)	82/999 (8.2)	5/999 (0.5)	232/912 (25)	420/912 (46)	32/912 (4)	228/912 (25)	652/912 (72) [k=0.43, 95% CI 0.37-0.49]
Winje et al (2008a)**[71]*** **≥10 mm**	1000	658/912 (72)	82/999 (8.2)	5/999 (0.5)	190/912 (21)	527/912 (58)	74/912 (8)	121/912 (13)	717/912 (79) [k=0.51, 95% CI 0.45-0.57]
Winje et al (2008a)**[71]*** **≥15 mm**	1000	658/912 (72)	82/999 (8.2)	5/999 (0.5)	104/912 (11)	611/912 (67)	160/912 (18)	37/912 (4)	715/912 (78) [k=0.39, 95% CI 0.32-0.47]
Children									
Tsiouris et al (2006)**[69]**	221	115/184 (72.3)	37/221 (16.7)[i]	0/221 (0.0)	51/184 (27.7)	94/184 (48.9)	10/184 (5.4)	29/184 (15.8)	145/184 (78.8) [k=0.56, 95% CI 0.44-0.68]
Winje et al (2008b)**[72]**	519	236/511 (46.2)	16/519 (3.1)[j]	NA	44/511 (9)	NA	NA	467/511 (91.4)	NA
Lucas et al (2010)[115]	523	361/523 (69)	70/460 (15)	37/341 (11)	20/239 (8.4)	151/239 (63.2)	6/239 (2.5)	26/239 (10.9)	171/239 (71.5) (k=0.46 [0.39-0.53])
Stefan et al (2010)[118] [c]	34	(99)[k]	5/34 (14.7)	0/34 (0.0)	1/29 (3.4)	24/29 (82.7)	2/29 (6.9)	2/29 (6.9)	25/29 (86.2) [k=0.26]
Ruhwald et al (2008)[65]	120	NR	NR	NR	NR	NR	NR	NR	70/93 (75) [k=0.50]
Nakaoka et al (2006)[58] **Low risk**	129	187/207 (90)	9/129	8/129	6/113 (5.3)	91/113 (80.5)	4/113 (3.5)	12/113 (10.6)	84/113 (74) [k=0.0246]
Nakaoka et al (2006)[58] **High risk**	78	187/207 (90)	5/78	0/78 (0.0)	34/66 (51.5)	15/66 (22.7)	15/66 (22.7)	2/66 (3.0)	49/66 (74) [k=0.498]

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Healthcare workers									
Cummings et al (2009)[43]	182	NR	10/182 (5)	0/182 (0.0)	0/172 (0)	165/172 (96)	3/172 (2)	4/172 (2)	165/172 (96)
Kariminia et al (2009)[50**] **Low risk group**	166	166/166 (100)	10/166 (6.0)	0/166 (0.0)	6/156 (3.85)	76/156 (48.71)	5/156 (3.21)	69/156 (44.23)	82/156 (52.6) [95% CI 44-60, k=0.019]
Kariminia et al (2009)[50] **Overall**	186	186/186 (100)	10/186 (5.4)	0/186 (0.0)	9/176 (5.12)	86/176 (48.86)	5/176 (2.84)	76/176 (43.18)	95/176 (89.3) [k=0.052]
Lien et al (2009)[54**] **One step ≥10 mm**	288	112/300 (37.3)	33/288 (11.4)	0/288 (0.0)	114/255 (44.7)	71/255 (27.8)	21/255 (8.2)	49/255 (19.2)	185/255 (72.5) [k=0.44 SE 0.06, p=0.0008, Chi-squared value 11.2]
Lien et al (2009)[54] **Two step ≥10 mm**	288	112/300 (37.3)	33/288 (11.4)	0/288 (0.0)	119/255 (46.7)	62/255 (24.3)	16/255 (6.3)	58/255 (22.7)	181/255 (71.0%) [k=0.41 SE 0.06, p<0.0001, Chi-squared value 23.8]
Alvarez-Leon et al (2009)[36]	134	37/134 (35.1)	3/134 (2.2)	8/134 (6.0)	5/123 (4)	111/123 (90)	3/123 (2)	4/123 (3)	116/123 (94) [k=0.56; 95% CI 0.27–0.85]
Vinton et al (2009)[70]	481	375/481 (78.0)	6/364 (1.6)	47/481 (9.8)	NR	NR	5/364 (1.4)	NR	258/364 (71) [k=0.16]
Mirtskhulava et al (2008)[57]	270	206/265 (77.7)	None reported	5/270 (1.8)	133/265 (50.2)	62/265 (23.4)	26/265 (9.8)	44/265 (16.6)	195/265 (73.6) [k=0.43, 95% CI 0.33-0.55]
Pai et al (2005)[62]	726	514/726 (71)	1/725 (0.1)	5/725 (0.7)	226/719 (31.4)	359/719 (49.9)	62/719 (8.6)	72/719 (10.0)	585/719 (81.4) (k=0.61; 95% CI 0.56-0.67)
Military personnel									
Franken et al (2007)[47] **≥10 mm**	746	108/909 (11.9)	0/746 (0.0)	70/746 (9.4)	19/676 (2.8)	535/676 (79.1)	2/676 (0.3)	120/676 (17.7)	554/676 (82.0) [k=0.19]
Franken et al (2007)[47**] **≥15 mm**	746	108/909 (11.9)	0/746 (0.0)	70/746 (9.4)	10/676 (1.5)	614/676 (90.8)	11/676 (1.6)	41/676 (6.1)	624/676 (92.3) [k=0.24]
Mixed population									
Nienhaus et al (2008b)[60] **Contact cases and HCWS**	1040	448/1033 (43.4)	7/1040 (0.7)	0/1040 (0.0)	66/1033 (6.4)	808/1033 (78.2)[l]	34/1033 (3.3)	125/1033 (12.1)	874/1033 (84.2)
Other high risk population									
Rivas et al (2009)[117] **High risk (drug and alcohol detoxification)**	135[m]	NR	2/135	0/100	NR	NR	NR	NR	(85) [k=0.62, 95% CI 0.45-0.80]

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-GIT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-GIT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Healthy individuals									
Mahomed et al (2006)[107]	358	289/358 (80.7)	5/364 (1.4)	1/364 (0.3)	189/358 (53)	57/358 (16)	12/358 (3)	100/358 (28)	246/358 (69) [k=0.32]

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a Agreement only reported for 66 patients (includes indeterminate results).

b Includes five patients who refused TST.

c The distribution of indeterminate IGRA and TST results is not available so only final number per patient group is reported.

d No results could have been considered to be indeterminate as the positive control tube was not available.

e A further 53 patients were excluded from the total cohort based on BCG vaccination.

f Only patients with valid results for both QTF-GIT and ELISPOT were reported.

g Includes two participants who refused venipuncture.

h Includes one patient in which a TST was not performed.

i Thirty seven patients had unsuccessful phlebotomy.

j Among 58 children with a positive first QTF analysis, 16 (28%) had a negative result on the confirmatory analysis of the same plasma sample and the result was considered non-conclusive. Eight of them submitted a new blood sample for QTF testing and are included in the study group based on the second test result; the remaining eight were excluded from analysis.

k Study estimates BCG vaccination in 99% of patients, but not explicitly reported.

l Calculated during assessment

m 13 patients had a history of TB disease

Figure 10 presents the meta-analysis of the overall agreement between QTF-GIT and TST (ITT) by population type. This analysis shows the proportion of overall agreement between QTF-GIT and TST as 0.69 (95% CI: 0.65, 0.73) with a significant amount of heterogeneity ($I^2 = 94.8\%$). There does not appear to be any difference in overall agreement by population type.

Figure 11 presents the overall agreement between QTF-GIT and TST (ITT) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in populations with a lower proportion of BCG vaccinated individuals.

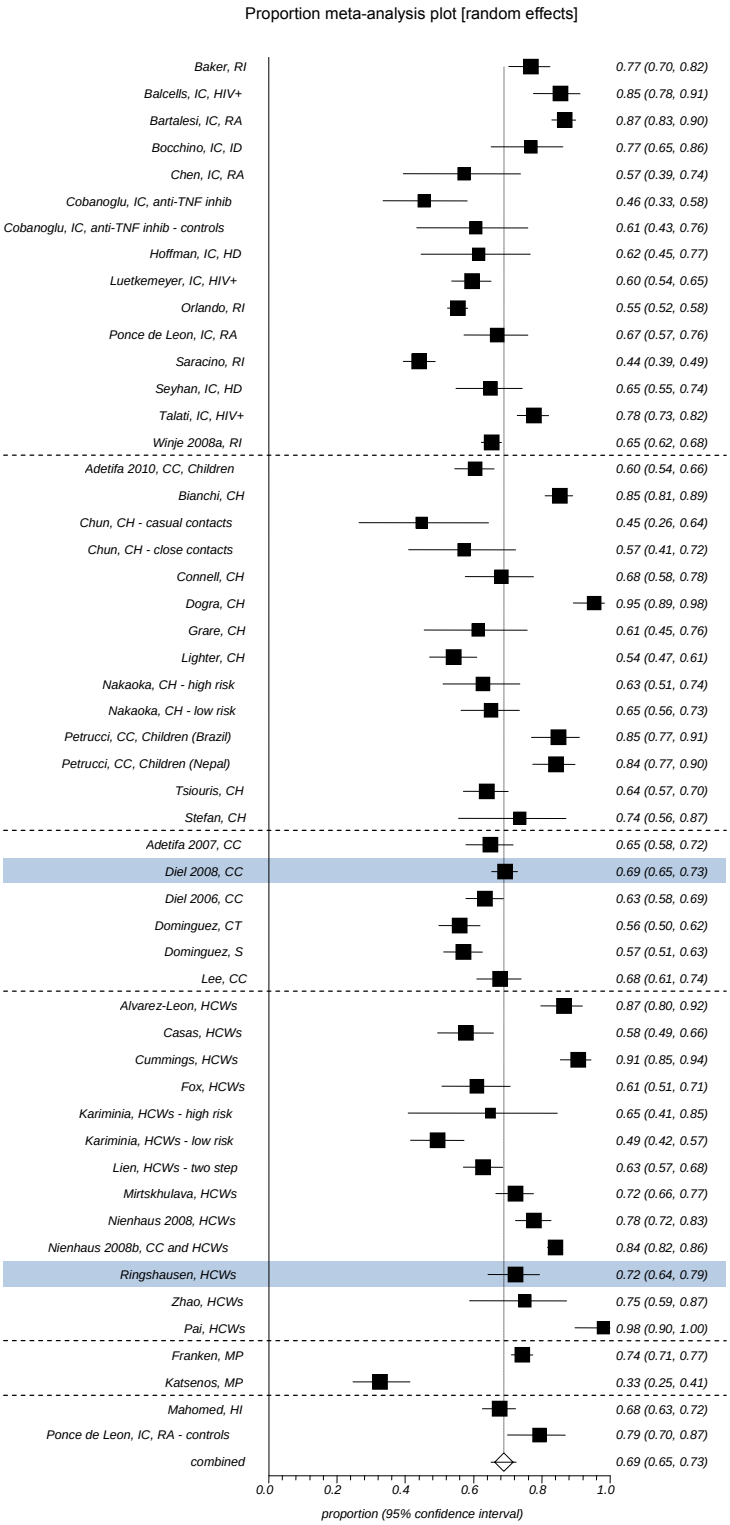


Figure 10: Meta-analysis of overall agreement between QTF-GIT and TST, (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; MP = military personnel;

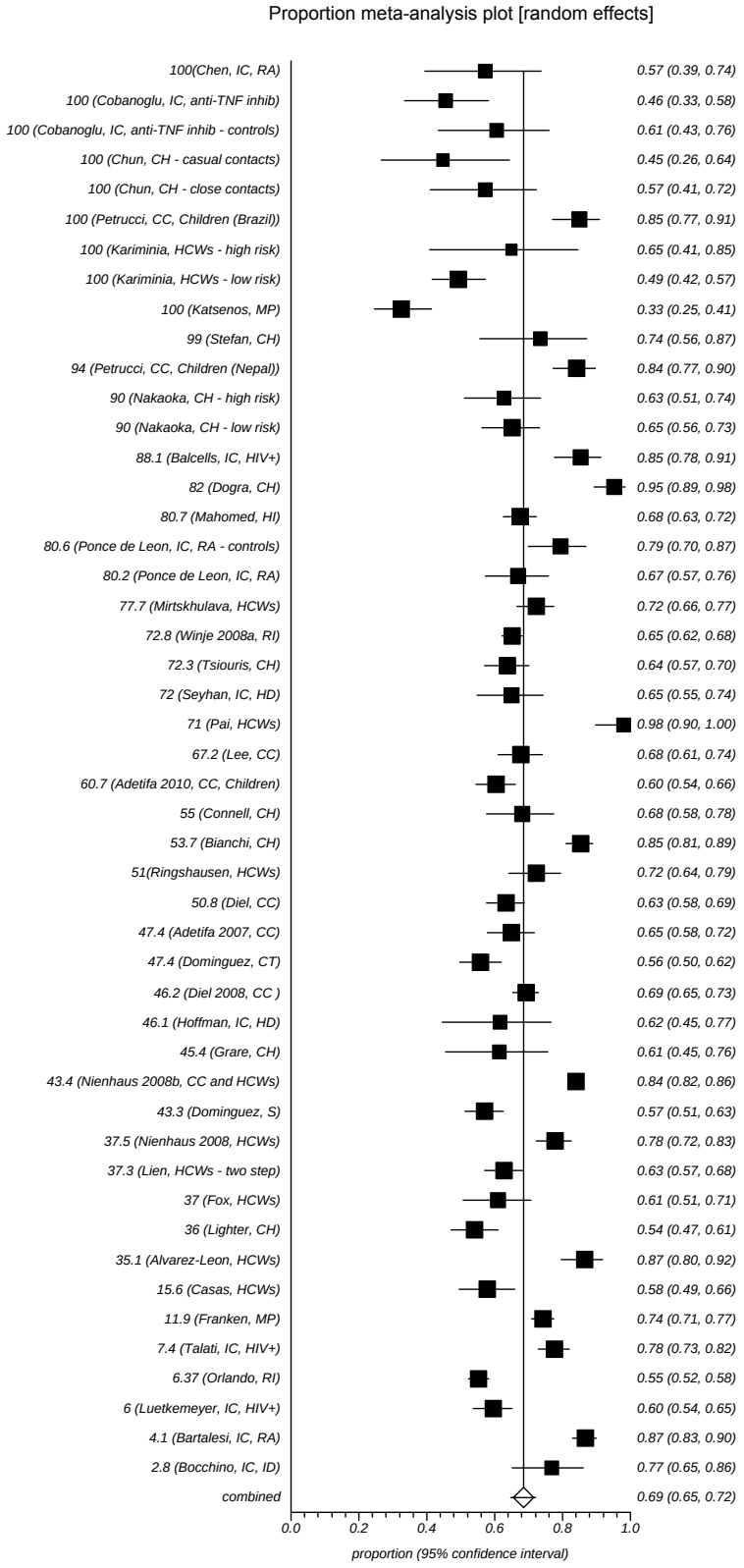


Figure 11: Meta-analysis of overall agreement between QTF-GIT and TST, by BCG vaccination (%), (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; MP = military personnel.

Figure 12 presents the meta-analysis of the overall agreement between QTF-GIT and TST (PP) by population type. This analysis shows the proportion of overall agreement between QTF-GIT and TST as 0.79 (95% CI: 0.76, 0.82) with a significant amount of heterogeneity ($I^2 = 93\%$). There does not appear to be any difference in overall agreement by population type.

Figure 13 presents the overall agreement between QTF-GIT and TST (PP) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in populations with a lower proportion of BCG vaccinated individuals.

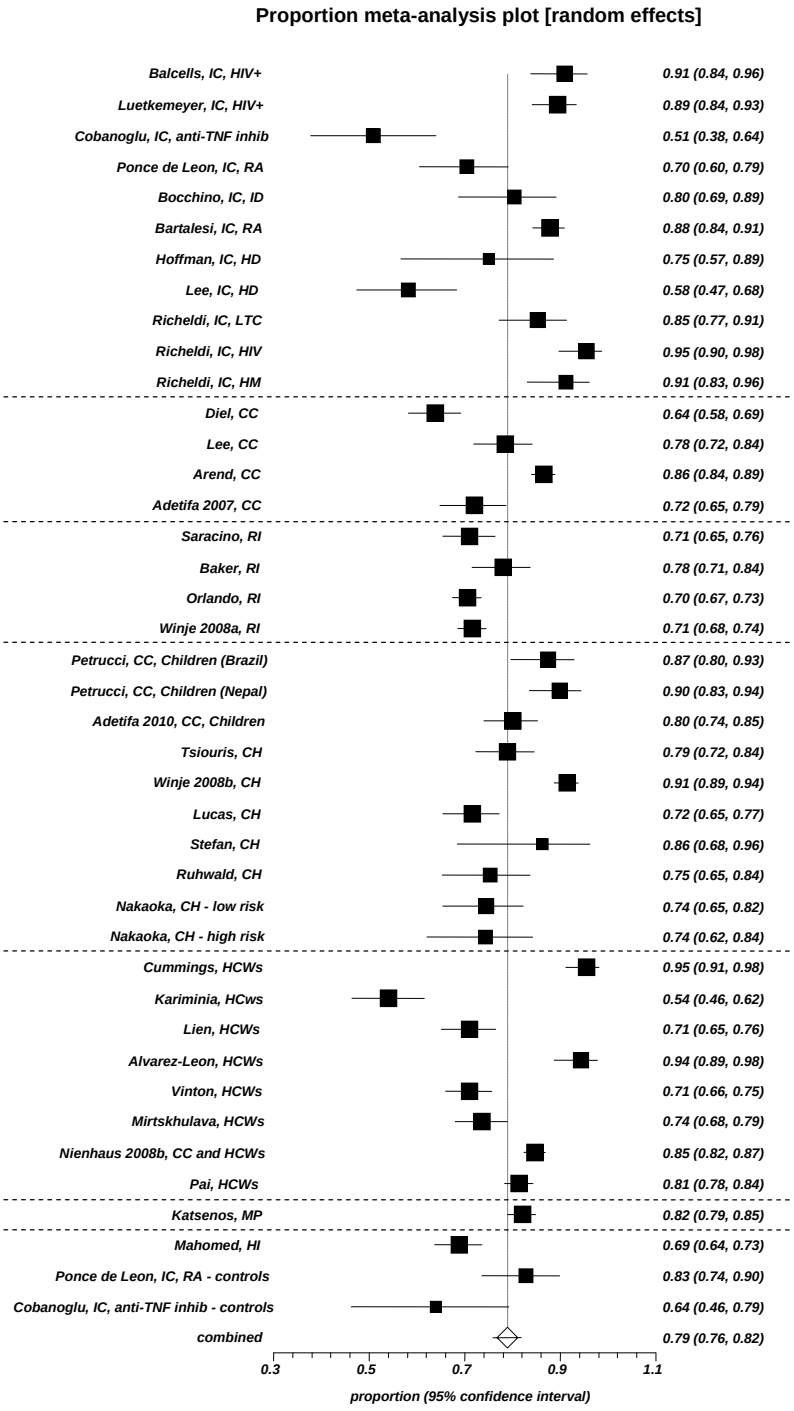


Figure 12: Meta-analysis of overall agreement between QTF-GIT and TST, (PP)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; MP = military personnel.

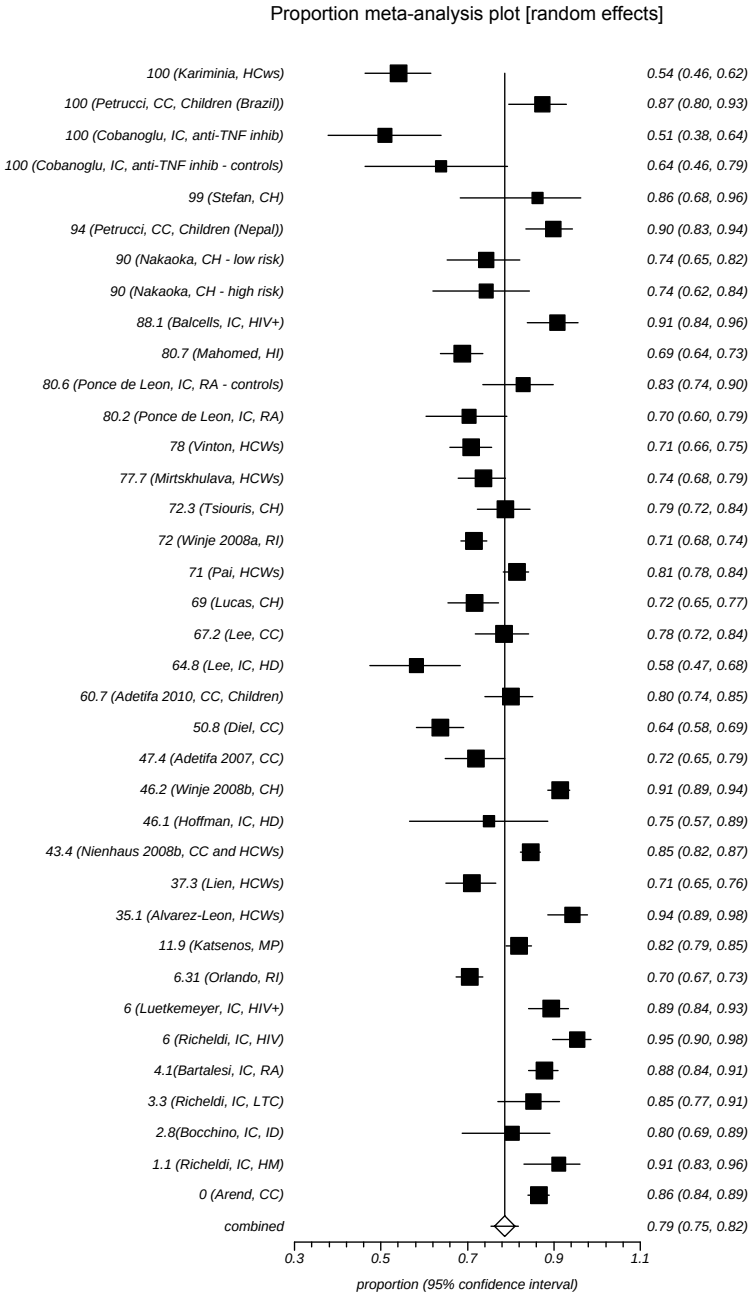


Figure 13: Meta-analysis of overall agreement between QTF-GIT and TST, by BCG vaccination (%), (PP)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; MP = military personnel.

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This assessment identified 33 studies that compared QTF-G with TST. Table 19 and Table 20 report the individual study results for the agreement between QTF-G and TST (intention to treat [ITT]) and QTF-G and TST (per protocol [PP]), respectively.

Forest plots for the meta-analyses of overall agreement are presented in Figure 14 to Figure 17.

Table 19: Agreement of QTF-G and TST (ITT)

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Inanc et al (2009)[80] **Total cohort (RA and AS)**	140	118/140 (84.3)	8/140 (5.7)	0/140 (0.0)	44/140 (31.4)	37/140 (26.4)	6/140 (4.3)	45/140 (32.1)	81/140 (57.8)
Inanc et al (2009)[80]** **RA**	82	63/82 (77)	5/82 (6)	0/82 (0.0)	25/82 (30.5)	29/82 (35.4)	5/82 (6.1)	18/82 (21.9)	54/82 (65.8)
Inanc et al (2009)[80]** **AS**	58	55/58 (95)	3/58 (5.2)	0/58 (0.0)	19/58 (32.7)	8/58 (13.8)	1/58 (1.7)	27/58 (46.5)	27/58 (46.5)
Shovman et al (2009)[89] **RA**	35	9/26 (35)[a]	10/35 (28.6)	13/35 (37)	3/35 (8.6)	11/35 (31.4)	1/35 (2.8)	10/35 (28.6)	14/35 (40.0)
Shovman et al (2009)[89] **RA - controls**	15	9/26 (35)[a]	2/15 (13.3)	12/15 (0.0)	NR	NR	NR	NR	11/15 (73.3)
Soborg et al (2009)[90] **RA, AS, PA, & Sarcoidosis pts** **Danish guidelines**	241[b]	152/302 (50)	13/294 (5)[b]	0/241 (0.0)[b]	9/241 (3.7)	180/241 (74.7)	9/241 (3.7)	36/241 (14.9)	189/241 (78.4)
Soborg et al (2009)[90]** **RA, AS, PA, &Sarcoidosis pts** **US guidelines**	241[b]	152/302 (50)	13/294 (5)[b]	0/241 (0.0)[b]	9/241 (3.7)	159/241 (66.0)	9/241 (3.7)	57/241 (23.6)	168/241 (69.7)
Lee et al (2009)[34] **ESRD**	32	23/32 (71.9)	2/32 (6.25)	0/32 (0.0)	NR	NR	NR	NR	21/32 (66.7) [k=0.36, 95% CI 0.03-0.69]
Lee et al (2009)[34] **ESRD – healthy controls**	32	28/32 (87.5)	0/32 (0.0)	0/32 (0.0)	NR	NR	NR	NR	17/32 (53.1) [k=0.22, 95% CI 0.01-0.43]
Manuel et al (2007)[84] **Chronic liver disease**	163	116/142 (82)	12/163 (7.4)	10/163 (6.1)	25/163 (15.3)	95/163 (58.3)	9/163 (5.5)	12/163 (7.4)	120/163 (73.6)
Contact cases									
Brock et al (2004)[74] **Total cohort**	85[c]	0/85 (0)	0/85 (0)	0/85 (0)	25/85 (29.4)	55/85 (64.7)	1/85 (1.2)	4/85 (4.7)	80/85 (94) [k=0.866; 95% CI 89-99%]
Brock et al (2004)[74]** **Low risk**	40[c]	0/40 (0)	0/40 (0)	0/40 (0)	2/40 (5.0)	36/40 (90.0)	0/40 (0.0)	2/40 (5.0)	38/40 (95.0) [95% CI 88-102%]

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Brock et al (2004)[74**] **High risk**	45[c]	0/45 (0)	0/45 (0)	0/45 (0)	23/45 (51.1)	19/45 (42.2)	1/45 (2.2)	2/45 (4.4)	42/45 (93) [95% CI 86-100%]
O'Neal et al (2009)[87]	61	14/61 (22.9)	NR	NR	NR	NR	NR	NR	43/61 (69.5) [k=41.9]
Diel et al (2006)[44]	311	157/309 (50.8)	0/311 (0.0)	2/311 (0.6)	28/311 (9.0)	169/311 (54.3)	3/311 (1.0)	109/311 (35.0)	197/311 (63.3)
Recent immigrants									
Carvalho et al (2007)[75]	127	83/130 (64)	0/127 (0.0)	27/127 (21.2)	15/127 (11.8)	56/127 (44.1)	0/127 (0.0)	29/127 (22.8)	71/127 (55.9)
Children									
Connell et al (2006)[77]	92	50/92 (54.3)	17/92 (18.5)	5/106 (5)	11/92 (11.9)	38/92 (41.3)	0/92 (0.0)	26/92 (28.3)	49/92 (53.3)
Okada et al (2007)[86] **Household contacts**	217	191/217 (88.0)	22/217 (10.1)	0/217 (0.0)	28/217 (12.9)	143/217 (65.9)	5/217 (2.3)	19/217 (8.7)	171/217 (78.8)
Taylor et al (2007)[92]	120	56/120 (47)	7/120 (5.8)	11/120 (9.2)	5/120 (4.2)	61/120 (50.8)	1/120 (0.8)	41/120 (34.2)	66/120 (55.0)
Lee et al (2006)[124]	131	131/131 (100)	0/131 (0.0)	0/131 (0.0)	3/131 (2.3)	95/131 (72.5)	8/131 (6.1)	25/131 (19.1)	98/131 (74.8)
Healthcare workers									
Soborg et al (2007)[27]	139	106/139 (76)	0/139 (0.0)	0/139 (0.0)	2/139 (1.4)	92/139 (66.2)	0/139 (0.0)	45/139 (32.4)	94/139 (67.6)
Choi et al (2008)[76]	82	84/84 (100)	2/82 (2.4)	0/82 (0.0)	13/82 (15.8)	41/82 (50.0)	3/82 (3.6)	23/82 (28.0)	54/82 (65.8)
Kobashi et al (2007)[82]	190	148/190 (78)	0/190 (0.0)	0/190 (0.0)	3/190 (1.6)	140/190 (73.7)[d]	2/190 (1.0)[d]	45/190 (23.7)	143/190 (75.2)
Pollock et al (2008)[126**]	143	133/143 (93)	2/143 (1.0)	NA	26/143 (18)	NA	NA	115/143 (81)	NA
Taggart et al (2006)[91] **Laboratory workers - low risk**	81	0/81 (0.0)	0/81 (0.0)	0/81 (0.0)	1/81 (1.2)	78/81 (96.3)	0/81 (0.0)	2/81 (2.5)	79/81 (97.5)
Taggart et al (2006)[91] **Laboratory workers - BCG vaccinated and risk factors for exposure**	30	30/30 (100)	0/30 (0.0)	0/30 (0.0)	5/30 (16.7)	4/30 (13.3)	0/30 (0.0)	21/30 (70.0)	9/30 (30.0)
Taggart et al (2006)[91] **Laboratory workers - low risk with previous positive TST**	26	0/26 (0.0)	0/26 (0.0)	0/26 (0.0)	9/26 (34.6)	0/26 (0.0)	17/26 (65.4)	0/26 (0.0)	9/26 (34.6)
Lee et al (2009)[34]	196	182/196 (92.9)	0/196 (0)	0/196 (0)	22/196 (11.2)	89/196 (45.4)	6/196 (3.1)	79/196 (40.3)	111/196(54.9) [k=0.151, 95% CI 0.047-0.245]

Study	n, study cohort	BCG vaccinated, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Lee et al (2008)[83] **Recent contact**	39	39/39 (100)	0/39 (0.0)	0/39 (0.0)	3/39 (7.7)	5/39 (12.8)	1/39 (2.6)	30/39 (76.9)	8/39(18.0) [k=-0.03; 95% CI -0.08-0.02, p=0.75]
Hotta et al (2007)[79] **Healthcare students**	207	190/207 (92)	5/207 (2.4)	0/207 (0.0)	3/207 (1.4)	147/207 (71.0)	0/207 (0)	52/207 (25.1)	150/207 (72.5) [k=0.077]
Healthy individuals									
Soysal et al (2008)[128]	47	39/47 (83)	0/47 (0)	0/47 (0)	5/47 (10.6)	21/47 (44.7)	0/47 (0.0)	20/47 (42.5)	26/47 (55.3)
Mahomed et al (2006)[107]	364	289/358 (80.7)	5/364 (1.4)	1/364 (0.3)	129/364 (35.4)	61/364 (16.7)	8/364 (2.2)	160/364 (43.9)	190/364 (52.2)
Army recruits									
Mazurek et al (2007)[85]	856	19/856 (2.2)	28/856 (3.3)[e]	14/856 (1.6)[f]	5/856 (0.6)	767/856 (89.6)	0/856 (0.0)	38/856 (4.4)	772/856 (90.2)
Mixed population									
Kang et al (2005)[81] **Medical students, HCWS, and close contacts**	219	190/219 (86.87)	0/219 (0.0)	0/219 (0.0)	NR	NR	NR	NR	k=0.16
Hospital patients									
Ferrara et al (2005)[78]	255	53/205 (25.8)	50/255 (19.6)[g]	0/255 (0.0)	50/255 (19.6)	94/255 (36.9)	12/255 (4.7)	49/255 (19.2)	144/255 (56.5)
Jail inmates									
Porsa et al (2006)[88]	471	22/447 (4.9)	11/471 (2.3)	51/471 (10.8)[h]	9/471 (1.9)	359/471 (76.2)	13/471 (2.8)	28/471 (5.9)	368/471 (78.1)

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a BCG vaccination reported for total cohort.

b Eight participants did not have information available for QTF-G and 61 did not undergo TST testing (clinic did not administer test).

c Only contacts that were BCG unvaccinated (85/125) underwent TST in accordance with Danish guidelines.

d Calculated during assessment.

e Eleven of these 28 patients did not have QTF-Gold completed due to blood clotting (n = 1) and insufficient quantity of blood (n = 10).

f An additional 4 TSTs were not placed.

g Authors note that QTF-Gold results were significantly more likely to be indeterminate in patients with a TST results of <5 mm than those with a result of ≥15 mm ($p<0.05$) and those with a TST result of ≥10 and <15 mm ($p<0.005$).

h Left jail prior to having TST results read.

Table 20: Agreement of QTF-G and TST (PP)

Study	n, study cohort	BCG vaccination, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised - HIV									
Mandalakas et al (2008)[125]** **HIV positive - total cohort**	43	35/43 (81.4)	14/43 (32.6)[a]	4/43 (9.3)	NR	NR	(0.0)	(26.9)	k=0.49
Mandalakas et al (2008)[125]** **HIV positive - children**	23	21/23 (91.3)	11/23 (47.8)[a]	0/23 (0.0)	NR	NR	(0.0)	(25.0)	k=0.44
Mandalakas et al (2008)[125]** **HIV positive - adults**	20	14/20 (70.0)	3/20 (15.0)	4/20 (20. 0)	NR	NR	(0.0)	(28.6)	k=0.46
Rangaka et al (2006)[127]** **HIV infected**	74	36/71 (51)	5/74 (7)	7/67 (10.4)	NR	NR	NR	NR	(79) [k=0.58, p<0.001]
Rangaka et al (2006)[127]** **HIV uninfected**	86	56/79 (71)	4/86 (4.6)	9/77 (11.7)	NR	NR	NR	NR	(53) [k=0.07, p=0.189]
Stephan et al (2008)[129]** **HIV positive**	286	19/286 (6.64)	12/286 (4.2)[b]	9/286 (3.1)	NR	NR	NR	NR	[k=0.335]
Inanc et al (2009)[80] **Total cohort (RA and AS)**	140	118/140 (84.3)	8/140 (5.7)	0/140 (0.0)	44/132 (33.3)	37/132 (28.0)	6/132 (4.5%)	45/132 (34.1)	81/132 (61) [k=0.29]
Inanc et al (2009)[80] **RA pts**	82	63/82 (77)	5/82 (6)	0/82 (0.0)	25/77 (32.5)	29/77 (37.7)	5/77 (6.5)	18/77 (23.4%)	54/77 (70.1) [k=0.42]
Inanc et al (2009)[80] **AS pts**	58	55/58 (95)	3/58 (5.2)	0/58 (0.0)	19/55 (34.5)	8/55 (14.5)	1/55 (1.8)	27/55 (49.1%)	27/55(49.1) [k=0.14]
Shovman et al (2009)[89] **RA pts**	35	9/26 (35)[c]	10/35 (28.6)	0/35 (0.0)	3/25 (12.0)	11/25 (44.0)	1/25 (4.0)	10/25 (40.0%)	14/25 (56.0)
Shovman et al (2009)[89] **Healthy controls**	15	9/26 (35)[c]	2/15 (13.3)	0/15 (0.0)	NR	NR	NR	NR	11/13 (84.0)
Soborg et al (2009)[90] **RA, AS, PA, & Sarcoidosis pts Danish guidelines**	241	152/200 (76)	13/294 (5)	0/241 (0.0)	9/234 (4)	180/234 (77)	9/234 (4)	36/234 (15)	189/234 (81) [k=0.2, 95% CI 0.04–0.3, p=0.002]
Soborg et al (2009)[90]** **RA, AS, PA, & Sarcoidosis pts US guidelines**	241	152/200 (76)	13/294 (5)	0/241 (0.0)	9/234 (4)	159/234 (68)	9/234 (4)	57/234 (24)	168/234 (72) [k=-0.04, 95% CI -0.1–0.0, p= 0.05]

Study	n, study cohort	BCG vaccination, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Winthrop et al (2008)[130] **ESRD patients - contact investigation**	100	NR	6/100 (6.0)	0/100 (0.0)	NR	NR	NR	NR	(79)
Manuel et al (2007)[84] **Chronic liver disease**	163	116/142 (82)	12/163 (7.4)	10/163 (6.1)	25/141 (17.7)	95/141 (67.4)	9/141 (6.4)	12/141 (8.5)	120/141 (85.1) [k=0.60, *p*<0.001]
Contact cases									
Higuchi et al (2007)[24] **Students**	349	349/349 (100)	0/88 (0.0)	0/349 (0.0)	4/88 (4.5)	NR	NR	82/88 (93.2)	NA
Diel et al (2006)[44]	311	157/309 (50.8)	0/311 (0.0)	2/311 (0.6)	28/309 (9.1)	169/309 (54.7)	3/309 (1.0)	109/309 (35.3)	197/309 (63.8) [k =0.20, 95% CI 0.14–0.23]
Hesseling et al (2008)[123**] **Total cohort**	82	NR	3/74 (4.1)	4/82 (4.9)	NR	NR	NR	NR	(70.6) [k=0.45, 95% CI 0.28-0.62]
Hesseling et al (2008)[123] **Children**	29	29/29 (100)	11/29 (37.9)	1/29 (3.5)	NR	NR	NR	NR	(88.9) [k=0.78, 95% CI 0.50-1.00]
Hesseling et al (2008)[123] **Adults**	53	NR	0/53 (0.0)	3/53 (5.7)	NR	NR	NR	NR	(60.0) [k=0.34, 95% CI 0.16-0.52]
Recent immigrants									
Carvalho et al (2007)[75]	127[d]	83/130 (64)	0/127 (0.0)	27/127 (21.2)[d]	15/100 (15)	56/100 (56)	0/100 (0.0)	29/100 (29)	71/100 (71) [k=0.37]
Children									
Okada et al (2007)[86] **Household contacts**	217	191/217 (88.0)	22/217 (10.1)	0/217 (0.0)	28/195 (14.3)	143/195 (73.3)	5/195 (2.6)	19/195 (9.7)	171/195 (87.7) [k=0.626]
Taylor et al (2007)[92]	120	56/120 (47)	7/120 (5.8)	11/120 (9.2)	5/108 (4.6)	61/108 (56.5)	1/108 (0.9)	41/108 (38.0)	66//108 (61.1)
Healthcare workers									
Choi et al (2008)[76]	82	84/84 (100)	2/82 (2.4)	0/82 (0.0)	13/80 (16)	41/80 (93)	3/80 (3.7)	23/80 (28.7)	54/80 (67.5) [k=0.31; 95% CI 0.22-0.40]
Healthy individuals									
Soysal et al (2008)[128]	47	39/47 (83)	0/47 (0)	0/47 (0)	5/46 (10.9)	21/46 (45.6)	0/46 (0.0)	20/46 (43.5)	26/46 (56.5)
Mahomed et al (2006)[107]	364	289/358 (80.7)	5/364 (1.4)	1/364 (0.3)	129/358 (36)	61/358 (17)	8/358 (2)	160/358 (45)	190/358 (53) [k=0.18]
Army recruits									
Mazurek et al (2007)[85]	856	19/856 (2.2)	28/856 (3.3)[e]	14/856 (1.6)	5/810 (0.6)	767/810 (94.7)	0/810 (0.0)	38/810 (4.7)	772/810 (95.3)

Study	n, study cohort	BCG vaccination, n/N (%)	QTF-G result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	QTF-G / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Hospital patients									
Ferrara et al (2005)[78]	255	53/205 (25.8)	50/255 (19.6)[f]	0/255 (0.0)	50/205 (24.4)	94/205 (45.8)	12/205 (5.8)	49/205 (23.9)	144/205 (70.2) [k=0.40; 95% CI 0.27–0.52]
Jail inmates									
Porsa et al (2006)[88]	471	22/447 (4.9)	11/471 (2.3)	51/471 (10.8)[g]	9/409 (2.2)	359/409 (87.8)	13/409 (3.2)	28/409 (6.8)	368/409 (90.0) (95% CI 0.87-0.93%) [k=0.25, 95% CI 0.10-00.41])

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a 11 patients with failed phlebotomy

b Includes 11 patients with no result due to technical error.

c BCG vaccination percentage reported for total cohort only

d Three additional subjects excluded due to suggestive diagnosis of active TB (n=2) and HIV-seropositive (n=1).

e 11/ 28 patients did not have QTF-G due to blood clotting (n=1) and insufficient quantity of blood (n=10)

f Authors note that QTF-Gold results were significantly more likely to be indeterminate in patients with a TST results of <5 mm than those with a result of ≥15 mm ($p<0.05$) and those with a TST result of ≥10 and <15 mm ($p<0.005$).

g Left jail prior to having TST results read.

Figure 14 presents the meta-analysis of the overall agreement between QTF-G and TST (ITT) by population type. This analysis shows the proportion of overall agreement between QTF-G and TST as 0.65 (95% CI: 0.59, 0.71) with a significant amount of heterogeneity ($I^2 = 95.2\%$). There does not appear to be any difference in overall agreement by population type.

Figure 15 presents the overall agreement between QTF-G and TST (ITT) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in populations with a lower proportion of BCG vaccinated individuals.

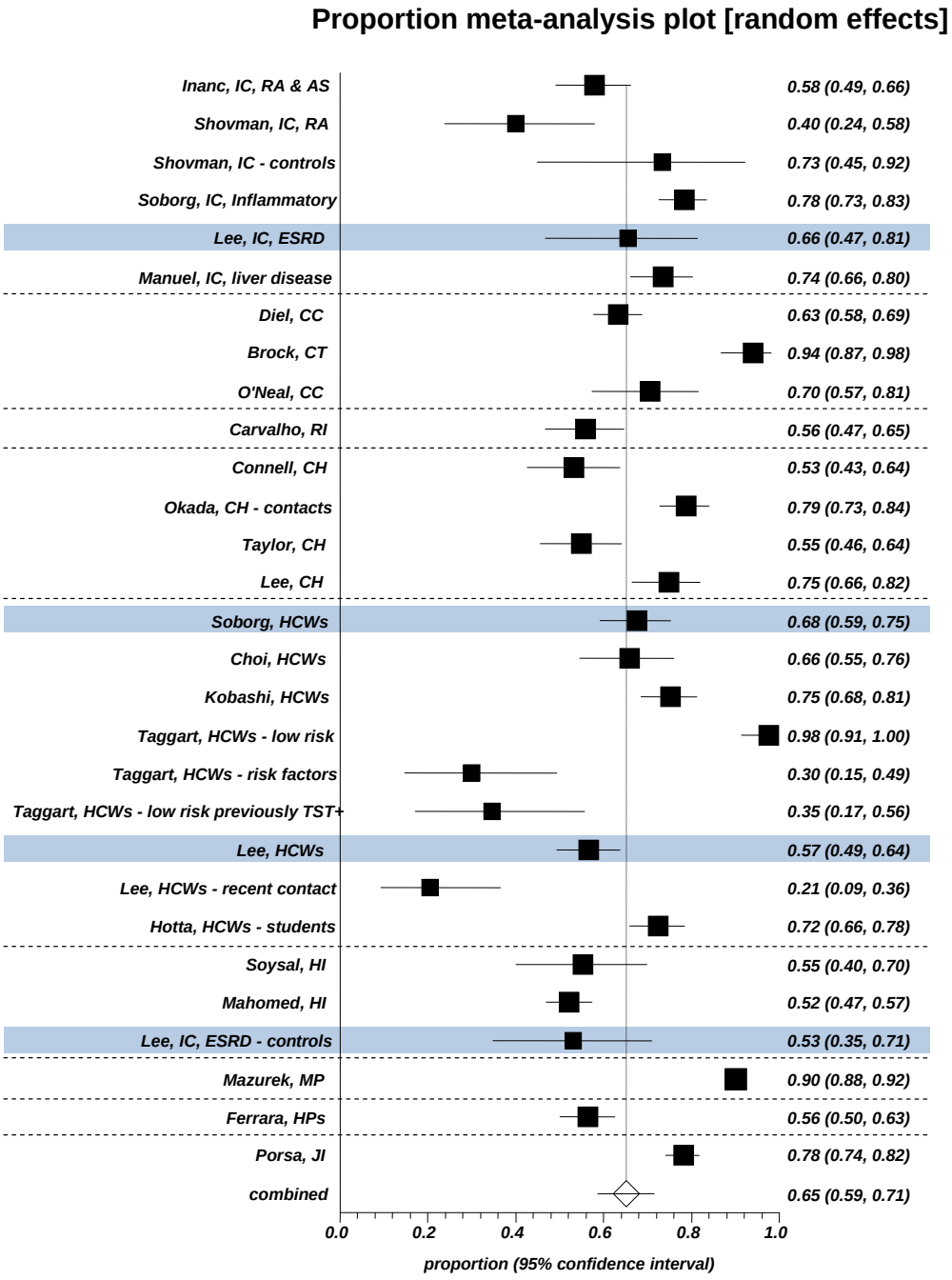

Figure 14: Meta-analysis of overall agreement between QTF-G and TST (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; MP = military personnel; HP = hospital patients; JI = jail inmates

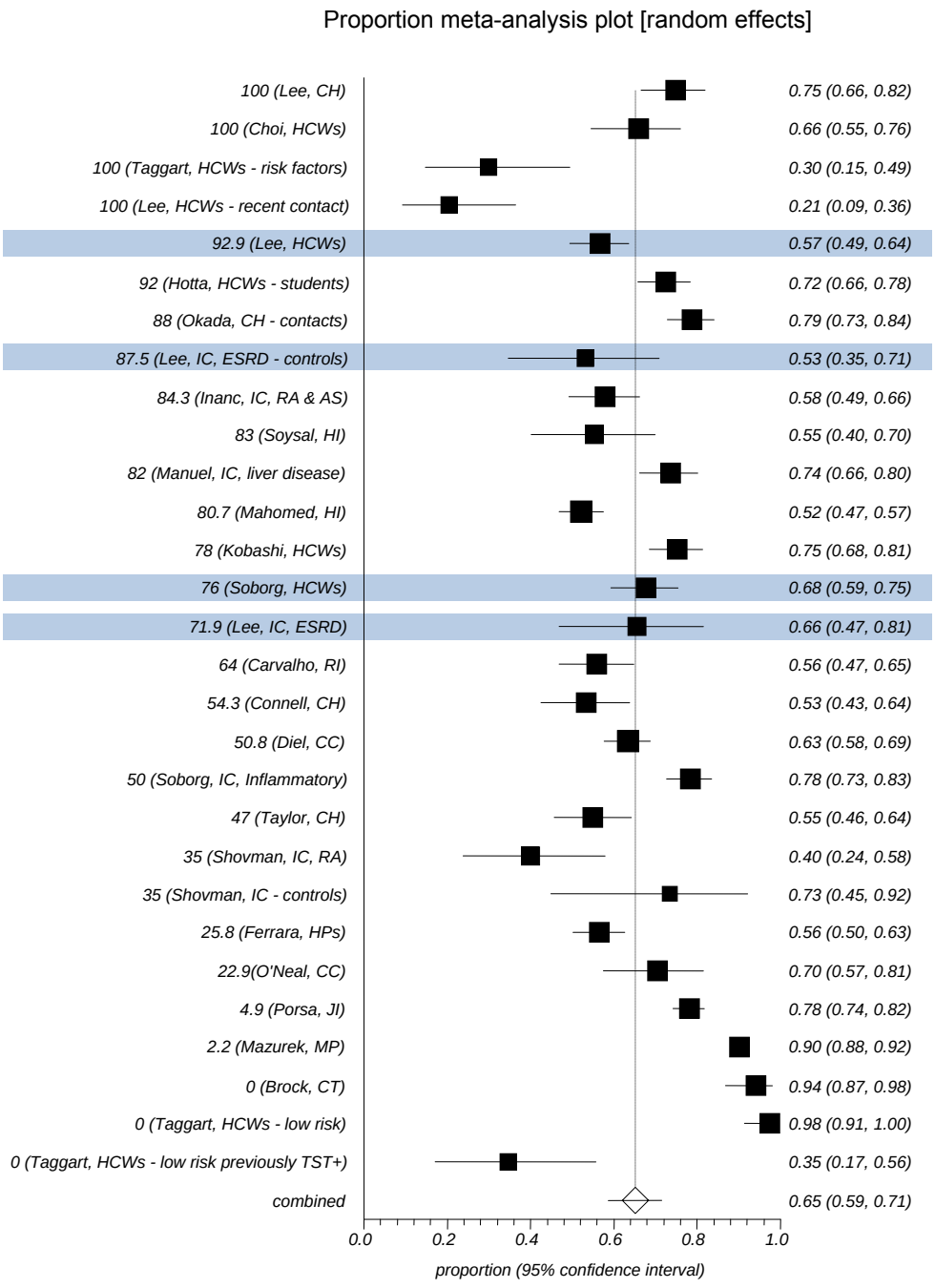

Figure 15: Meta-analysis of overall agreement between QTF-G and TST, by BCG vaccination (%), (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; MP = military personnel; HP = hospital patients; JI = jail inmates

Figure 16 presents the meta-analysis of the overall agreement between QTF-G and TST (PP) by population type. This analysis shows the proportion of overall agreement between QTF-G and TST as 0.73 (95% CI: 0.63, 0.82) with a significant amount of heterogeneity (I^2 = 97.1%). Agreement does not appear to be affected by study population.

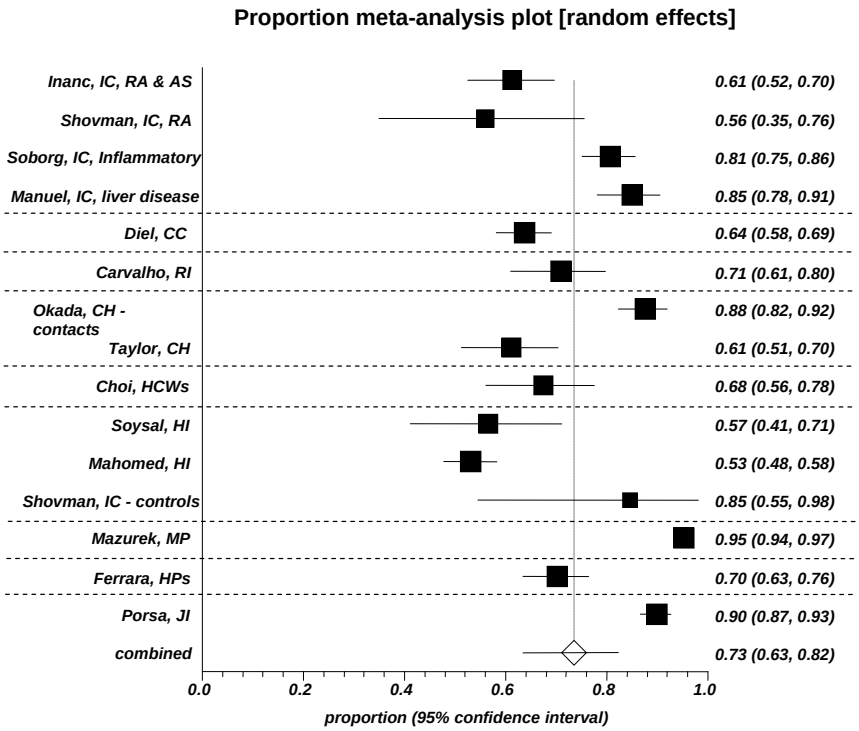

Figure 16: Meta-analysis of overall agreement between QTF-G and TST, (PP)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; MP = military personnel; HP = hospital patients; JI = jail inmates

Figure 17 presents the overall agreement between QTF-G and TST (PP) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in populations with a lower proportion of BCG vaccinated individuals.

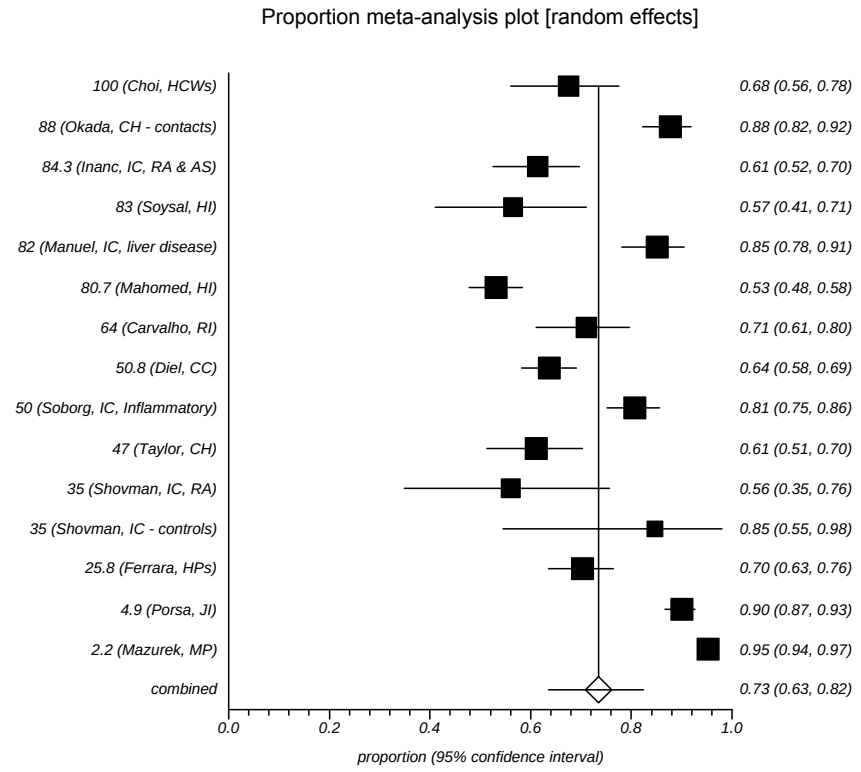

Figure 17: Meta-analysis of overall agreement between QTF-G and TST, by BCG vaccination (%), (PP)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; MP = military personnel; HP = hospital patients; JI = jail inmates

T.SPOT®-TB

A total of 37 studies were identified which reported the agreement between T.SPOT®-TB and TST. Table 21 and Table 22 report the individual study results for the agreement between T.SPOT®-TB and TST (ITT) and T.SPOT®-TB and TST (PP), respectively.

Forest plots for the meta-analyses of overall agreement are presented in Figure 18 to Figure 21.

Table 21: Agreement of T.SPOT®-TB and TST (ITT)

Study	n, study cohort	BCG vaccination, n/N (%)	T.SPOT®-TB result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	T.SPOT®-TB / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Talati et al (2009)[119] **HIV positive**	336	25/336 (7.4)	47/336 (14.0)	58/336 (17.3)	2/336 (0.6)	219/336 (65.2)	10/336 (3.0)	4/336 (1.2)	221/336 (65.8) [k=0.16, 95% CI (-0.06, 0.39)]
Jiang et al (2009)[99] **HIV infected**	70	68/68 (100)	2/70 (2.8)	0/70 (0.0)	27/70 (38.6)	21/70 (30.0)	19/70 (27.1)	1/70 (1.4)	48/70 (68.6)
Vassilopolos et al (2008)[106] **Rheumatic disease - total cohort**	70	28/70 (40)	0/70 (0.0)	0/70 (0.0)	12/70 (17.1)	39/70 (55.7)	4/70 (5.7)	15/70 (21.4)	51/70 (72.8)
Vassilopolos et al (2008)[106]** **Rheumatic disease – immunosuppressed**	43	NR	0/43 (0.0)	0/43 (0.0)	9/43 (20.9)	23/43 (53.5)	3/43 (7.0)	8/43 (18.6)	32/43 (74.4)
Vassilopolos et al (2008)[106]** **Rheumatic disease - no immunosuppression**	27	NR	0/27 (0.0)	0/27 (0.0)	3/27 (11.1)	16/27 (59.3)	1/27 (3.7)	7/27 (25.9)	19/27 (70.4)
Lee et al (2009)[25] **ESRD**	32	23/32 (71.9)	0/32 (0.0)	0/32 (0.0)	NR	NR	NR	NR	20/32 (62.5) [k=0.25, 95% CI -0.10-0.59]
Passalent et al (2007)[102] **HD patients**	203	NR	14/203[a] (6.9)	0/203 (0.0)	19/203 (9.3)	124/203 (61.1)	53/203 (26.1)	7/203 (3.4)	143/203 (70.4) [k=0.25, 95% CI 0.12-0.37]
Leung et al (2008)[100]** **Silicotic pts - ≥5 mm**	134	2/134 (1.5)	6/134 (4.3)[b]	0/134 (0.0)	77/134 (57.5)	19/134 (14.2)	9/134 (6.7)	29/134 (21.6)	96/134 (71.6) [k=0.321, p<0.001]
Leung et al (2008)[100] **Silicotic pts - ≥10 mm**	134	2/134 (1.5)	6/134 (4.3)[b]	0/134 (0.0)	72/134 (53.7)	28/134 (20.9)	14/134 (20.9)	20/134 (14.9)	100/134 (74.6) [k=0.432, p<0.001]
Leung et al (2008)[100]** **Silicotic pts - ≥15 mm**	134	2/134 (1.5)	6/134 (4.3)[b]	0/134 (0.0)	53/134 (39.5)	38/134 (28.3)	33/134 (24.6)	10/134 (7.5)	91/134 (67.9) [k=0.369, p<0.001]
Piana et al (2006)[30] **Haematology patients exposed to smear-positive TB**	138	2/84 (2.4)	9/138 (6.5)	16/138 (11.6)	21/138 (15.2)	57/138 (41.3)	34/138 (24.6)	3/138 (2.2)	78/138 (56.5)
Contact cases									
Adetifa et al (2010)[108] **Children**	285	173/285 (60.7)	2/256 (0.8)	36/285 (12.6)	43/256 (17.0)	130/215 (50.8)	28/256 (5.1)	14/256 (5.5)	173/256 (67.6)

Study	n, study cohort	BCG vaccination, n/N (%)	T.SPOT®-TB result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	T.SPOT®-TB / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Arend et al (2006)[109]	782	0/782 (0.0)	23/782 (2.9)	27/865 (3.1)[c]	80/782 (10.2)	541/782 (69.2)	62/782 (7.9)	76/782 (9.7)	621/782 (79.4)
Dominguez et al (2008)[114]	270	128/270 (47.4)	3/270 (1.1)	0/270 (0.0)	NR	NR	NR	NR	177/270 (65.6) [k=0.35, SE 0.046]
Dominguez et al (2008)[114]	314	136/314 (43.3)	1/314 (0.3)	0/314 (0.0)	NR	NR	NR	NR	191/314 (60.8) [k=0.30, SE 0.037]
Janssens et al (2008)[98**] **>5 mm (ATS/CDC guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	86/295 (29)	84/295 (28)	29/295 (10)	81/295 (27)	170/295 (57.6)
Janssens et al (2008)[98] **>10 mm (Swiss national guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	78/295 (26)	100/295 (34)	37/295 (13)	65/295 (22)	178/295 (60.3)
Janssens et al (2008)[98**] **>5 mm if vaccinated, otherwise >15 mm (British NICE guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	43/295 (15)	137/295 (46)	72/295 (24)	28/295 (10)	180/295 (61.0)
Ozekinci et al (2007)[101]	56	92/122 (75.4)[d]	0/56 (0.0)	0/56 (0.0)	9/56 (16.1)	22/56 (39.3)	7/56 (12.5)	18/56 (32.1)	31/56 (53.6)[c] [k=0.011, p>0.05]
Children									
Stefan et al (2010)[118]	34	(99)	11/34 (32.3)	0/34 (0.0)	2/34 (5.9)	16/34 (47.0)	4/34 (11.8)	1/34 (2.9)	18/34 (52.9)
Hansted et al (2009)[97] **Low risk**	52	52/52 (100)	0/52 (0.0)	0/52 (0.0)	3/52 (5.8)	16/52 (30.7)	2/52 (3.8)	31/52 (59.6)	19/52 (36.5)
Hansted et al (2009)[97] **High risk**	45	45/45 (100)	0/45 (0.0)	0/45 (0.0)	7/45 (15.6)	17/45 (7.8)	1/45 (2.2)	20/45 (44.4)	24/45 (53.3)
Lee et al (2006)[124]	131	131/131 (100)	0/131 (0.0)	0/131 (0.0)	10/131 (7.6)	93/131 (71.0)	10/131 (7.6)	18/131 (27.5)	103/131 (78.6)
Soysal et al (2008)[104]	209	188/209 (90.0)	5/209 (2.0)	NA	26/209 (12.4)	88/209 (42.1)	5/209 (2.4)	85/209 (40.7)	114/209 (54.5)
Connell et al (2008)[113]	91	48/87 (55)	14/91 (15.4)	4/91 (4.4)	15/91 (16.5)	38/91 (41.7)	1/91 (1.1)	19/91 (20.9)	53/91 (58.2)
Connell et al (2008)[113**] **Contacts only**	35	NR	7/35 (20.0)	2/35 (5.7)	10/35 (28.6)	5/35 (14.3)	1/35 (2.8)	10/35 (28.6)	15/35 (42.8)
Healthcare workers									
Barsegian et al (2008)[93]	95	34/95 (35.8)	0/95 (0.0)	0/95 (0.0)	1/95 (1.0)	63/95 (66.1)	0/95 (0.0)	31/95 (32.6)	64/95 (67.4)
Pollock et al (2008)[126]	36	36/36 (100)	0/36 (0.0)	NA	5/36 (14)	NA	NA	31/36 (86)	NA
Casas et al (2009)[112] **Total cohort**	147	23/147 (15.6)	2/147 (1.4)	0/147 (0.0)	53/147 (36.0)	39/147 (26.5)	4/147 (2.7)	49/147 (33.3)	92/147 (62.6)

Study	n, study cohort	BCG vaccination, n/N (%)	T.SPOT®-TB result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	T.SPOT®-TB / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Casas et al (2009)[112]** **Previously positive TST**	95	19/95 (20.0)	1/95 (1.1)	0/95 (0.0)	34/95 (35.8)	NA	NA	59/95 (62.1)	NA
Casas et al (2009)[112]** **No previous positive TST**	52	4/52 (7.7)	1/52 (1.9)	0/52 (0.0)	8/52 (15.4)	39/52 (75.0)	4/52 (7.7)	0/52 (0.0)	47/52 (90.4)
Storla et al (2009)[105] **Exposed to TB**	155	(99)	0/155 (0.0)	0/155 (0.0)	5/155 (3.2)	113/155 (72.9)	0/155 (0.0)	37/155 (23.9)	118/155 (76.1)
Storla et al (2009)[105] **Healthy controls**	48	(99)	0/48 (0.0)	0/48 (0.0)	0/48 (0.0)	45/48 (93.7)	0/48 (0.0)	3/48 (6.2)	45/48 (93.7)
Chee et al (2009)[96] **Healthcare students**	207	207/207 (100)	2/207 (1.0)	2/207 (1.0)	9/207 (4.3)	28/207 (13.5)	0/207 (0.0)	168/207 (81.1)	37/207 (17.9)
Ozekinci et al (2007)[101]	66	92/122 (75.4)[d]	0/66 (0.0)	0/66 (0.0)	14/66 (21.2)	28/66 (42.4)	2/66 (3.0)	22/66 (33.3)	42/66 (63.6) [k=0.305, p=0.006]
Healthy individuals									
Soysal et al (2008)[128]	47	39/47 (83)	0/47 (0)	0/47 (0)	7/47 (14.9)	21/47 (44.7)	0/47 (0.0)	18/47 (38.3)	28/47 (59.6)
Bienek et al (2009)[94] **Total cohort**	414	14/414 (3.3)	22/414 (5.3)	66/414 (15.9)	2/414 (0.5)	318/414 (76.8)	6/414 (1.5)	0/414 (0.0)	320/414 (77.3)
Bienek et al (2009)[94]** **Low risk**	354	NR	18/354 (5.1)	58/354 (16.4)	0/354 (0.0)	275/354 (77.7)	3/354[e] (0.8)	0/354 (0.0)	275/354 (77.7)
Bienek et al (2009)[94]** **High risk**	60	NR	4/60 (6.7)	8/60 (13.3)	2/60 (3.3)	43/60 (71.7)	3/60[f] (5.0)	0/460 (0.0)	45/60 (75.0)
Ozekinci et al (2007)[101]	28	NR	0/28 (0.0)	0/28 (0.0)	1/28 (3.6)	11/28 (39.3)	2/28 (7.1)	14/28 (50.0)	12/28 (42.8)
Recent immigrants									
Kik et al (2010)[35]	339	278/339 (80.8)	40/339 (11.8)	11/541 (2.0)	181/339 (53.4)	NA	NA	118/339 (34.8)	NA
Jail inmates									
Porsa et al (2007)[103]	447	22/447 (4.9)	22/447 (4.9)	35/447 (7.8)[g]	20/447 (4.5)	303/447 (67.8)	54/447 (12.1)	13/447 (2.9)	323/447 (72.2)

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a Four (4/14) patients underwent retesting, three of which yielded a determinate result.

b Six indeterminate results were repeated and yielded a determinate result.

c A further 53 patients were excluded from the total cohort based on BCG vaccination.

d BCG vaccination status reported for combined cohort of contact cases and HCWs.

Table 22: Agreement of T.SPOT®-TB and TST (PP)

Study	n, study cohort	BCG vaccination, n/N (%)	T.SPOT®-TB result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	T.SPOT®-TB / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Mandalakas et al (2008)[125]** **HIV positive - all subjects**	43	35/43 (81.4)	2/43 (4.7)	4/43 (9.3)	NR	NR	(29.7)	(10.8)	[k=0.21]
Mandalakas et al (2008)[125]** **HIV positive - children**	23	21/23 (91.3)	0/23 (0.0)	12/23 (0.0)	NR	NR	(39.1)	(13.0)	[k=-0.2]
Mandalakas et al (2008)[125]** **HIV positive - adults**	20	14/20 (70.0)	2/20 (10.0)	4/20 (20. 0)	NR	NR	(14.3)	(7.1)	[k=0.43]
Rangaka et al (2006)[127] **HIV infected**	74	36/71 (51)	2/73 (2.7)[a]	7/67 (10.4)	NR	NR	NR	NR	(80) [k=0.60, p<0.001]
Rangaka et al (2006)[127] **HIV uninfected**	86	56/79 (71)	0/86 (0.0)	9/77 (11.7)	NR	NR	NR	NR	(65) [k=0.17, p=0.035]
Stephan et al (2008)[129] **HIV infected**	286	19/286 (6.64)	19/286 (6.6)[b]	9/286 (3.1)	NR	NR	NR	NR	[k=0.201]
Triverio et al (2009)[120] **HD patients with ESRD**	62	14/62 (23)	7/62 (11)	0/62 (0)	NR	NR	NR	NR	[k=0.32; *P*=0.007]
Richeldi et al (2009)[116] **LTC group**	108[c]	4/120 (3.3)	NR	NR	NR	NR	NR	5/108 (4.6)	(80.6) [k=0.47; SE 0.09\
Richeldi et al (2009)[116] **HIV group**	109[c]	7/116 (6.0)	NR	NR	NR	NR	NR	5/109 (4.6)	(92.7) [k=0.16; SE 0.09]
Richeldi et al (2009)[116] **HM group**	89[c]	1/95 (1.1)	NR	NR	NR	NR	NR	1/89 (1.1)	(80.9) [k=0.40; SE 0.09]
Bocchino et al (2008)[110] **Inflammatory diseases pts[w]**	69	2/69 (2.8)	4/69 (5.8)	0/69 (0.0)	12/66 (18.2)[d]	40/66 (60.6)[d]	7/66 (10.6)[d]	3/66 (4.5)[d]	52/66 (78.4)[d] [p=0.002, k=0.21]
Bruzzese et al (2009)[111] **Children (RA/nodose panarteritis/liver transplantation)**	80	0/80 (0.0)	(13.5)	0/80 (0.0)		NR	NR	NR	NR
Contact cases									
Hesseling et al (2008)[123]** **Total cohort**	82	NR	1/81 (1.2)	4/82 (4.9)	NR	NR	(21.1)	(13.2)	(65.8) [k=0.12, 95% CI -0.11-0.36]

Hesseling et al (2008)[123] **Children**	29	29/29 (100)	1/28 (3.6)	1/29 (3.5)	NR	NR	(46.2)	(7.7)	(46.1) [k=-0.15, 95% CI -0.35-0.05]
Hesseling et al (2008)[123] **Adults**	53	NR	0/53 (0.0)	3/53 (5.7)	NR	NR	(8)	(16)	(76.0) [k=0.38, 95% CI -0.10-0.66]
Adetifa et al (2010)[108] **Children**	285	173/285 (60.7)	2/256 (0.8)	36/285 (12.6)	43/215 (20.0)	130/215 (60.5)	28/215 (13.0)	14/215 (6.5)	173/215 (80.5) [k=0.54 (0.41-0.68), *P*<0.0001)
Arend et al (2006)[109]	782	0/782 (0.0)	23/782 (2.9)	27/865 (3.1)[e]	80/759 (10.5)	541/759 (71.3)	62/759 (8.2)	76/759 (10.0)	621/759 (81.8) [OR 9.19 (95% CI 6.10-13.8), k=0.42]
Janssens et al (2008)[98**] **>5 mm (ATS/CDC guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	86/295 (29)	84/295 (28)	29/295 (10)	81/295 (27)	170/280 (60.7) (k=0.24, 95% CI 0.14-0.33)
Janssens et al (2008)[98] **>10 mm (Swiss national guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	78/295 (26)	100/295 (34)	37/295 (13)	65/295 (22)	178/280 (63.6) (k=0.27, 95% CI 0.16-0.38)
Janssens et al (2008)[98**] **>5 mm if vaccinated, otherwise >15 mm (British NICE guidelines)**	295	238/295 (80.6)	15/295 (5.1)	0/295 (0.0)	43/295 (15)	137/295 (46)	72/295 (24)	28/295 (10)	180/280 (64.2) (k=0.22, 95% CI 0.10-0.33)
Children									
Lucas et al (2010)[115]	524	361/523 (69)	65/477 (13.6)	37/341 (11)	18/239 (7.5)	184/239 (77.0)	5/239 (2.1)	28/239 (11.7)	202/239 (84.5) [k=0.45; 0.38-0.53]
Stefan et al (2010)[118 a]	34	(99)[f]	11/34 (32.3)[g]	0/34 (0.0)	2/23 (8.7)	16/23 (69.6)	4/23 (17.4)	1/23 (4.3)	18/23 (78.3) [K=0.33]
Soysal et al (2008)[104]	209	188/209 (90.0)	5/209 (2.0)	NA	26/204 (12.7)	88/204 (43.1)	5/204 (2.4)	85/204 (41.7)	114/204 (55.9)
Healthcare workers									
Chee et al (2009)[96] **Healthcare students**	207	207/207 (100)	2/207 (1.0)	2/207 (1.0)	9/205 (4.4)	28/205 (13.6)	0/205 (0.0)	168/205 (81.9)	37/205 (18.0)
Healthy individuals									
Soysal et al (2008b)[128]	47	39/47 (83)	0/47 (0)	0/47 (0)	7/46 (15.2)	21/46 (45.6)	0/46 (0.0)	18/46 (39.1)	28/46 (60.9)
Bienek et al (2009)[94] **Total cohort**	414	14/414 (3.3)	22/414 (5.3)	66/414 (15.9)	2/326 (0.6)	318/326 (97.5)	6/326 (1.8)	0/326 (0.0)	320/326 (98.2) [95% CI 96.0-99.3]
Bienek et al (2009)[94**] **Low risk**	354	NR	18/354 (5.1)	58/354 (16.4)	0/278 (0.0)	275/278 (98.9)	3/278 (1.1)[h]	0/278 (0.0)	275/278 (98.9) [95% CI 96.9-99.8]
Bienek et al (2009)[94**] **High risk**	60	NR	4/60 (6.7)	8/60 (13.3)	2/48 (4.2)	43/48 (89.6)	3/48 (6.2)[i]	0/48 (0.0)	45/48 (93.8) [95% CI 82.8-98.7]

Jail inmates									
Porsa et al (2007)[103]	447	22/447 (4.9)	22/447 (4.9)	35/447[j] (7.8)	20/390 (5.1)	303/390 (77.7)	54/390 (13.8)	13/390 (3.3)	323/390 (82.8) [95% CI 79.0-87.0%] [k=0.29, 95% CI 0.17-0.41]
Screening clinic									
Brodie et al (2008)[95] **High risk individuals - public screening**	96	66/96 (68.0)	8/96 (8.3)	4/96 (4.2)	NR	NR	NR	NR	(64) [95% CI 54-74%] [k=0.33, 95% CI 0.19-0.48]
Other high risk population									
Rivas et al (2009)[117] **High risk (drug and alcohol detoxification)**	135[k]	NR	1/135	0/100	NR	NR	NR	NR	(83) [k=0.57, 95% CI 0.39-0.75]

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a Includes 1 patient with insufficient sample.

b Includes 11 patients with no result due to technical error.

c The distribution of indeterminate IGRA and TST results is not available so only final number per patient group is reported.

d Agreement only reported for 66 patients (includes indeterminate results).

e A further 53 patients were excluded from the total cohort based on BCG vaccination.

f Study estimate.

g Includes four indeterminate, six with inadequate cell counts, and one clotted sample.

h Of the three discordant results where T.SPOT was positive and TST negative, one sample reacted with ESAT-6 only and two reacted with CFP-10 only.

i Of the three discordant results where T.SPOT was positive, two samples reacted with CFP-10 only.

j Patients left jail before TST results were read.

k 13 patients had a history of TB disease.

Figure 18 presents the meta-analysis of the overall agreement between T.SPOT®-TB and TST (ITT) by population type. This analysis shows the proportion of overall agreement between T.SPOT®-TB and TST as 0.64 (95% CI: 0.59, 0.70) with a significant amount of heterogeneity (I^2 = 93.4%). There does not appear to be any difference in overall agreement by population type.

Figure 19 presents the overall agreement between T.SPOT®-TB and TST (ITT) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in studies with a lower proportion of BCG vaccinated individuals.

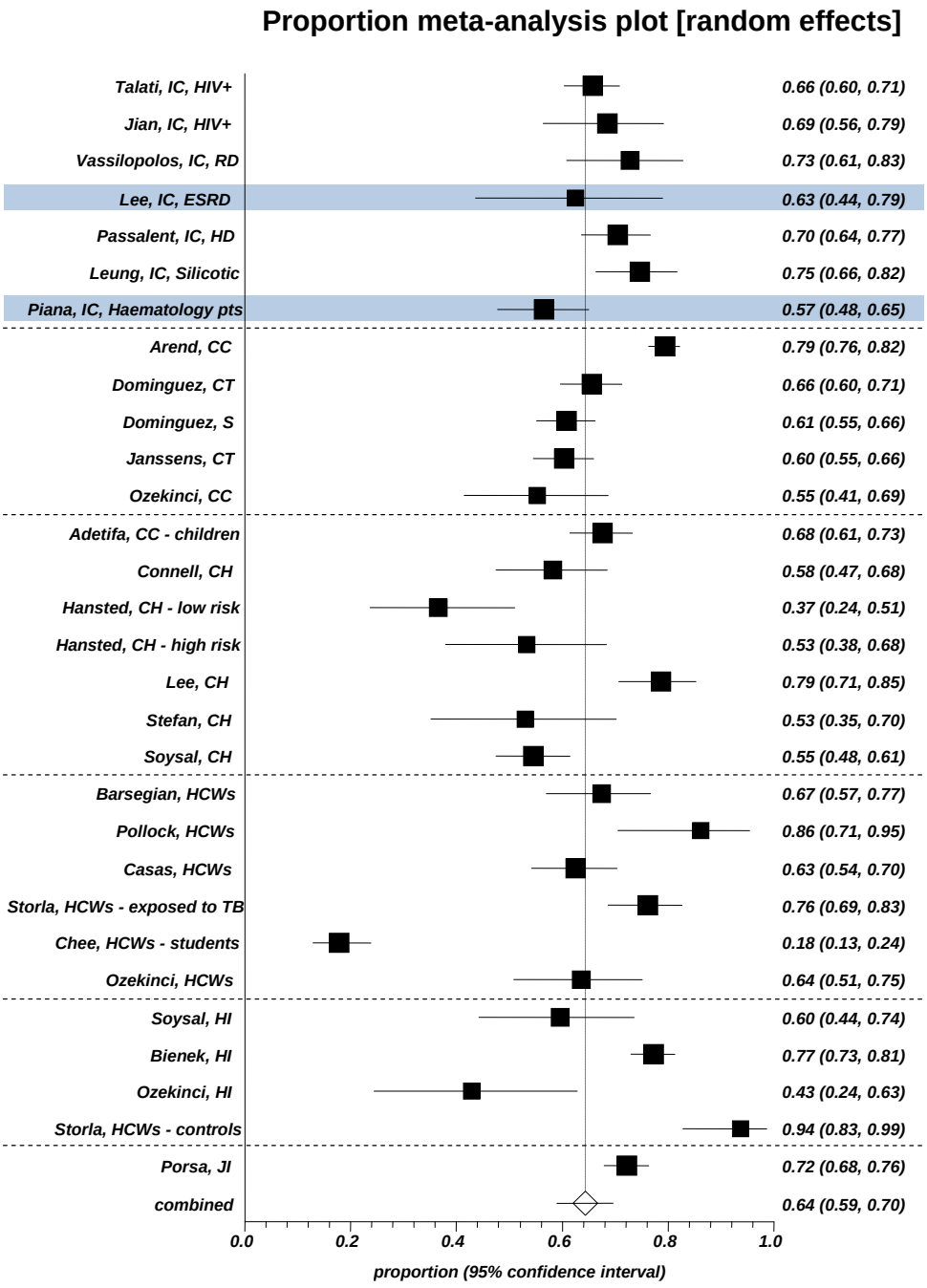

Figure 18: Meta-analysis of overall agreement between T.SPOT®.TB and TST, (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; JI = jail inmates

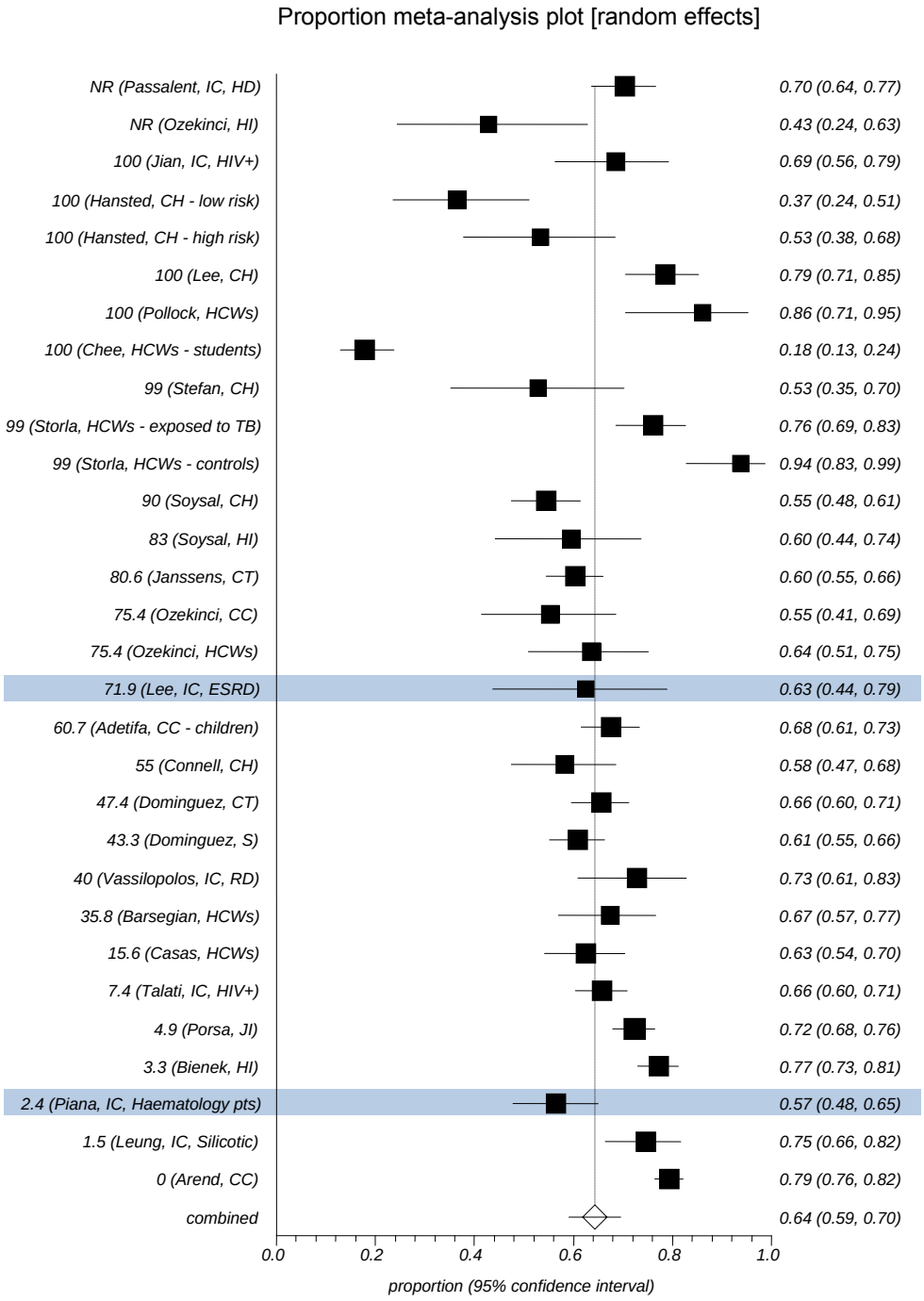

Figure 19: Meta-analysis of overall agreement between T.SPOT®.TB and TST, by BCG vaccination (%), (ITT)

IC = immunocompromised; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; JI = jail inmates

Figure 20 presents the meta-analysis of the overall agreement between T.SPOT®-TB and TST (PP) by population type. This analysis shows the proportion of overall agreement between T.SPOT®-TB and TST as 0.64 (95% CI: 0.59, 0.70) with a significant amount of heterogeneity (I^2 = 98.3%). There does not appear to be any difference in overall agreement by population type.

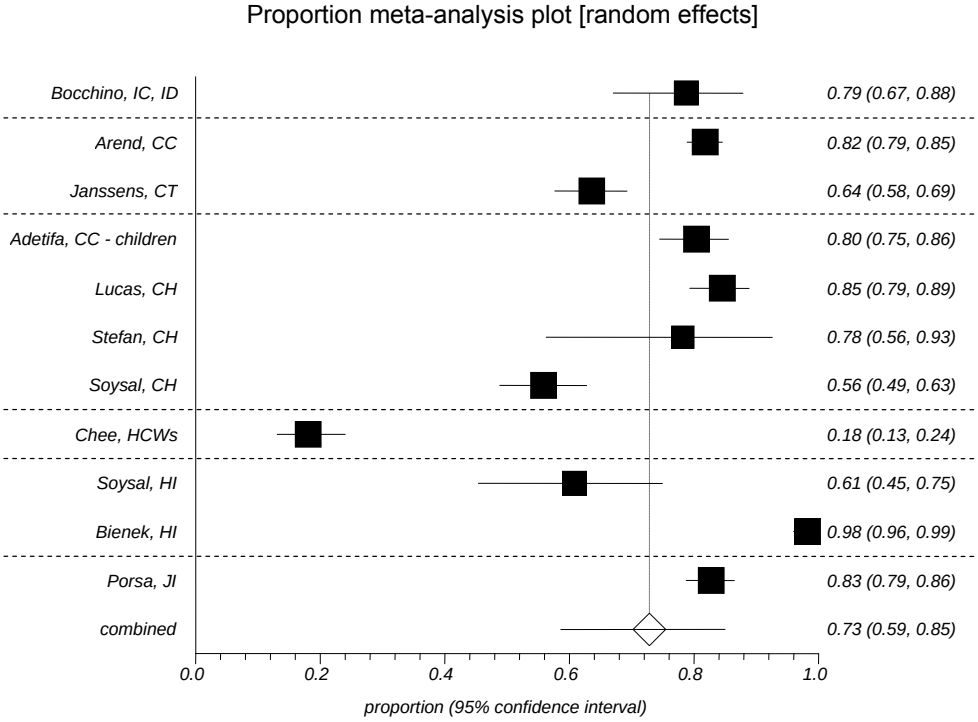

Figure 20: Meta-analysis of overall agreement between T.SPOT®.TB and TST, (PP)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; JI = jail inmates

Figure 21 presents the overall agreement between T.SPOT®-TB and TST (PP) ordered by the proportion of the study population that was BCG vaccinated. There appears to be a trend towards greater agreement in studies with a lower proportion of BCG vaccinated individuals

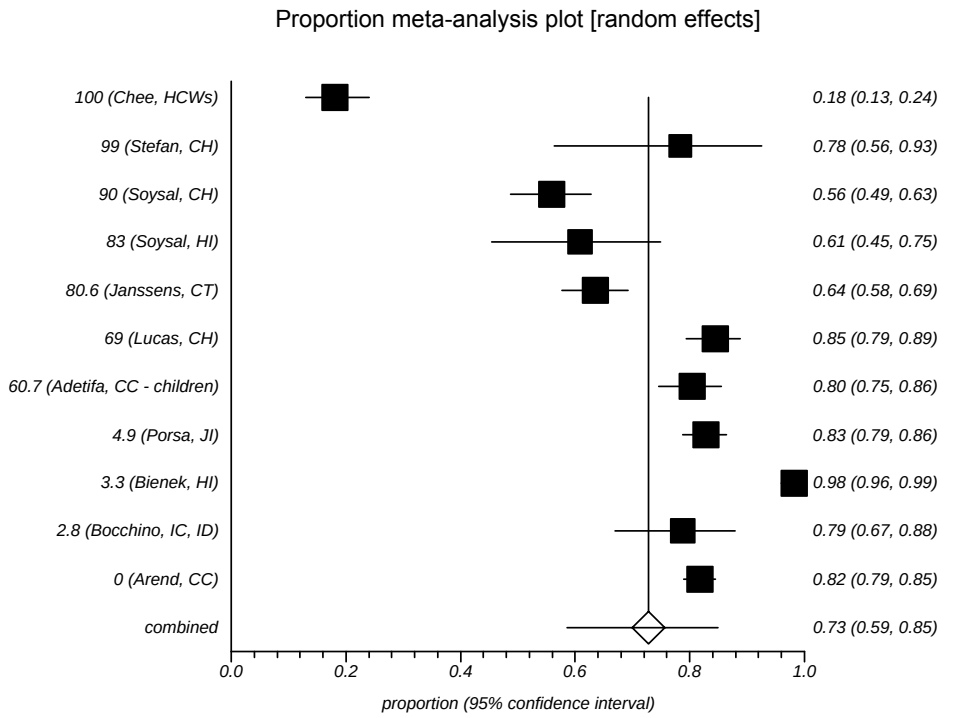

Figure 21: Meta-analysis of overall agreement between T.SPOT®.TB and TST, by BCG vaccination (%), (PP)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; S = screening; HCWs = healthcare workers; HI = health individuals; JI = jail inmates

ELISPOT

A total of 19 studies reported the agreement between ELISPOT and TST. Table 23 and Table 24 report the individual study results for the agreement between ELISPOT and TST (ITT) and ELISPOT and TST (PP), respectively.

Forest plots for the meta-analyses of overall agreement are presented in Figure 22 to Figure 25.

Table 23: Agreement of ELISPOT and TST (ITT)

Study	n, study cohort	BCG vaccinated, n/N (%)	ELISPOT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	ELISPOT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Chapman et al (2002)[132] **HIV positive**	21	21/21 (100)	0/21 (0.0)	7/21 (33.3)	3/21 (14.3)	6/21 (28.6)	3/21 (14.3)	2/21 (9.5)	9/21 (42.8)
Chapman et al (2002)[132] **HIV negative**	54	36/54 (66.7)	0/54 (0.0)	19/54 (35.2)	19/54 (35.2)	2/54 (3.7)	5/54 (9.2)	9/54 (16.7)	21/54 (38.9)
Karam et al (2008)[138] **HIV positive**	285	207/285 (72.6)	38/285 (13.3)	0/285 (0.0)	41/285 (14.4)	110/285 (38.6)	84/285 (29.5)	12/285 (4.2)	151/285 (53.0)
Murakami et al (2009)[140] **RA patients[a] CDC guidelines**	71	71/71 (100)	0/71 (0.0)	0/71 (0.0)	4/71 (5.6)	50/71 (70.4)	6/71 (8.4)	11/71 (15.5)	54/71 (76.0)
Murakami et al (2009)[140]** **RA patients[a] Japanese guidelines**	71	71/71 (100)	0/71 (0.0)	0/71 (0.0)	6/71 (8.4)	48/71 (67.6)	4/71 (5.6)	13/71 (18.3)	54/71 (76.0)
Contact cases									
Adetifa et al (2007)**Error! Bookmark not defined.**	194[b]	92/194 (47.4)	12/194 (6.2)	NA	62/194 (31.9)	38/194 (19.6)	52/194 (26.8)	23/194 (11.8)	100/194 (51.5)
Codecasa et al (2006)[133]	119	67/119 (56.3)	0/119 (0.0)	0/119 (0.0)	36/119 (30.2)	39/119 (32.8)	3/119 (2.5)	41/119 (34.4)	75/119 (63.0) [k=0.328, 95% CI 0.198-0.459]
Hill et al (2007)[31]	655	NR	45/655 (6.8)	52/655 (7.9)	165/655 (25.2)	100/655 (15.3)	58/655 (8.8)	235/655 (35.9)	265/655 (40.4)
Mantegani et al (2006)**Error! Bookmark not defined. Surveillance program of high risk**	86	38/86 (44.2)	0/86 (0.0)	0/86 (0.0)	44/86 (51.2)	15/86 (17.4)	2/86 (2.3)	25/86 (29.1)	59/86 (68.6) [k=0.344, 95% CI 0.175-0.513]
Mutsvangwa et al (2010)[141]** **Total cohort**	222	(86)[c]	0/222 (0.0)	0/222 (0.0)	67/222 (30.2)	49/222 (22.1)	12/222 (5.4)	94/222 (42.3)	116/222 (52.2) [k=0.15, p=0.001]
Mutsvangwa et al (2010)[141] **HIV+**	55	(86)[c]	0/55 (0.0)	0/55 (0.0)	15/55 (27.3)	24/55 (43.6)	4/55 (7.3)	12/55 (21.8)	39/55 (70.9) [k=0.41, p<0.001]
Mutsvangwa et al (2010)[141] **HIV-**	167	(86)[c]	0/167 (0.0)	0/167 (0.0)	52/167 (31.1)	25/167 (15.0)	8/167 (4.8)	82/167 (49.1)	77/167 (46.1) [k=0.08, p=0.06]
Mutsvangwa et al (2010)[141] **Controls - total cohort**	176	(86)[c]	0/176 (0.0)	0/176 (0.0)	50/176 (28.4)	41/176 (23.3)	3/176 (1.7)	82/176 (46.6)	91/176 (51.7) [k=0.19, p<0.001]

Study	n, study cohort	BCG vaccinated, n/N (%)	ELISPOT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	ELISPOT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Mutsvangwa et al (2010)[141] **Controls - HIV+**	18	(86)[c]	0/18 (0.0)	0/18 (0.0)	2/18 (11.1)	11/18 (61.1)	1/18 (5.5)	4/18 (22.2)	13/18 (72.2) [k=0.29, p=0.09]
Mutsvangwa et al (2010)[141] **Controls - HIV-**	158	(86)[c]	0/158 (0.0)	0/158 (0.0)	48/158 (30.4)	30/158 (19.0)	2/158 (1.3)	78/158 (49.4)	78/158 (49.4) [k=0.17, p<0.001]
Richeldi et al (2004)[142] **Maternity ward - total cohort**	92	9/92 (9.8)	0/92 (0.0)	0/92 (0.0)	2/92 (2.2)	73/92 (79.3)	15/92 (16.3)	2/92 (2.2)	75/92 (81.5)
Richeldi et al (2004)[142**] **Maternity ward - adults**	51	NR	0/51 (0.0)	0/51 (0.0)	2/51 (3.9)	34/51 (66.7)	13/51 (25.5)	2/51 (3.9)	36/51 (70.6)
Richeldi et al (2004)[142] **Maternity ward - newborns**	41	NR	0/41 (0.0)	0/41 (0.0)	0/41 (0.0)	39/41 (95.1)	2/41 (4.9)	0/41 (0.0)	39/41 (95.1)
Shams et al (2005)[143]	416	204/413 (49.4)	3/416 (0.7)	0/416 (0.0)	133/416 (32.0)	175/416 (42.1)	30/416 (7.2)	75/416 (18.0)	308/416 (74.0)
Children									
Hill et al (2006b)[136]	917	313/718 (43.6)	199/917[a] (21.7)	224/917 (24.4)	165/917 (18.0)	413/917 (45.0)	55/917 (6.0)	60/917 (6.5)	578/917 (63.0) [k=0.62]
Army personnel									
Wu et al (2009)[33]	100	45/100 (45)	0/100 (0.0)	0/100 (0.0)	15/100 (15)	53/100 (53)	6/100 (6)	26/100 (26)	68/100 (68)

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 =good; 0.80-1.00 = very good.

a Undergoing screening before anti-TNF therapy.

b Only patients with valid results for both QTF-GIT and ELISPOT were reported.

c BCG vaccination reported for total cohort only.

Table 24: Agreement of ELISPOT and TST (PP)

Study	n, study cohort	BCG vaccinated, n/N (%)	ELISPOT result indeterminate, n/N (%)	TST lost to follow up, n/N (%)	ELISPOT / TST, n/N (%)				Overall agreement, n/N (%)
					+/+	-/-	+/-	-/+	
Immunocompromised									
Chapman et al (2002)[132] **HIV positive**	21	21/21 (100)	0/21 (0.0)	7/21 (33.3)	3/14 (21.4)	6/14 (42.8)	3/14 (21.4)	2/14 (14.3)	9/14 (64.3)
Chapman et al (2002)[132] **HIV negative**	54	36/54 (66.7)	0/54 (0.0)	19/54 (35.2)	19/35 (54.3)	2/35 (5.7)	5/35 (14.3)	9/35 (25.7)	21/35 (60.0)
Karam et al (2008)[138] **HIV positive**	285	207/285 (72.6)	38/285 (13.3)	0/285 (0.0)	41/247 (16.6)	110/247 (44.5)	84/247 (34.0)	12/247 (4.9)	151/247 (61.1) [k= 0.23]
Winthrop et al (2008)[130]** **ESRD - contact investigation**	100	NR	3/100 (3.0)	0/100 (0)	NR	NR	NR	NR	(71)
Contact cases									
Adetifa et al (2007)**Error! Bookmark not defined.**	194[a]	92/194 (47.4)	12/194 (6.2)	NA	62/175 (35.4)	38/175 (21.7)	52/175 (29.7)	23/175 (13.1)	100/175 (57.1)
Hill et al (2004)[134]	856	282/629 (45)	NR	NR	162/735 (22.0)	380/735 (51.7)	137/735 (18.6)	56/735 (7.6)	542/735 (73.7)
Hill et al (2006)[135]**	795[b]	321/720 (44.6)	75/795[c] (9.4)	29/720 (4.0)	NR[d]	NR[d]	NR[d]	NR[d]	(75.0) [k=0.43]
Hill et al (2008)[32]	2348	981/2348 (41.8)	NR	NR	428/1648 (26.0)	813/1648 (49.3)	177/1648 (10.7)	230/1648 (13.9)	1241/1648 (75.3)
Jackson-Sillah et al (2007)[137]	1656	NR	NR	118/2381[b] (4.9)	375/1656 (22.6)	884/1656 (53.4)	106/1656 (6.4)	291/1656 (17.6)	1259/1656 (76.0) [k=0.54, 95% CI 0.42-0.61]
Krummel et al (2010)[139]	274[e]	18/172 (10.5)	4/167 (2.4)	NR	2/83 (2.4)	76/83 (91.6)	1/83 (1.2)	4/83 (4.8)	78/83 (94.0) (k=0.42 [SE 00.1])
Leyten et al (2007)**Error! Bookmark not defined.** **TST conversion during contact tracing and controls**	37	16/40 (40.0)	3/40 (7.5)	0/40 (0.0)	NR	NR	NR	NR	(65) [k=0.35]
Shams et al (2005)[143]	416	204/413 (49.4)	3/416 (0.7)	0/416 (0.0)	133/413 (32.2)	175/413 (42.4)	30/413 (7.3)	75/413 (18.1)	308/413 (74.6)
Children									
Hill et al (2006b)[136]	917	313/718 (43.6)	199/917 (21.7)	224/917 (24.4)	165/693 (23.8)	413/693 (59.6)	55/693 (7.9)	60/693 (8.6)	578/693 (83) [k=0.62]

** Not reported in meta-analysis; TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; TB = tuberculosis; ITT = intention to treat (total population); PP = per protocol (number of participants in which intervention and reference test results were available for analysis and reported); n = number; NR = not reported; k = kappa; HD = haemodialysis; LTC = liver transplantation candidates; HM = hematologic malignancies; ESRD = end-stage renal disease; IBD = inflammatory bowel disease.

k values <1 can be considered: <0.20 = poor; 0.20-0.40 = fair; 0.40-0.60 = moderate; 0.60-0.80 = good; 0.80-1.00 = very good.

a Only patients with valid results for both QTF-GIT and ELISPOT were reported.

b 99/775 TB contacts were not selected for ELISPOT (reason not reported).

c 9/75 had an inadequate specimen, 66/75 had a failed test.

d The study reports conflicting values so have not been reported in this assessment.

e Although 274 contacts were included, only 83 underwent both ELISPOT and TST testing; reasons were not reported.

Figure 22 presents the meta-analysis of the overall agreement between ELISPOT and TST (ITT) by population type. This analysis shows the proportion of overall agreement between ELISPOT and TST as 0.62 (95% CI: 0.55, 0.68) with a significant amount of heterogeneity (I^2 = 93.2%). Overall agreement does not appear to be affected by study population type.

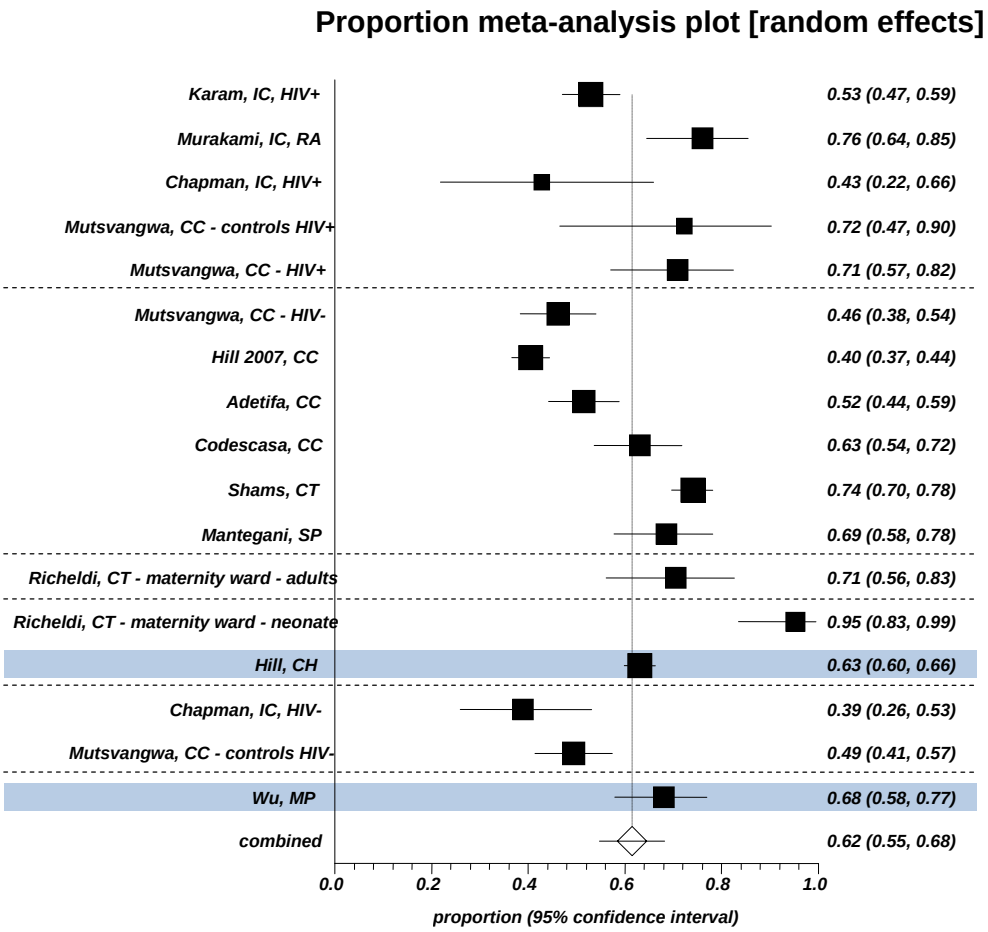

Figure 22: Meta-analysis of overall agreement between ELISPOT and TST, (ITT)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; SP = screening program; HCWs = healthcare workers; HI = health individuals; MP = military personnel

Figure 23 presents the overall agreement between ELISPOT and TST (ITT) ordered by the proportion of the study population that was BCG vaccinated. There does not appear to be any trend between the proportion of the study cohort that was BCG vaccinated and overall agreement, however the lowest proportion of BCG vaccinated individuals in any study cohort was 43.6% (Hill et al, 2006b[136]).

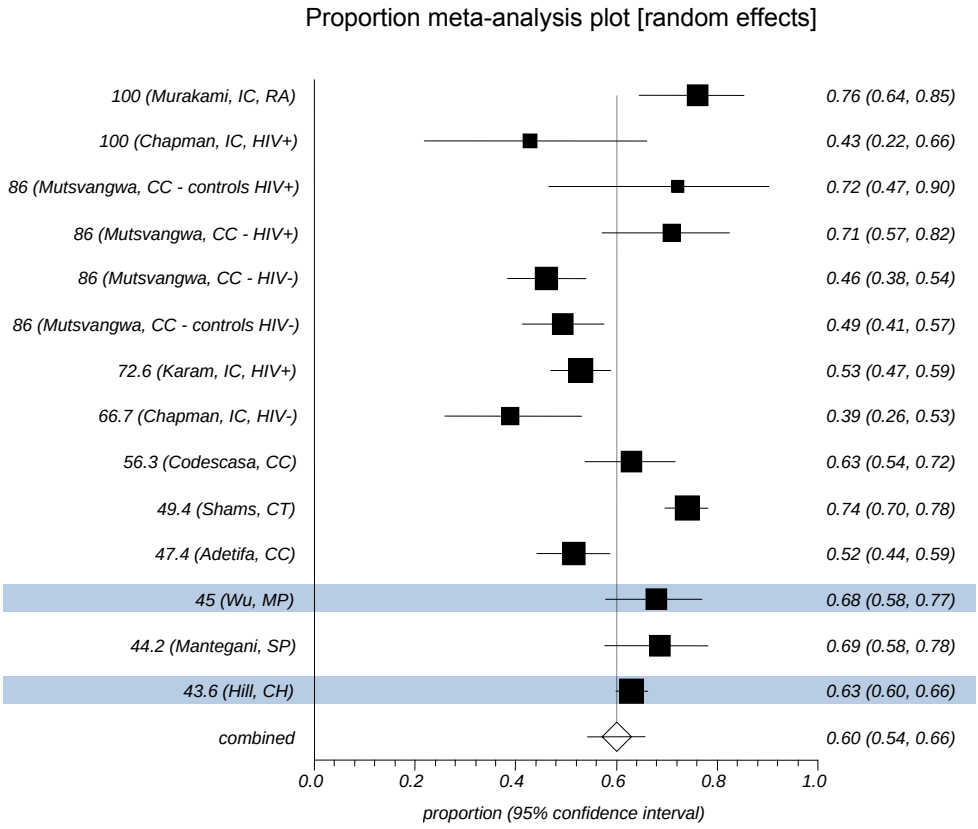

Figure 23: Meta-analysis of overall agreement between ELISPOT and TST, by BCG vaccination (%), (ITT)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing; SP = screening program; HCWs = healthcare workers; HI = health individuals; MP = military personnel

Figure 24 presents the meta-analyses of the overall agreement between ELISPOT and TST (PP) by study population. This analysis shows the proportion of overall agreement between ELISPOT and TST as 0.74 (95% CI: 0.69, 0.78) with a significant amount of heterogeneity (I^2 = 99.7%). Overall agreement does not appear to be affected by study population type.

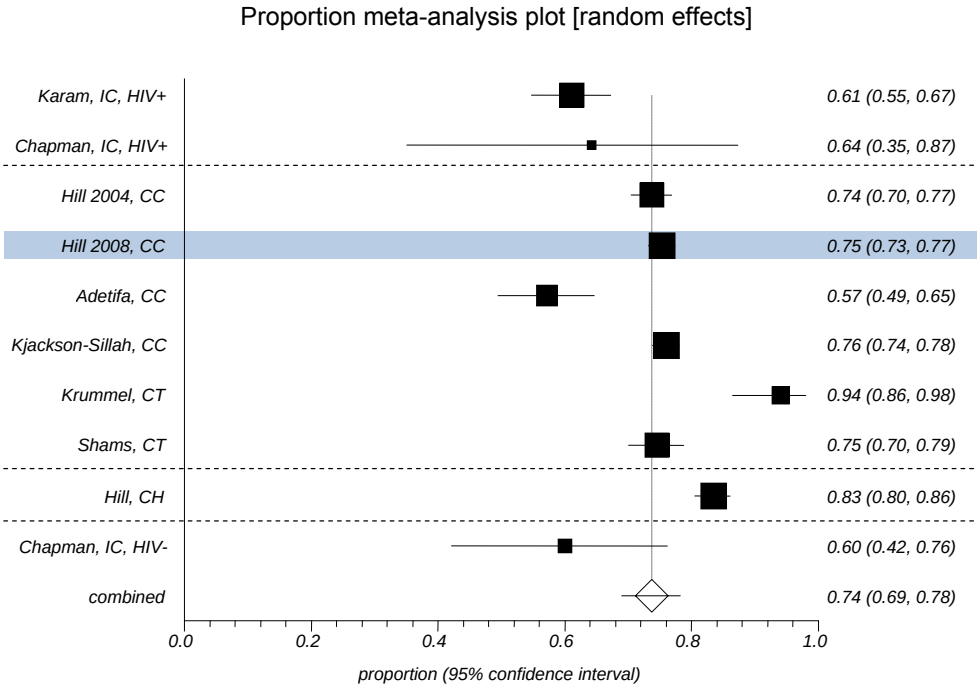

Figure 24: Meta-analysis of overall agreement between ELISPOT and TST, (PP)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing;

Figure 25 presents the overall agreement between ELISPOT and TST (PP) ordered by the proportion of the study population that was BCG vaccinated. With the greater range of the proportion of BCG vaccinated individuals in the indentified studies in the per-protocol analysis, a trend towards greater agreement in studies with a lower proportion of BCG vaccinated individuals can be seen.

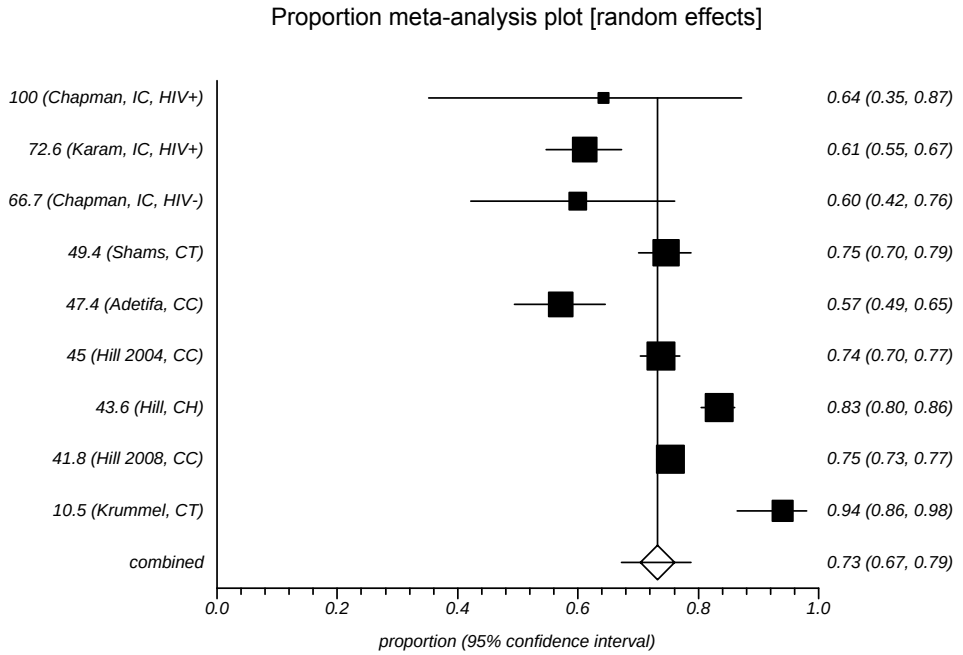

Figure 25: Meta-analysis of overall agreement between ELISPOT and TST, by BCG vaccination (%), (PP)

IC = immunocompromised; ID = inflammatory disease; RA = rheumatoid arthritis; CH = children; CC = contact cases; CT = contact tracing;

Concordance summary

The overall agreement (concordance) between IGRAs and TST (intention to treat analysis) was lowest in ELISPOT (0.62; 95% CI: 0.55, 0.68), and highest in QTF-GIT (0.69; 95% CI 0.65, 0.73). As would be expected, per-protocol analysis increased agreement overall, with QTF-G and T.SPOT®-TB with the lowest agreement (0.73; 95% CI: 0.63, 0.82 [QTF-G], 0.73; 95% CI: 0.59, 0.85 [T.SPOT®-TB]) and highest agreement in QTF-GIT (0.79; 95% CI 0.76, 0.82). In all IGRAs except T.SPOT®-TB (possibly due to inadequate study range), there was a trend towards greater agreement between IGRA and TST in studies that had a lower proportion of the study cohort that were BCG vaccinated.

As TST is not a perfect reference standard, and is known to be affected by BCG vaccination and environmental mycobacteria, disagreement between IGRAs and TST does not suggest inferiority to TST. The trend towards greater agreement in populations with lower BCG vaccination, or perhaps more importantly, greater disagreement in populations with high BCG vaccination status, suggests that there may be some value of IGRAs over TST in BCG vaccinated populations in reducing the number of false-positives identified.

Does it change patient management?

The management of patients differs according to whether they test positive or negative. Patients who test positive are managed by active surveillance and a proportion of these patients will be treated (Figure 2). Patients who test negative are not routinely followed up with active surveillance. As discussed above, IGRA appears to be a more efficient test than TST for identifying patients that will develop active TB. Fewer patients test positive with no increase in risk of false-negatives. This means that if IGRA is used in place of TST, there will be fewer patients unnecessarily undergoing active surveillance and perhaps treatment.

Does change in management improve patient outcomes?

It is likely that the harms of putting a patient under active surveillance and requiring a proportion of them to undergo treatment will be small. The main advantage of IGRA versus TST will be captured as savings due to reduced need for treatment and surveillance of patients. While preventive treatment has proven benefits if given to patients with positive TST or IGRA results, it also has a risk of toxicity.

Summary of effectiveness

Primary effectiveness outcomes

The comparison of IGRAs and TST indicates no statistically significant difference between the two tests regarding occurrence of false-negative test results. However, the rate of true-positives is higher in patients assessed by IGRA, and significantly fewer patients test positive to IGRA compared with TST. As significantly fewer patients test positive to IGRA than to TST with no increase in risk of false-negatives, this suggests that IGRA may be a more efficient test for LTBI than TST.

Secondary effectiveness outcomes

As TST is not a perfect reference standard, and is known to be affected by BCG vaccination and environmental mycobacteria, disagreement between IGRAs and TST does not suggest inferiority to TST. The trend towards greater agreement in populations with lower BCG vaccination, or perhaps more importantly, greater disagreement in populations with high BCG vaccination status, suggests that there may be some value of IGRAs over TST in BCG vaccinated populations in reducing the number of false-positives identified.

Other relevant considerations

The National Tuberculosis Advisory Committee (NTAC) has recently released a draft position statement, pending approval by the Communicable Diseases Network Australia (CDNA) on IGRAs for use in the detection of LTBI. In addition to the draft NTAC position statement there are three recent publications addressing the use of IGRAs. One is updated guidelines for the use of IGRAs by the Centers for Disease Control (CDC), another is a short clinical guideline published in 2010 by the National Institute for Health and Clinical Excellence (NICE) in the UK, and the third is a guidance published by the European Centre for Disease Prevention and Control (ECDC). The key points of the NTAC position statement and other relevant guidelines are summarised below.

NTAC – Position statement on IGRAs in the detection of LTBI

NTAC has reviewed recent literature on IGRAs and determined that the studies have not clearly demonstrated that IGRAs are superior to TST. NTAC also noted a continuing absence of cost-effectiveness studies of IGRAs under Australiasian TB program conditions, and that the long history of use of TST and longitudinal data provides important predictive information that is not yet available with IGRAs. On this basis, NTAC has concluded that TST remains the preferred test for LTBI in most patient groups. NTAC has recommended that IGRAs may be used as supplemental tests to improve specificity in screening immunocompetent subjects and also be used in addition to TST in immunocompromised patients at high risk of LTBI. The specific recommendations for different patient groups are as follows:

- **Contact investigation in adults:** TST remains the test of choice for investigation of contacts of active TB. TST has similar specificity to IGRAs in a non-BCG vaccinated cohort, therefore IGRAs do not add additional value in this group.

  In TST-positive subjects at low risk of LTBI and at low risk of progressing to active disease, an IGRA may be used as a supplementary test in a two-step process to confirm LTBI. The improved specificity of IGRA in this circumstance in subjects who have had previous BCG or NTM exposure may allow better targeting of preventative therapy.

  IGRAs may be a preferred option where resources, distance or other factors make TST impractical to administer.

- **Contact tracing in children:** IGRA does not replace TST for detection of LTBI in children and (like TST) cannot be used to exclude LTBI. IGRA may have additional value over TST in children that received BCG vaccination after the first year of life.

- **Screening of immigrants:** TST and supplemental IGRA assessment for people identified with a positive TST is the recommended diagnostic strategy in immunocompetent immigrants from countries where TB is highly prevalent.

- Immunocompromised individuals with HIV infection: TST remains the test of choice for detection of LTBI in HIV-infected individuals. However, recognising

the lowered sensitivity of TST in immunocompromised patients, an IGRA may be used as a supplementary test. An HIV-infected individual would be diagnosed with LTBI if either the TST or IGRA is positive.

- **Immunocompromised individuals receiving anti-tumour necrosis factor-α therapy:** Either TST or IGRA are acceptable for LTBI screening in immune-mediated inflammatory disease (IMID) patients. IGRA may be preferred if there is a history of BCG immunisation after age one year. Both TST and IGRA may be performed if the risk of LTBI is considered high; a diagnosis of LTBI would be made by a positive result in either test.

  The TB exposure history and chest X-ray are central in interpreting the TST/IGRA result and in determining the overall risk of LTBI in IMID patients.

- Other immunocompromised individuals: Either TST or IGRA are acceptable for LTBI screening in other immunocompromised patients. IGRA may be preferred if there is a history of BCG immunisation after age one year. Both TST and IGRA may be performed if the risk of LTBI is considered high; a diagnosis of LTBI would be made by a positive result in either test.

  The TB exposure history and chest X-ray are central in interpreting the TST/IGRA result and in determining the overall risk of LTBI in immunocompromised patients.

- **Serial testing of healthcare workers:** The problem of defining an appropriate cut-off point has resulted in a trend towards more cautious use of IGRAs for HCW screening. For the present, TST remains the preferred test for HCW screening in Australia with IGRA's role limited to supplementary testing as a specificity tool.

- **Indeterminate results:** IGRAs can produce un-interpretable (termed "indeterminate") results either due to inappropriately high or low IFN-γ response in the negative or positive controls, respectively. The handling of indeterminate results highlights an important principle. IGRAs should only be carried out by clinicians experienced in the diagnosis and management of TB and LTBI. The investigation and management of such patients should occur in liaison with the relevant state or territory TB service. Problematic IGRA results, including indeterminate reactions, can then be assessed expertly in the patient's clinical setting.

<u>CDC – Updated guidelines to detect TB infection[3]</u>

In 2010 the CDC published updated guidelines for the use of IGRAs for the detection of TB. This was largely to integrate QTF-GIT and T.SPOT®.TB into their existing guidelines, and the evidence presented was for only these two tests.

The assessment of accuracy, sensitivity and specificity noted these limitations in assessing accuracy:

- Assessments of accuracy of tests for *M. tuberculosis* infection are difficult because there is no "gold standard" to confirm a diagnosis of LTBI or culture-negative active tuberculosis.

- While approximations of accuracy, sensitivity, and specificity can be made by testing populations with known characteristics. However, although sensitivity and specificity are inherent characteristics of the tests, with no "gold standard," estimates of test performance might fluctuate as a result of differences in the study population and the rate of diagnostic misclassification because TSTs and IGRAs are indirect tests that measure immunologic responses and are not direct tests that detect the causative organism or components of the organism, assessments of sensitivity among persons with culture-confirmed active tuberculosis might not provide reliable estimates of sensitivity for LTBI.

- Assessment of test accuracy is complicated further by the use of different test methods and interpretation criteria for TST, QFT-GIT, and T-Spot in published reports.

The CDC report concluded that TST and IGRAs should be used as aids in diagnosing *M. tuberculosis* infection, and that IGRAs can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST testing. This differs from the recommendations of NICE (below), in which the joint use of TST and IGRAs is recommended across patient populations.

CDC nominated situations in which an IGRA is preferred, but a TST is acceptable:

- In groups that historically have low rates of returning to have TSTs read. For example, use of an IGRA might increase test completion rates for homeless persons and drug users.

- For persons who have received BCG (as a vaccine or for cancer therapy). Use of IGRAs in this population is expected to increase diagnostic specificity and improve acceptance of treatment for LTBI.

Use of a TST is preferred but an IGRA is acceptable:

- For testing children aged less than 5 years. Use of an IGRA in conjunction with TST has been advocated by some experts to increase diagnostic sensitivity in this age group.

Either a TST or an IGRA may be used:

- To test recent contacts of persons known or suspected to have active tuberculosis with special considerations for follow-up testing.

- For periodic screening of persons who might have occupational exposure to *M. tuberculosis* (e.g., surveillance programs for health-care workers) with special considerations regarding conversions and reversions.

Although CDC recommended against using both an IGRA and TST, they did specify situations in which such may be considered:

- When the initial test (TST or IGRA) is negative in the following situations:

    1) when the risk for infection, the risk for progression, and the risk for a poor outcome are increased (e.g., when persons with HIV infection or

children aged less than 5 years are at increased risk for *M. tuberculosis* infection)

2) when clinical suspicion exists for active tuberculosis (such as in persons with symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of *M. tuberculosis* infection is desired

- When the initial test is positive in the following situations:

1) when additional evidence of infection is required to encourage compliance (e.g., in foreign-born health-care workers who believe their positive TST result is attributable to BCG)

2) of healthy persons who have a low risk for infection and progression

NICE 2010[4]

In 2010 NICE published a short clinical guideline addressing the use of IGRAs for the diagnosis of LTBI. The populations considered were:

- Adults and children at increased risk of infection by *M. tuberculosis* complex specifically if they have arrived or returned from high-prevalence countries in the last five years, live with people diagnosed with active TB, have close contact with people diagnosed with active TB, are homeless or problem drug users, are or have recently been prisoners.

- Adults and children who are immunocompromised because of prolonged steroid use, TNF-α antagonist use, anti-rejection therapy such as cyclosporine, cytotoxic treatments and some treatments for inflammatory bowel disease, use of immunosuppression-causing medication and co-morbid states that affect the immune system, such as HIV, chronic renal disease, haematological and solid cancers, and diabetes.

The NICE Guideline made these recommendations regarding the use of IGRAs:

Offer TST for:

- Household contacts five years and older;

- Non-household contacts;

- Adult contacts.

Those with positive results (or for whom TST may be less reliable) should then be considered for IGRA testing.

For recent arrivals from highly prevalent countries:

- For people aged 5 to 34, offer a TST followed by an IGRA test if positive.

- In those aged 16 and older, an IGRA test alone can be used.

For under 5's:

- Use TST as initial diagnostic test. If the initial test is positive, taking into account the BCG history, then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI.

For household contacts under five years of age:

- Use TST as initial diagnostic test. If the initial test is positive taking into account the BCG history, then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI.

- If the initial TST is negative, then in those who are contacts of sputum smear positive disease, an IGRA test should be performed after an interval of six weeks as well as repeating the TST to increase the sensitivity. If either test is positive, assess and treat.

Contacts:

- In an outbreak situation among children aged 5 years and older where large numbers of individuals may need to be screened, a single IGRA test is appropriate.

Immunocompromised:

- For patients with HIV and CD4 counts of less than 200, perform an IGRA and a TST. If either test is positive, assess for active TB. Consider treatment of LTBI if active disease is excluded.

- For patients with HIV and CD4 counts of 200 – 500, perform an IGRA test alone or an IGRA test with a concurrent TST. If either test is positive, assess for active TB. Consider treatment of LTBI if active disease is excluded. For patients with CD4 counts above 500, consider as an immunocompetent adult.

- For other categories of immunocompromised patients, perform an IGRA test alone or an IGRA test with a concurrent TST. If either test is positive, assess for active TB. Consider treatment of LTBI if active disease is excluded.

Healthcare workers:

- Healthcare workers who have recently (up to 5 years) arrived from TB-prevalent countries, as defined by the Health Protection Agency, should be screened as recommended for recent arrivals from highly prevalent countries.

- Test other healthcare workers in contact with patients or clinical materials, and who have not had BCG (for example, without scar, other documentation or reliable history), for latent TB infection with either Mantoux testing or IGRA testing.

- Healthcare workers who have CD4 counts of 200 – 500 should be screened as recommended for the immunocompromised population.

No further evidence has been reviewed for other groups such as prisoners or prison staff, but the tests will be performed as with any other adults. In hard-to-reach populations a single IGRA test will be the most appropriate.

The NICE Guideline reported on results of a decision model used to compare the cost-effectiveness of four strategies of testing for LTBI (TST, IGRA, TST followed by IGRA for patients with a positive TST, and no test). The guideline reported that the two-stage strategy (TST followed by IGRA) was within the range usually considered cost-effective, at approximately £26,000/QALY gained. IGRAs alone were not cost-effective, at over £150,000/QALY gained, while TST alone was dominated (i.e., less effective and more costly than all other options).

ECDC Guidance[5]

The ECDC guidance document presented evidence-based expert opinion of an ad-hoc scientific panel on the use of IGRAs for the diagnosis of LTBI and active TB. The panel indicated that based on the available results on positive predictive value (PPV) for progression, and taking into consideration the low statistical power and low number of studies, IGRAs may be used as part of the overall risk assessment to identify individuals for preventive treatment (e.g., immunocompromised persons, children, close contacts, and recently-exposed individuals). Similarly, despite the limitations of available studies, the high NPV for progression of IGRAs indicates that at the time of testing and in the context of an overall risk assessment, progression to active TB in healthy immunocompetent individuals with negative IGRAs is very unlikely. Therefore, IGRAs may be used in this context. The panel noted that, particularly in risk groups and specific situations, a negative IGRA does not rule out LTBI.

Consumer implications and other considerations

There is a concern that MBS listing of IGRAs may affect the availability of TST, particularly in remote areas. The potential effect on consumers in remote areas was sought. Respondents from the Northern Territory acknowledged the potential benefit of IGRAs, but they also noted numerous logistical issues, particularly for communities that are located considerable distances from pathology laboratories.

What are the economic considerations?

Costing

As shown in Table 9, there were a total of 7280 TST tests conducted in the 2010–2011 financial year. With a cost of $11.30 per test, this indicates a total cost of TST of $82,264 to the MBS.

The estimated cost of IGRAs is $48.00 per test, based on advice provided by the Victorian Infectious Disease Reference Laboratory for the cost of QTF-GIT.

Economic evaluation

Economic analysis for IGRAs versus TST

Ideally, an economic analysis comparing IGRAs and TST would be structured as shown in Figure 26. The analysis shown takes into consideration incremental costs and incremental benefits. For the purposes of this assessment, it is assumed that there is no difference in patient outcomes regardless of whether patients are tested for LTBI using IGRA or using TST (i.e., it is assumed that the impact of putting patients who have falsely tested positive under surveillance [and perhaps requiring them to undergo treatment] on the patient's quality-adjusted survival is negligible). Because the assumption is made that outcomes are no worse if patients are assessed using IGRA rather than TST, then the analysis is reduced to a comparison of costs only (i.e., consideration of implications of false-positives and false-negatives). The structure of the simplified analysis is shown in Figure 27.

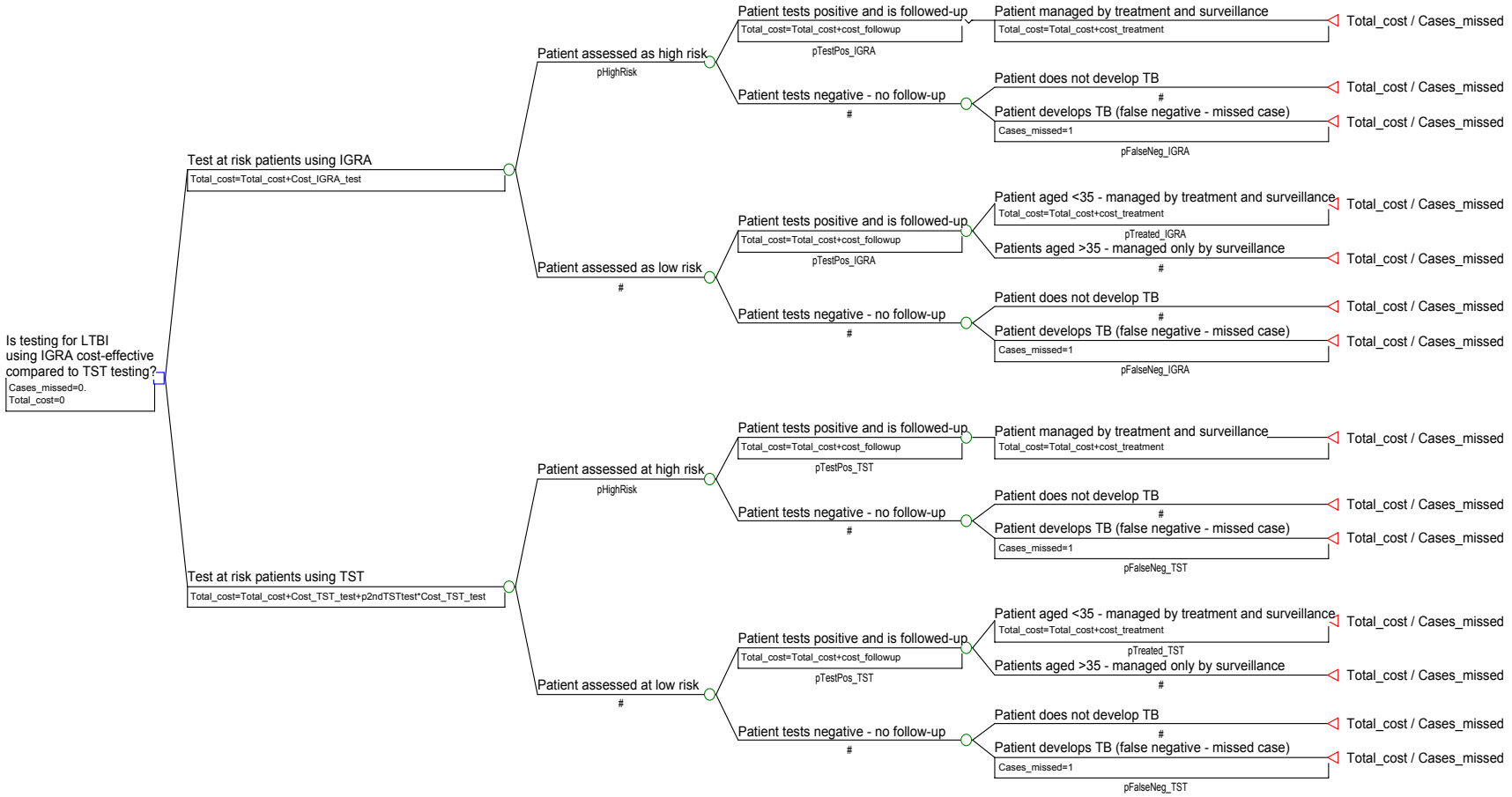

Figure 26: Structure of economic analysis model

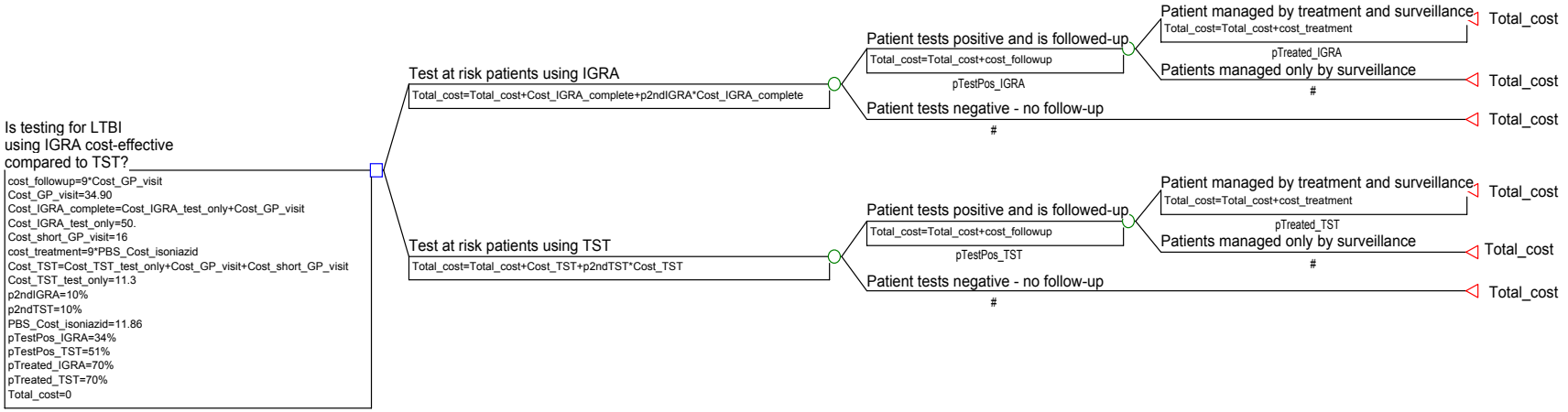

Figure 27: Simplified economic analysis model

The variables required to populate the simplified economic evaluation include:

- Cost of IGRA test (Cost_IGRA_test)
- Cost of TST (Cost_TST)
- Proportion of patients having a second test (p2ndIGRAtest / p2ndTST)
- Cost of follow-up if a patient tests positive to IGRA or TST (cost_followup)
- Cost of treatment of a patient who tests positive to IGRA or TST (cost_treatment)
- Proportion of patients testing positive/negative to IGRA (pTestPos_IGRA)
- Proportion of patients testing positive/negative to TST (pTestPos_TST)
- Of patients testing positive to IGRA, what proportion of patients receive treatment (pTreated_IGRA)
- Of patients testing positive to TST, what proportion of patients receive treatment (pTreated_TST)

Costs in each arm are calculated as shown in the Table 25:

Table 25: Calculations for the cost of IGRA and TST arms

	IGRA	TST	Increment
Cost of testing	$Cost for IGRA + p2ndIGRA x $Cost for IGRA (A)	$Cost for TST + p2ndTST x $Cost for TST (B)	A – B [i]
Cost of follow-up	pTestPos_IGRA x $Cost of followup (C)	pTestPos_TST x $Cost of followup (D)	C – D [ii]
Cost of treatment	pTestPos_IGRA x pTreated_IGRA x $Cost of treatment (E)	pTestPos_TST x pTreated_TST x $Cost of treatment (F)	E – F [iii]
Total costs	$ A + C + E	$ B + D + F	$ i + ii + iii

The values assumed to be applicable for the variables included in the economic evaluation are summarised in Table 26. As can be seen from this table the primary drivers of differences in costs across the two arms are: (i) cost of test (including assumptions as to need for second test); (ii) proportion of patients testing positive; and (iii) proportion of patients testing positive who receive treatment. There is considerable uncertainty around these variables. Therefore, the impact of uncertainty is explored in a series of one-way sensitivity analyses.

Table 26: Values assigned to economic evaluation variables

	Value in IGRA arm	Source	Value in TST arm	Source
Cost of test (Cost_IGRA / Cost_TST)	$55.10[a] + $34.90 = $90.00	Estimated fee for IGRA + Cost GP visit (MBS Item 23)	$11.30 + $34.90 +$16.00 = $62.20	MBS fee for TST (MBS Item 73811) + Cost GP visit (MBS Item 23) + Cost of short visit for assessment of result (MBS Item 3)
Proportion of patients having a second test (p2ndIGRA / p2ndTST)	10%	Estimate	10%	Estimate
Proportion of patients testing positive/negative (pTestPos_IGRA/ pTestPos_TST)	34%	Meta-analysis in Figure 9	51%	Meta-analysis in Figure 9
Cost of follow-up if a patient tests positive to IGRA or TST (cost_followup)	$314.10	Assumption: 9 monthly GP visits (MBS Item: 23)	$314.10	Assumption: 9 monthly GP visits (MBS Item: 23)
Cost of treatment of a patient who tests positive to IGRA or TST (cost_treatment)	$106.74	Assumption: treatment with 300mg isoniazid/day for 9 months (PBS cost per 100 tablets: $11.86)	$106.74	Assumption treatment with 300mg isoniazid/day for 9 months (PBS cost per 100 tablets: $11.86)
Of patients testing positive, what proportion of patients receive treatment (pTreated_IGRA/ pTreated_TST)	70%	Assumption	70%	Assumption

a The cost of the IGRA is based on test cost of $48.00 plus an MBS Patient Episode Initiation Fee (PEI) plus bulk-billing incentive fee. It was assumed that 80% of PEIs would be for private laboratories and 20% for public laboratories, with bulk-billing incentives occurring for 87% of episodes. The PEI fees are $5.10 for private laboratory collection centres (MBS 73928) and $2.05 for public laboratory collection centres (MBS 73929) with bulk-billing incentive fees of $3.40 for public and $1.40 for private.

Results of the economic analysis are summarised in Table 27, which shows that testing for LTBI using IGRAs appears to be cost-saving compared to TST. Costs of treatment are likely to be underestimated in the analysis presented because there are likely to be costs associated with treatment beyond drug costs. These include costs associated with consultations with clinicians, costs to manage adverse events, and costs associated with monitoring of the patient (e.g., liver function tests). However, the inclusion of such costs will not affect the overall conclusion of dominance of IGRA versus TST. In fact, inclusion of such costs will make IGRA more cost-saving compared with TST.

The robustness of the conclusion of dominance is explored in the sensitivity analyses presented in Figure 28 to Figure 30. The results of the sensitivity analyses indicate that the analysis is most sensitive to the extent of difference in proportion of patients testing positive to IGRA compared with proportion testing positive to TST.

Table 27: Summary of economic analysis results[a]

	IGRA	TST	Increment
Cost of testing	$99.00 (1.1 x $84.90)	$68.42 (1.1 x $62.20)	$30.58
Cost of follow-up	$106.79 (34% x $314.10)	$160.19 (51% x $314.10)	- $53.40
Cost of treatment	$25.40 (34% x 70% x $106.74)	$38.11 (51% x 70% x $106.74)	- $12.71
Total costs	**$231.19**	**$266.72**	**- $35.52**

a Values in this table may differ due to rounding.

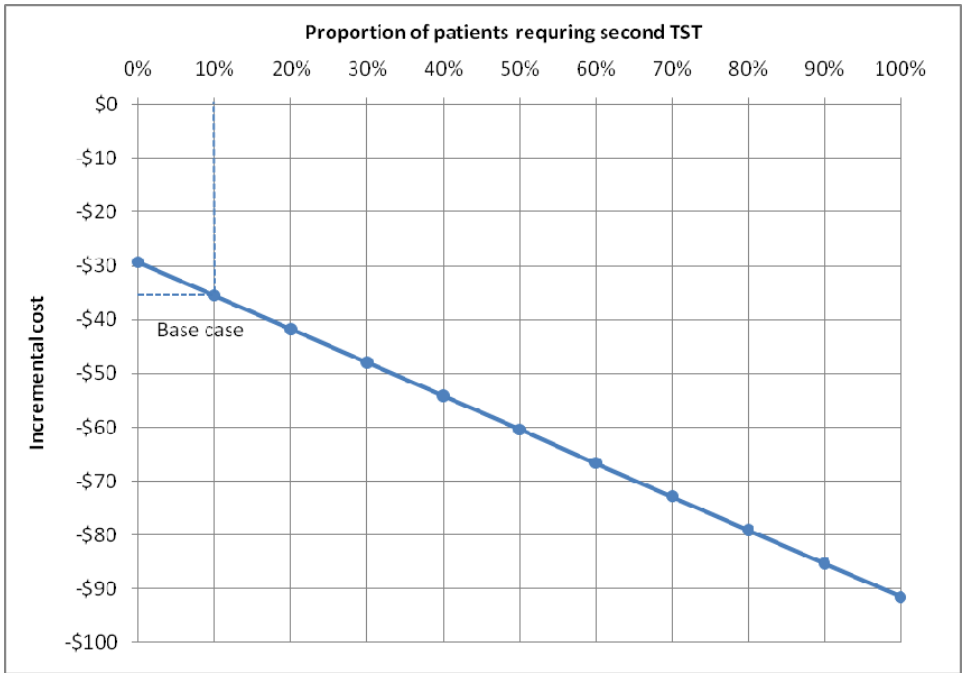

Figure 28: Sensitivity analysis around proportion of TST patients requiring a second TST.

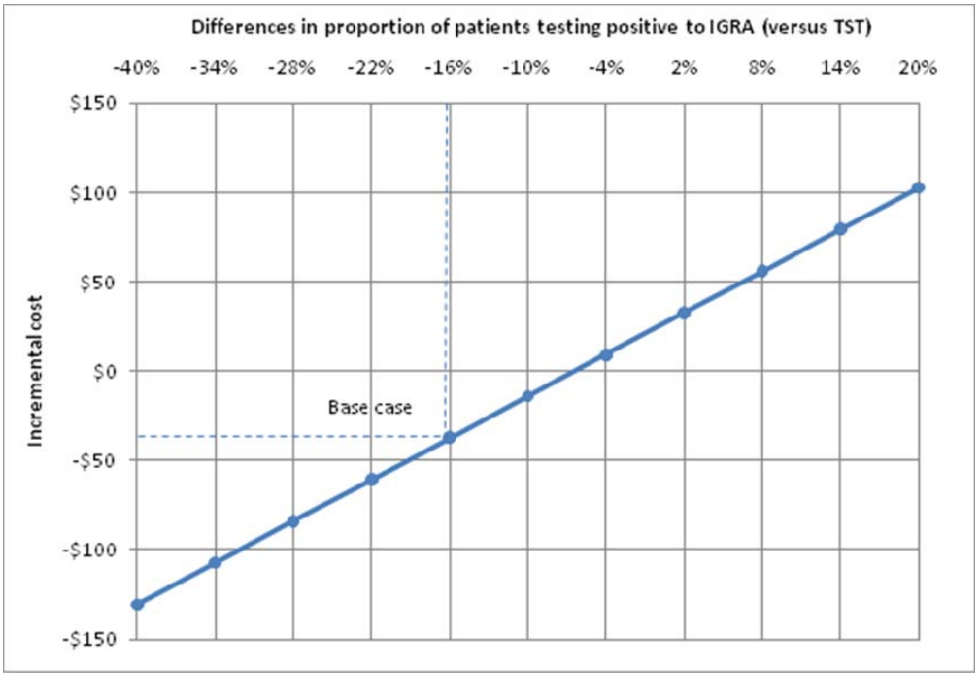

Figure 29: Sensitivity analysis around proportion of patients tested with IGRA who test positive (43% of patients tested with TST reported positive)

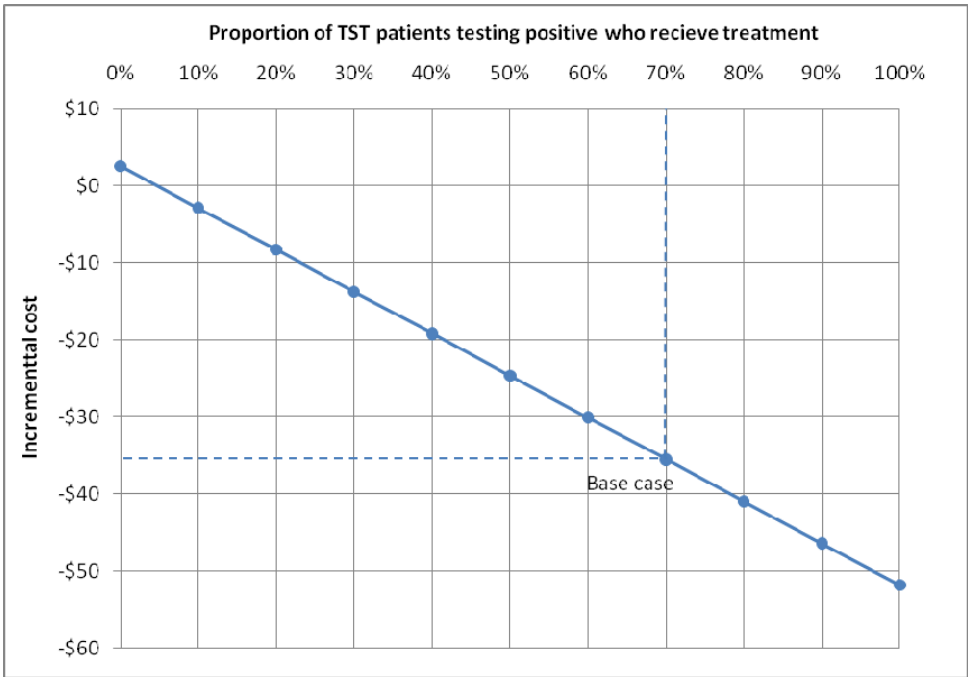

Figure 30: Sensitivity analysis around proportion of patients testing positive to TST who receive treatment (51% of patients test positive to TST).

Conclusions

Safety

Given the nature of IGRA tests, it is not anticipated that they will be associated with any safety issues beyond issues associated with collection of blood by venipuncture.

Effectiveness

Diagnostic accuracy

The comparison of IGRAs and TST indicates no statistically significant difference between the two tests regarding occurrence of false-negative results. However, the rate of true-positives is significantly higher in patients assessed by IGRA, and significantly fewer patients test positive to IGRA compared to TST. The comparison of overall positive test results indicates that IGRA may be a more efficient test for LTBI than TST because significantly fewer patients tested positive to IGRA than to TST, with no increase in risk of false-negatives.

Impact on patient management

As stated above, IGRAs appear to be more efficient than TST for identifying patients that will progress to active TB. Fewer patients test positive with no increase in risk of false-negatives. This means that if IGRA is used in place of TST, fewer patients will unnecessarily undergo active surveillance and perhaps treatment.

Impact on health outcomes

The main advantage of IGRAs compared to TST regarding health outcomes will be captured as savings due to reduced need for treatment and surveillance of patients.

Economic considerations

As exact costs for IGRA tests are not available, it was not possible to accurately estimate costs to the MBS or Government. The cost of TST in the 2010–2011 financial year was $82,264 to the MBS, based on a test cost of $11.30 and 7280 tests.

Using an estimated cost of $55.10 for an IGRA test, and based on the assumption that outcomes are no worse if patients are assessed using IGRA rather than TST, a cost comparison analysis was conducted. This analysis indicated that testing for LTBI using IGRAs appears to be cost-saving compared to using TST, with an estimated saving of $35.52 per patient.

Costing

There is a lack of information available regarding the use of IGRAs. In particular, there is uncertainty concerning potential shift from the public to the private sector and a lack of information regarding the cost of IGRAs; therefore, an estimate of expected uptake and cost to the MBS has not been provided.

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian health care system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services including those that involve new or emerging technologies and procedures, and, where relevant, amendment to existing MBS items in relation to:
  - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
  - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
  - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
  - the circumstances, in which there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
  - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to undertake its role effectively. MSAC may delegate some of its functions to its executive sub-committee.

The membership of MSAC at the 55th meeting held March 2012 comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers and health administration and planning:

Member	**Expertise or Affiliation**
Professor Robyn Ward (Chair)	Medical Oncology
Dr Frederick Khafagi (Deputy Chair)	Nuclear Medicine
Professor Jim Butler (Chair, Evaluation Sub-Committee)	Health Economics
Associate Professor John Atherton	Cardiology
Professor Chris Baggoley	Commonwealth Chief Medical Officer (*ex officio*)
Associate Professor Michael Bilous	Anatomical Pathology
Associate Professor Kirsty Douglas	General Practice/Research
Professor Kwun Fong	Thoracic Medicine
Professor Paul Glasziou	Evidence-based health care
Mr Scott Jansson	Pathology
Professor David Little	Orthopaedics
Mr Russell McGowan	Consumer Health Representative
Professor David Roder	Health medicine/Epidemiology
Associate Professor Bev Rowbotham	Haematology
Dr Graeme Suthers	Genetics/Pathology
Dr Christine Tippett	Obstetrics/Gynaecology
Dr Simon Towler	AHMAC Representative (*ex officio*)
Associate Professor David Winlaw	Paediatric Cardiothoracic Surgery

Appendix B Advisory Panel and Evaluators

Advisory Panel - Pathology tests for latent mycobacterial infection (1144)

Member	Nomination / Expertise or Affiliation
Dr Graeme Suthers (Chair)	Member of MSAC; Genetics/pathology
Assoc Prof Michael Bilous (Dep Chair)	Member of MSAC; Anatomical pathology
Assoc Prof James Black	Public health physician
Dr Sharon Chen	Royal College of Pathologists of Australasia; Senior staff specialist and medical mycologist
Assoc Prof Stephen Graham	Member of NTAC; Paediatric TB specialist
Dr Vitali Sintchenko	Staff specialist in infectious diseases
Mr Keith Williams	Consumer health forum nominee

Evaluation Sub-Committee input

Name	
Prof Justin Beilby	Member of MSAC Evaluation Sub-Committee, General practice

Evaluators

Name	Organisation
Bridie Murphy	Deakin University
Patti Whyte	Deakin University
Liliana Bulfone	Deakin University

Appendix C Search strategies

Medline

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>
Search Strategy:

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1 exp Randomized Controlled Trial/ (297894)
2 exp Controlled Clinical Trial/ (82294)
3 exp Random Allocation/ (69619)
4 exp Double-Blind Method/ (108269)
5 exp Single-Blind Method/ (14353)
6 1 or 2 or 3 or 4 or 5 (442022)
7 exp Clinical Trial/ (623164)
8 (clinical adj2 trial).ab,ti. (57454)
9 (control$ adj2 trial).ab,ti. (56127)

10 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti. (111397)
11 random$.ab,ti. (523396)
12 7 or 8 or 9 or 10 or 11 (950135)
13 Comparative Study/ (1499676)
14 exp Evaluation Studies/ (138983)
15 exp Follow-Up Studies/ (410823)
16 exp Prospective Studies/ (285755)
17 (control$ or prospectiv$ or volunteer$).ab,ti. (2346242)
18 13 or 14 or 15 or 16 or 17 (3918394)
19 6 or 12 or 18 (4323453)
20 exp Tuberculosis/ (134788)
21 TB.mp. (17654)
22 Latent Tuberculosis.mp. (1108)
23 latent TB.mp. (454)
24 LTBI.mp. (427)
25 20 or 21 or 22 or 23 or 24 (141518)
26 *Interferon-gamma/ (15629)
27 Quantiferon TB gold.mp. (290)
28 QTF-G.mp. (1)
29 interferon gamma release assay*.mp. (263)
30 IGRA.mp. (153)

31 *immunoenzyme techniques/ or *enzyme-linked immunosorbent assay/ (16675)
32 enzyme-linked immunosorbent spot.mp. (214)
33 ELISPOT.mp. (2885)
34 esat-6.mp. (685)
35 cfp 10.mp. (347)
36 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (35372)
37 25 and 36 (1794)
38 19 and 37 (963)
39 Mantoux.mp. (1198)
40 *Tuberculin Test/ (4072)
41 Tuberculin skin test.mp. (1854)
42 TST.mp. (1861)
43 Tuberculin sensitivity test.mp. (2)
44 pirquet.mp. (74)
45 purified protein derivative.mp. (2738)
46 PPD.mp. (5951)
47 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (13460)
48 38 and 47 (458)
49 limit 48 to humans (384)

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Medline

mantoux:ab,ti OR 'tuberculin test'/exp OR 'tuberculin skin test':ab,ti OR tst:ab,ti OR 'tuberculin sensitivity test':ab,ti OR pirquet:ab,ti OR 'purified protein derivative':ab,ti OR ppd:ab,ti AND ('interferon gamma'/exp OR 'inf gamma':ab,ti OR 'interferon type ii':ab,ti OR 'quantiferon tb gold':ab,ti OR 'qft-g':ab,ti OR 'interferon gamma release assay':ab,ti OR 'interferon gamma release assays':ab,ti OR igra:ab,ti OR 'immunoenzyme technique'/exp OR 'enzyme-linked immunosorbent assay'/exp OR 'enzyme-linked immunosorbent spot':ab,ti OR elispot:ab,ti OR 'esat-6':ab,ti OR 'cfp 10':ab,ti) AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'random allocation'/exp OR 'double-blind method'/exp OR 'single-blind method'/exp OR 'clinical trial'/exp OR (clinical NEXT/2 trial):ab,ti OR (control* NEXT/2 trial):ab,ti OR ((singl* OR doubl* OR trebl* OR tripl*) NEXT/2 (blind* OR mask*)):ab,ti OR random*:ab,ti OR 'comparative study'/exp OR 'evaluation studies'/exp OR 'follow-up studies'/exp OR 'prospective studies'/exp OR control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti) AND ('tuberculosis'/exp OR tb:ab,ti OR 'latent tuberculosis'/exp OR 'latent tuberculosis':ab,ti OR 'latent tb':ab,ti OR 'ltbi':ab,ti)

Appendix D Studies included in the review

Study profiles of included studies on diagnostic accuracy with follow-up

Study and location	Level of evidence and quality assessment	Study design	Study population	Intervention	Inclusion/exclusion criteria	Outcomes assessed	Duration of follow-up
Aichelburg et al (2009)[18] Austria	III-2 High	Diagnostic accuracy Prospective Longitudinal cohort study Subject selection method not reported	HIV infected patients	QTF-GIT	Inclusion/exclusion criteria: none stated.	• QTF-GIT assay result • TST result • Development of active TB disease • AIDS and death	2 years
Diel et al (2008)[19] Germany	III-2 High	Diagnostic accuracy Prospective Subject selection reported as "all contacts"	Close contacts of AFB smear-positive, culture confirmed MTB cases.	QTF-GIT	Inclusion criteria: aggregate exposure time of the contact of not less than 40 hours in closed rooms. Exclusion criteria: none stated.	• QTF-GIT assay result • TST result • QTF-GIT/TST agreement • Development of active TB disease	1 year
Harstad et al (2010)[20] Norway	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Asylum seekers aged ≥18 years	QTF-GIT	Inclusion criteria: TST ≥6 mm, a positive chest x-ray, or positive QTF-GIT result. Exclusion criteria: asylum seekers who had left the National Reception Centre without a forwarding address, if they had left the country, been deported, or died before leaving the centre.	• Development of active TB disease	23-32 months
Mahomed et al (2011)[21] South Africa	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Adolescents aged 12 to 18 years.	QTF-GIT	Inclusion criteria: none stated. Exclusion criteria: prior or current TB, indeterminate QTF-GIT result, or missing QTF-GIT or TST result.	• QTF-GIT assay result • TST result • QTF-GIT/TST agreement • Development of active TB disease	22-24 months
Ringshausen et al (2009)[22] Germany	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers in-hospital contact investigation	QTF-GIT	Inclusion criteria: aged 18 years and above, contact to the index case during infectivity and written informed consent. Exclusion criteria: none stated.	• QTF-GIT assay result • TST result • QTF-GIT/TST concordance • Development of active TB disease	2 years
Santin et al	III-2	Diagnostic accuracy	HIV positive patients	QTF-GIT	Inclusion criteria: none stated	• QTF-GIT result	1-24

(2011)[23] Spain	High	Prospective Longitudinal Subject selection method not reported	≥18 years old seen for the first time at an outpatient clinic		Exclusion criteria: patients with an active AIDS-defining event, current active TB, or ongoing treatment for LTBI.	• TST result • Development of active TB disease	months
Higuchi et al (2007)[24] Japan	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Student contact cases	QTF-G	Inclusion criteria: same grade as the index case. Exclusion criteria: none stated.	• QTF-G assay result • TST result • QTF-G/TST agreement • Development of active TB disease	3.5 years
Lee et al (2009)[25] South Korea	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Newly employed nurses (HCWs)	QTF-G	Inclusion/exclusion criteria: none stated.	• QTF-G/TST agreement • QTF-G/TST result at follow-up • Development of active TB disease	1 year
Noorbakhsh et al (2011)[26] Iran	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts <20 years old	QTF-G	Inclusion criteria: contact was defined as any person who had lived with the index case (confirmed by positive culture or sputum smear-positive TB) for more than 3 months. Exclusion criteria: contacts treated for TB in the past year or had a known immunodeficiency state on history or clinical signs (malignancy, corticosteroid therapy, HIV, etc).	• QTF-G/TST agreement • Development of active TB disease	1 year
Soborg et al (2007)[27] Denmark	III-2 High	Diagnostic accuracy Prospective All permanent HCWs invited to participate	Healthcare workers	QTF-G	Inclusion criteria: permanent staff. Exclusion criteria: none stated.	• QTF-G assay result • TST result • Development of active TB disease	18 months
Kim et al (2011)[28] South Korea	III-2 High	Diagnostic accuracy Prospective Subject selection reported as 'all"	Patients admitted for kidney transplantation	T.SPOT®-TB	Inclusion criteria: none stated. Exclusion criteria: refusal of informed consent, presence of active TB, presence of skin disease that precluded TST, paediatric renal transplant candidates (<16 years old), presence of any contraindication for kidney transplant (e.g., malignancy) and pancreas transplantation alone.	• T.SPOT®-TB assay result • TST result • T.SPOT®-TB /TST agreement • Development of active TB disease (primary outcome)	1-2.5 years
Leung et al (2011)[29] China	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Silicotic patients	T.SPOT®-TB	Inclusion criteria: male patients with silicosis with profusion of opacites at category 1 or above, without clinical suspicion of active TB, past history of TB, or treatment for LTBI. Exclusion criteria: active TB	• T.SPOT®-TB assay result • TST result • T.SPOT®-TB /TST agreement • Development of active TB disease	2 years
Piana et al	III-2	Diagnostic accuracy	Immunosuppressed	T.SPOT®-TB	All patients identified as nosocomial contacts of the	• T.SPOT®-TB assay result	1 year

(2006)[30] Italy	High	Prospective Subject selection method not reported	haematology patients exposed to smear-positive TB		index case.	• TST result • T.SPOT®-TB /TST agreement • Development of active TB disease	
Hill et al (2007)[31] The Gambia	III-2 High	Diagnostic accuracy Prospective Consecutive subject recruitment	Household contacts >15 years of age	ELISPOT	Inclusion/exclusion criteria: none stated.	• T.SPOT®-TB assay result • TST result • Development of secondary TB cases • Test result conversion	18 months
Hill et al (2008)[32] The Gambia	III-2 High	Diagnostic accuracy Prospective Maximum 12 contacts had an ELISPOT per day, the rest randomly excluded	Household contacts	ELISPOT	Household contacts at least 6 months of age living the majority of the time on the same compound of a sputum smear positive pulmonary TB case	• ELISPOT assay result • TST result • ELISPOT/TST agreement • Development of active TB disease	2 years
Wu et al (2009)[33] China	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Army recruits	ELISPOT	Inclusion criteria: new recruits. Exclusion criteria: none stated.	• ELISPOT assay result • TST result • ELISPOT/TST agreement • Development of active TB disease	2 years
Lee et al (2009)[34] Taiwan	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	ESRD patients on hemodialysis	QTF-G and T.SPOT®TB	Inclusion/exclusion criteria: none stated.	• IGRA assay result • TST result • IGRA/TST agreement • Development of active TB disease	2 years
Kik et al (2010)[35] The Netherlands	III-2 High	Diagnostic accuracy Prospective Subject selection method not reported	Immigrant close contacts	QTF-GIT and T.SPOT®-TB	Inclusion criteria: close contacts of sputum smear-positive pulmonary TB aged ≥16 years and born in a TB endemic country. Dutch-born individuals when at least one of their parents were born in a TB endemic country and were BCG vaccinated. 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 therapy.	• IGRA assay result • TST result • IGRA/TST agreement • Development of active TB disease	2 years

TST = tuberculin skin test; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; ELISPOT = enzyme-linked immunosorbent assay; IGRA = interferon gamma release assay; TB = tuberculosis; AFB = acid-fast bacilli; BCG = bacillus Calmette-Guérin; HCWs = healthcare workers; HIV = human immunodeficiency virus ; AIDS = acquired immune deficiency syndrome; MTB = Mycobacterial tuberculosis.

Appendix E Studies included in the assessment of diagnostic accuracy

Table 28: Study profiles of included studies on diagnostic accuracy of QTF-GIT

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Aichelburg et al (2009)[18] Austria	Diagnostic accuracy Prospective Longitudinal cohort study Subject selection method not reported	HIV infected patients	830	NR	IFN-γ ≥0.35 IU/mL above negative control and ≥25% of nil value.	2 TU of PPD RT23	≥5 mm
Alvarez-Leon et al (2009)[36] Spain	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers	134 (123)	37/134 (35.1)	IFN-γ ≥ 0.35 IU/ml.	2 TU of PPD Evans 2 TU	Non-BCG vaccinated ≥5 mm BCG vaccinated ≥15 mm
Baker et al (2009)[37] USA	Diagnostic accuracy Prospective Subject selection method not reported	High risk refugee/immigrants (adult and children) < 6 months since immigration	198 (195)	NR	≥ 0.35 IU/mL IFN-γ.	5 TU of PPD-S	≥10 mm
Balcells et al (2008)[38] Chile	Diagnostic accuracy Prospective Subject selection method not reported	HIV-positive individuals from a low TB prevalence country	116 (109)	96/109 (88.1)	Manufacturer's instructions.	2 TU of PPD RT23	≥5 mm
Bartalesi et al (2009)[39] Italy	Diagnostic accuracy Prospective Consecutive subject selection Blinded readings	Immunocompromised (rheumatic diseases or other immunomediated chronic diseases)	398 (393)	16/393 (4.1)	Manufacturer's instructions.	5 TU of PPD	Interpreted relative to risk in accordance with publish guidelines
Bianchi et al (2009)[40] Italy	Diagnostic accuracy Prospective Consecutive subject selection	Children (<16 years) at risk for TB[b]	336 (320)	172/320 (53.7)	IFN-γ ≥0.35 IU/mL above negative control.	5 TU of PPD	Close contact or suspected TB ≥5 mm Country of birth high prevalence of TB or recently immigrated ≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Chun et al (2008)[41] South Korea	Diagnostic accuracy Prospective Subject selection method not reported	Children (<15 years) Close contacts Casual contacts Controls	227 (136) (91 clinically ill with symptoms related to Tb not reported)	136/136 (100)	Manufacturer's instructions	2 TU of PPD RT23	≥5 mm (≥10 mm also reported)
Cobanoglu et al (2007)[42] Turkey	Diagnostic accuracy Prospective Subject selection method not reported	Immunosupressed (patients receiving TNF-α blockers)	106 (97) (38 healthy individuals)	106/106 (100)	IFN-γ ≥0.35 IU/mL above negative control.	5 TU of PPD	Immunosuppressed ≥10 mm Healthy individuals ≥15 mm
Cummings et al (2009)[43] USA	Diagnostic accuracy Prospective Subject selection method not reported	Low risk healthcare workers	182 (182)	NR	Manufacturer's instructions.	Two step Tubersol or Aplisol	Based on current recommendations
Diel et al (2006)[44] Germany	Diagnostic accuracy Prospective Subject selection method not reported	Close contact cases[c]	309 (309)	157/309 (50.8)	≥ 0.35 IU/mL IFN-γ.	5 TU of PPD-S	>5 mm
Diel et al (2008)[19] Germany	Diagnostic accuracy Prospective Subject selection reported as "all contacts"	Close contacts of active TB	601	278/601 (46.3)	Manufacturer's instructions.	0.1 mL of Tuberculin-10-GT 0.1 PPD-RT-23	>5 mm
Dogra et al (2006)[45] India	Diagnostic accuracy Prospective Cross-sectional study Consecutive subject selection	Children (aged 1-12 years admitted to paediatric ward) with clinical suspicion of TB or history of contact with an adult with active TB	105 (30% with symptoms suggestive of TB)	86/105 (82.0)	IFN-γ ≥0.35 IU/mL above negative control.	1 TU PPD RT23 (standard dosage in India)	≥10 mm
Fox et al (2009)[46] Israel	Diagnostic accuracy Prospective Consecutive subject selection	Healthcare workers	100 (100)	37/100 (37.0)	IFN-γ ≥0.35 IU/mL above negative control.	5 TU of PPD Two-stage TST performed in 72	≥10 mm
Franken et al (2007)[47] Holland	Diagnostic accuracy Prospective Cross-sectional observational study Subject selection method not reported	Military personnel	909 (746) Includes 9 with reported past treatment for LTBI 1-14 years previously	108/909 (11.9)	Manufacturer's instructions. No positive control tube was available.	2 TU PPD RT23	Not explicit, both ≥15 mm and ≥10 mm reported

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Grare et al (2010)[48] France	Diagnostic accuracy Prospective Consecutive subject selection Clinicians blind to QTF-GIT results	Children (<18 years) at risk for TB[d]; Healthy contacts	13 (13) 31 (23)	12/31 (39) 8/13 (62)	IFN-γ ≥0.35 IU/mL above negative control.	5-IU tuberculin, 0.1 mL	≥15 mm ≥10 mm (for suspicion of TB) ≥5 mm (unspecific reaction due to BCG vaccine)
Harstad et al (2010)[20] Norway	Diagnostic accuracy Prospective Subject selection method not reported	Asylum seekers aged ≥18 years	823	NR	IFN-γ ≥0.35 IU/mL above negative control.	2 TU PPD RT23	≥6 mm
Hoffmann et al (2010)[49] Switzerland	Diagnostic accuracy Prospective Subject selection method not reported	HD patients (adults)	39 (32)	18/39 (46.1)	≥ 0.35 IU/ml IFN-γ above negative control.	2 units PPD-23 SSI	≥10 mm
Kariminia et al (2009) Iran[50]	Diagnostic accuracy Prospective Subject selection method not reported	TB screening for employment grouped into low or high risk groups	186 (176)	186/186 (100)	IFN-γ ≥0.35 IU/mL above negative control.	5 TU of PPD	≥10 mm
Katsenos et al (2010)[51] Greece	Diagnostic accuracy Prospective Subject selection method not reported	Army recruits	1750 (129)	1750/1750 (100)	IFN-γ in negative control <8.0 IU/ml and the value of the TB antigen minus negative control was ≥0.35 IU/ml and ≥25% of the negative control IFN-γ value	2 TU of PPD RT23	≥10 mm
Lee et al (2010)[52] South Korea	Diagnostic accuracy Prospective Subject selection reported as "all"	Contact cases	214 (185)	135/201 (67.2)	≥0.35 UI/ml above and ≥25% of nil control.	2 TU PPD-RT23	≥10 mm
Lee et al (2010b)[53] Taiwan	Diagnostic accuracy Prospective Cross-sectional Subject selection method not reported	Dialysis patients[e]	93	57/93 (64.8)	≥0.35 UI/ml above background level and at least 25% of background in the absence of high background level (≤8.0 IU/ml).	Two step 2 TU PPD RT-23 SI	≥10 mm
Lien et al (2009)[54] Japan	Diagnostic accuracy Prospective Subject selection method not reported "cross-sectional"	Healthcare workers (TB and non-TB hospital)	300 (255)	97/255 (38.0)	IFN-γ ≥0.35 IU/mL above negative control.	5 TU of PPD Two-step TST performed in 112	≥10 mm (≥15 mm also analysed)
Lighter et al (2009)[55] USA	Diagnostic accuracy Prospective Subject selection method not reported	Children attending well-child clinic, pediatric chest clinic or pediatric in patient ward	207	74/207 (36)	IFN-γ ≥0.35 IU/mL above negative control and ≥25% of nil value.	Not reported	≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Luetkemeyer et al (2007)[56] USA	Diagnostic accuracy Prospective Subject selection method not reported	HIV infected individuals (aged >18 years)	294	18/294 (6.0)	IFN-γ ≥0.35 IU/mL above negative control and ≥25% of nil value. Positive if one or both of the replicate tests are positive.	5 TU of PPD	≥5 mm
Mahomed et al (2011)[21] South Africa	Diagnostic accuracy Prospective Subject selection method not reported	Adolescents aged 12 to 18 years.	5244	4917/5244 (93.8)	Manufacturer's recommendations.	2 TU of RT23	≥10 mm
Mirtskhulava et al (2008)[57] Georgia	Diagnostic accuracy Prospective Cross-sectional study Subject selection reported as "all"	Healthcare workers	270 (265)	206/265 (77.7)	IFN-γ ≥0.35 IU/mL above negative control and ≥25% of nil value.	5 TU of PPD	≥10 mm
Nakaoka et al (2006)[58] Nigeria	Diagnostic accuracy Prospective Subject selection method not reported	Children in contact with an adult with active TB	207 children (78 high risk;129 low risk)	187/207 (90)	IFN-γ ≥0.35 IU/mL above negative control.	10 U of PPD	≥10 mm
Nienhaus et al (2008a)[59] Germany	Diagnostic accuracy Prospective Subject selection method not reported TST and IGRA results blinded	Healthcare workers	261 (261)	98/261 (37.5)	IFN-γ ≥0.35 IU/mL above negative control.	2 TU of PPD RT23	≥5 mm
Nienhaus et al (2008b)[60] Germany	Diagnostic accuracy Prospective Subject selection method not reported	Combined study population of general population in contact tracing (n=601) and healthcare workers (n=432)	1040 (1033)	448/1033 (43.4)	≥ 0.35 IU/ml IFN-γ above negative control.	2 TU PPD-RT23	≥10 mm[j]
Orlando et al (2010)[61] Italy	Diagnostic accuracy Prospective Consecutive subject selection	High risk immigrants	1130 (887)	56/887 (6.31) Unknown in 42/887 [4.7])	≥0.35 UI/ml[§] and ≥25% of nil control.	5 TU of PPD	≥10 mm (arrived ≤5 years) ≥15 mm (arrived for >5 years)
Pai et al (2005)[62] India	Diagnostic accuracy Prospective Cross-sectional Subject selection method not reported	Healthcare workers	726 (720)	514/726 (71)	≥0.35 IU/ml after subtracting the value of the negative control.	1 TU PPD RT23	≥10 mm (≥5 and ≥15 mm also evaluated)
Petrucci et al (2008)[63] Brazil and Nepal	Diagnostic accuracy Prospective Cross-sectional Subject selection method not reported	Children (aged 0-15 years) in contact with adults with active TB	259 (146 in Nepal and 113 in Brazil)	137/146 (94) 113/113 (100)	According to manufacturer's software.	2 TU PPD RT23	≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Ponce de Leon et al (2008)[64] Perú	Diagnostic accuracy Prospective Consecutive subject selection Cross-sectional design	Rheumatoid arthritis (RA) patients and healthy controls	106 RA patients (101) 97 controls(93)	81/101 (80.2) RA patients 75/93 (80.6) controls	≥ 0.35 IU/ml IFN-γ above negative control.	2 TU PPD-RT23	≥ 5 mm for RA patients ≥ 10 mm for controls
Ringshausen et al (2009)[22] Germany	Diagnostic accuracy Prospective Subject selection method not reported	In-hospital contact investigation	144	73/143 (51.0)	IFN-γ ≥0.35 IU/mL above negative control.	2 TU PPD-RT23	>5 mm
Ruhwald et al (2008)[65] Nigeria	Diagnostic accuracy Prospective Consecutive subject selection	Children living in households with adults diagnosed with culture positive TB and community controls	128 (120)	'BCG routinely given at birth'	IFN-γ ≥0.35 IU/mL above negative control.	10 units PPD	>10 mm
Santin et al (2011)[23] Spain	Diagnostic accuracy Prospective Longitudinal Subject selection method not reported	HIV positive patients ≥18 years old	135 HIV-seropositive 135 controls	46/135 (34.1) 57/135 (42.2)	≥0.35 UI/ml§ and ≥25% of nil control.	2 U PPD RT23	≥5 mm
Saracino et al (2009)[66] Italy	Diagnostic accuracy Prospective Subject selection method not reported	Recent immigrants (<2 months) from high-incidence countries	452 (279)	NR	IFN-γ ≥0.35 IU/mL above negative control.	5 TU PPD	≥10 mm
Schoepher et al (2008)[67] Switzerland	Diagnostic accuracy Prospective Consecutive subject selection	Patients with inflammatory bowel disease treated with anti-TNF-α medication and controls.	168 IBD 44 controls	118/168 (70.2) 33/44 (75.0)	Manufacturer's instructions.	2 TU PPD RT 23 SSI	≥5 mm Controls ≥10 mm and ≥15 mm (dependent on risk factors)
Seyhan et al (2010)[68] Turkey	Diagnostic accuracy Prospective Subject selection method not reported	Immunocompromised (hemodialysis patients)	100 (100)	72/100 (72)	≥ 0.35 IU/mL of IFN- γ above negative control.	5 TU of PPD	≥10 mm Two step performed 1 week later if initial test negative
Tsiouris et al (2006)[69] South Africa	Diagnostic accuracy Prospective Subject selection method not reported	Children (aged 5-15 years)	221 (184)	115/184 (72.3)	≥ 0.35 IU/ml IFN-γ above negative control.	2 TU PPD-RT23	≥10 mm
Vinton et al (2009)[70] Australia	Diagnostic accuracy Prospective "all hospital staff were invited to participate"	HCWs	481	375/481 (78.0)	Manufacturers guidelines.	10 IU PPD	≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-GIT	TST	Cut-off for positive TST
Winje et al (2008a)[71] Norway	Diagnostic accuracy Prospective Consecutive patient selection	Recent immigrants	999 (912)	658/912 (72)	IFN-γ ≥0.35 IU/mL	2 TU of PPD RT23	≥6 mm
Winje et al (2008b)[72] Norway	Diagnostic accuracy Prospective Consecutive patient selection	Screened TST positive schoolchildren (9th grade)[f]	519 (511)[g]	236/511 (46.2)	IFN-γ ≥0.35 IU/mL	2 TU of PPD RT23	≥6 mm
Zhao et al (2009)[73] USA	Diagnostic accuracy Retrospective (TST only) Subjects chosen according to previous TST result (note: pilot study)	Healthcare workers	40 (40)	NR	IFN-γ ≥0.35 IU/mL above negative control and ≥25% of nil value.	Historically performed TST	NR

BCG = Bacillus Calmette-Guėrin; HCWs = healthcare workers; HD = Haemodialysis; HIV = human immunodeficiency virus; IFN-γ = interferon gamma; IGRA = interferon gamma release assay; IU = international units; n = number; NR = not reported; PPD = purified protein derivative; QTF-GIT = QuantiFERON®-TB Gold In-Tube; TB = tuberculosis; TNF-α = tumour necrosis factor-alpha; TST = tuberculin skin test; TU = tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Children with clinical suspicion of TB disease, in close contact with recently diagnosed cases of contagious TB disease, internationally adopted or recently immigrated (within the last 2 years) from countries with a high prevalence of TB.

c Household and intimate contacts, employees with continuous exposure to contact case, and pupils sharing the same classroom.

d Children with recent TB contact and/or recent immigration from a country with high incidence of TB.

e Includes 9 people with history of TB disease.

f 531 were TST positive and referred for QTF-GIT testing. 519 consented to participate in the study.

Table 29: Study profiles of included studies on diagnostic accuracy of QTF-G

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-G	TST	Cut-off for positive TST
Brock (2004)[74] Denmark	Diagnostic accuracy Prospective All nearest contacts of the index case were asked to participate	Contacts of a sputum and culture positive TB student in a high school	125 (85)	40/125 (32.0)	≥0.35 IU/ml of IFN-γ	2 TU PPD RT23 (BCG unvaccinated individuals only)	>10 mm
Carvalho et al (2007)[75] North Italy	Diagnostic accuracy Prospective Subject selection method not reported	Immigrants from countries of high TB incidence (>50/100,000)	127 (100)	83/130[b] (64)	IFN-γ ≥ 0.35 IU/ml	5 IU of PPD-S	≥10 mm
Choi et al (2008)[76] South Korea	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers	82 (80)	84/84 (100)	IFN-γ ≥ 0.35 IU/ml	2 TU of PPD RT23	≥10 mm
Connell (2006)[77] Australia	Diagnostic accuracy Prospective Subject selection method not reported	Children referred for evaluation (high risk) of LTBI and TB disease	106	50/92 (54.3)	≥0.35 IU/ml of IFN-γ	10 IU tuberculin	>10 mm Prior BCG vaccination >15 mm TB contacts >5 mm
Ferrara et al (2005)[78] Italy	Diagnostic accuracy Prospective Consecutive patient selection TST results collected from clinical record	Hospital patients (inpatients and outpatients of any ward)	255 (205)	53/205 (25.8)	IFN-γ ≥ 0.35 IU/ml above the nil well	5 TU of PPD	Interpreted according to level of risk as reported in guidelines
Higuchi et al (2007)[24] Japan	Diagnostic accuracy Prospective Subject selection method not reported	Contact cases	339 (88)	339/339 (100)	IFN-γ ≥ 0.35 IU/ml above the nil well	0.1mL 0.05μg PPD	≥30 mm
Hotta et al (2007)[79] Japan	Diagnostic accuracy Prospective Subject selection method not reported	Health care students	371 (207)	190/207 (92)	IFN-γ ≥ 0.35 IU/ml[b]	3 TU of PPD-S	≥15 mm (also report ≥5 and ≥10 mm)
Inanc et al (2009)[80] Japan	Diagnostic accuracy Prospective Consecutive patient selection	Patients with inflammatory diseases (RA and AS patients)	140 (132)	118/140 (84.3)	Manufacturer's recommendations	0.1ml of PPD	≥5 mm (RA/AS patients) Cut-off for controls not reported

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-G	TST	Cut-off for positive TST
Kang et al (2005)[81] Republic of Korea	Diagnostic accuracy Prospective Subject selection method not reported Investigator blinded to patient history	Medical students (low risk) Healthcare workers (casual contacts) Contact cases (close contacts)	99 72 48	93/99 (94) 65/72 (90) 32/48 (67)	IFN-γ ≥ 0.35 IU/ml	2 TU of PPD RT23	≥10 mm
Kobashi et al (2007)[82] Japan	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers with recent contact of smear and culture positive TB	190	148/190 (78)	IFN-γ ≥ 0.35 IU/ml[b]	3 TU of PPD-S	≥30 mm
Lee et al (2008)[83] Taiwan	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers (contact investigation)	39	39/39 (100)	IFN-γ ≥ 0.35 IU/ml. A second test was performed at ≥8 weeks after exposure ended in those that were initially negative	Two-step TST 2 TU of PPD RT23	≥10 mm
Lee et al (2009)[25] South Korea	Diagnostic accuracy Prospective Subject selection method not reported	Newly employed nurses (HCWs)	196	182/196 (92.9)	Manufacturer's instructions	Two-step TST 2 TU of PPD RT23	≥10 mm
Manuel et al (2007)[84] Canada	Diagnostic accuracy Prospective Subject selection method not reported TST collected from medical record if performed in the previous month	Patients with chronic liver disease awaiting transplantation	163 (153)	116/142 (82)	0.35 IU/ml above the nil well	5 IU of PPD RT23	≥5 mm
Mazurek et al (2007)[85] United States	Diagnostic accuracy Prospective Subject selection method not reported ("all recruits")	Navy recruits	856 (828)	19/856 (2.2)	IFN-γ ≥ 0.35 IU6/mL and ≥50% of nil	5 TU Tubersol	≥10 mm
Noorbakhsh et al (2011)[26] Iran	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts <20 years old	59	NR	Kit instructions	5 TU PPD	≥10 mm
Okada et al (2007)[86] Cambodia	Diagnostic accuracy Prospective Consecutive	Children aged ≤5 years (household contacts)	217	191/217 (88.0)	IFN-γ ≥ 0.35 IU/ml	2.5TU of PPD-S	≥10 mm
O'Neal et al (2009)[87] Canada	Diagnostic accuracy Prospective Subject selection method not reported	Contact investigation	61	14/61 (22.9)	IFN-γ ≥ 0.35 IU/ml above control	Details not reported	≥5 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive QTF-G	TST	Cut-off for positive TST
Porsa et al (2006)[88] United States	Diagnostic accuracy Prospective Subject selection method not reported	Jail inmates	471 (409)	NR	Manufacturer's recommendations	5 TU of Tubersol	≥10 mm
Shovman et al (2009)[89] Israel	Diagnostic accuracy Prospective Consecutive patient selection	Patients with rheumatoid arthritis Healthy controls	35 15	9/26 (35%)	IFN-γ ≥ 0.35 IU/ml above control	2 TU of PPD	≥5 mm
Soborg et al (2007)[27] Denmark	Diagnostic accuracy Prospective All permanent HCWs invited to participate	Healthcare workers	139	106/139 (76.0)	IFN-γ ≥ 0.35 IU/ml above control	0.1 mL tuberculin PPD RT23	≥12 mm
Soborg et al (2009)[90] Denmark	Diagnostic accuracy Prospective Subject selection method not reported	Patients with inflammatory diseases (RA, AS PA and Sarcoidosis)	302 (241)	152/200 (76)	IFN-γ ≥ 0.35 IU/ml above control	2 TU of PPD RT23	Danish guidelines > 12 mm (BCG vaccinated) > 6 mm (unvaccinated) US guidelines > 5, > 10, or > 15 mm depending on risk factors
Taggart et al (2006)[91]	Diagnostic accuracy Prospective Subject selection method not reported	Laboratory employees with - No risk factors and no BCG - Possible risk factors for exposure and BCG - No risk factors with previous positive TST	81 30 26	0/81 (0.0) 30/30 (100) 0/26 (0.0)	IFN-γ ≥ 0.35 IU/ml above control	5 TU of PPD	Increased risk factors ≥10 mm No known risk factors ≥15 mm
Taylor et al (2007)[92] United Kingdom	Diagnostic accuracy Retrospective audit of health records	Children who had QFT-G testing performed between March 2004 and November 2005	120 (108)	56/120 (47)	Manufacturer's instructions	Details not reported	NR

BCG = Bacillus Calmette-Guérin; HCWs = healthcare workers; IFN-γ = interferon gamma; IU = international units; n = number; NR = not reported; PPD = purified protein derivative; QTF-G = QuantiFERON®-TB Gold; TB = tuberculosis; TST = tuberculin skin test; TU = tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Three additional subjects excluded due to suggestive diagnosis of active TB (n=2) and HIV-seropositive (n=1).

Table 30: Study profiles of included studies on diagnostic accuracy of T.SPOT®-TB

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive T.SPOT®-TB	TST	Cut-off for positive TST
Barsegian et al (2008)[93] Germany	Diagnostic accuracy Prospective All employees	Healthcare workers	95 (95)	34/95 (35.8)	≥6 spots increment	PPD RT 23 (units not reported)	>5 mm
Bienek et al (2009)[94] USA	Diagnostic accuracy Prospective Subject selection method not reported	Low prevalence	414 (354 low risk; 60 intermediate risk)	14/414 (3.3)	Manufacturer's instructions	5 TU PPD diluted (Aplisol®)	≥10 mm
Brodie et al (2008)[95] USA	Diagnostic accuracy Prospective Subject selection method not reported	High risk individuals (i.e., close contacts, recent immigrants) in a public health screening clinic (≥5 years old)	96	66/96 (68.0)	Manufacturer's instructions	5 TU PPD	As per CDC guidelines
Chee et al (2009)[96] Singapore	Diagnostic accuracy Prospective Consecutive cohorts	Final year medical students	207	207/207 (100)	Either or both antigen panel ≥6 spots above the negative control	2 TU RT23 PPD	≥10 mm Two step TST performed if first result <10 mm
Hansted et al (2009)[97] Lithuania	Diagnostic accuracy Prospective Subject selection method not reported	Children ("high risk" and "low risk" for TB)[b]	45 (45) high risk 52 (52) low risk	45/45 (100) 52/52 (100)	≥6 spots in test wells	2 U PPD	≥10 mm
Janssens et al (2008)[98] Switzerland	Diagnostic accuracy Prospective Subject selection reported as "all subjects"	Contact tracing	295 (295)	238/295 (80.6)	≥6 SFC more than the negative control	2 U PPD RT 23	ATS/CDC guidelines: >5 mm Swiss national guidelines >10 mm NICE guidelines >5 mm (BCG unvaccinated) >15 mm (BCG unvaccinated)
Jiang et al (2009)[99] China	Diagnostic accuracy Prospective Subject selection method not reported	HIV-infected individuals	68	68/68 (100)	Either or both antigen panel ≥6 spots above the negative control and at least 2x greater than the number of spots in the negative control	5 TU RT23 PPD	NR
Kim et al (2011)[28] South Korea	Diagnostic accuracy Prospective Subject selection reported as 'all"	Patients admitted for kidney transplantation	312 (296)	256/312 (82.0)	Manufacturer's recommendations	2 TU PPD RT23	≥10 mm
Leung et al (2008)[100] China	Diagnostic accuracy Prospective Subject selection reported as 'all"	Silicotic patients	134	2/134 (1.5)	Manufacturer's instructions	2 TU RT23 PPD	≥5, 10 and 15 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated, n/N (%)	Cut-off for positive T.SPOT®-TB	TST	Cut-off for positive TST
Leung et al (2011)[29] China	Diagnostic accuracy Prospective Subject selection method not reported	Silicotic patients	331	NR	Manufacturer's instructions	2 TU RT23 PPD	≥10 mm
Ozekinci et al (2007)[101] Turkey	Diagnostic accuracy Prospective Subject selection method not reported	Mixed population - House hold contacts - Healthcare workers - Healthy individuals	150 - 56 - 66 - 28	92/122 (75.4)	Manufacturer's recommendations	5 TU PPD RT23	BCG unvaccinated ≥15 mm BCG vaccinated ≥10 mm
Passalent et al (2007)[102] Canada	Diagnostic accuracy Prospective Subject selection reported as 'all" Lab technician blinded to test results	Haemodialysis patients	203[d]	NR	Manufacturer's instructions	5 IU PPD-S (Tubersol)	As per national guidelines Two step performed in patents <10 mm
Piana et al (2006)[30] Italy	Diagnostic accuracy Prospective Subject selection method not reported	Immunosuppressed haematology patients exposed to smear-positive TB	138 (122)[c]	2/84 (2.4)	≥6 SFC more than the negative control	5 TU BiocineTest-PPD	≥10 mm
Porsa et al (2007)[103] USA	Diagnostic accuracy Prospective Subject selection method not reported	Jail inmates	447	22/447 (4.9)	A well containing ≥6 spots above the negative control	0.1 ml 5TU Tubersol	≥10 mm HIV-positive ≥5 mm
Soysal et al (2008)[104] Turkey	Diagnostic accuracy Prospective Subject selection method not reported	Children (aged 6-10)	1,331 (209)	188/209 (90.0)	If negative control well had 0-5 SFUs, ≥ 6 SFUs in either or both antigen wells. If negative control well ≥6 SFUs, ≥ 2x SFUs in antigen wells.	5TU PPD Tween-80	≥15 mm
Storla et al (2009)[105] Norway	Diagnostic accuracy Prospective Subject selection method not reported	HCWs exposed to TB	203 (155 HCWs; 48 healthy controls)	NR	Manufacturer's instructions	2 TU RT23 PPD	As per national guidelines
Vassilopolos et al (2008)[106]	Diagnostic accuracy Prospective Consecutive patient selection	Rheumatic disease patients	70	28/70 (40)	≥6 SFUs in either or both antigen wells (if negative control ≤5 SFUs) ≥2 x SFUs in antigen well (If negative control well ≥6 SFUs)	2 TU RT23 PPD	≥5 mm

BCG = Bacillus Calmette-Guérin; HCWs = healthcare workers; HIV = human immunodeficiency virus; IU = international units; n = number; NR = not reported; PPD = purified protein derivative; SFC = spot-forming cells; SFUs = spot-forming units; TB = tuberculosis; TST = tuberculin skin test; TU = tuberculin units; U = units.

a Number of participants in which index and reference standard results were available for analysis and reported.

b "High risk" subjects are those living with a family member with TB or having contact with such a person in their school class. "Low risk" are subjects with no identifiable risk for TB.

Table 31: Study profiles of included studies on diagnostic accuracy of QTF-GIT and QTF-G

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
Mahomed et al (2006)[107] South Africa	Diagnostic accuracy Prospective Cross-sectional Subject selection method not reported	Healthy individuals	(367) 358	289/358 (80.7)	QTF-GIT	Manufacturer's instructions	0.1 mL of PPD RT23	≥15 mm
					QTF-G	Manufacturer's instructions		

BCG = bacillus Calmette-Guérin; n = number; PPD = Purified protein derivative; QTF-G = QuantiFERON®-TB Gold; QTF-GIT = QuantiFERON®-TB Gold In-Tube; TST = tuberculin skin test.

a Number of participants in which intervention and reference test results were available for analysis and reported.

Table 32: Study profiles of included studies on safety and effectiveness of QTF-GIT and T.SPOT®-TB

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
Adetifa et al (2010)[108] The Gambia	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts (aged 6 months to 14 years)	285	173/285 (60.7)	QTF-GIT	IFN-γ ≥0.35 IU/ml above negative control	2 TU of PPD RT23	≥10 mm
					T.SPOT®-TB	Where negative control 0-5 spots, ≥6 spots above the negative control in either panel. Where negative control >6 spots, at least twice the number of spots in the negative control		
Arend et al (2006)[109] The Netherlands	Diagnostic accuracy Prospective Random subject selection for pre TST reading recruitment only	Contact investigation (BCG unvaccinated adults)	785	0/785 (0.0)	QTF-GIT	Manufacturer's instructions	2 TU of PPD RT23	≥15 mm
			782	0/782 (0.0)	T.SPOT®-TB	Manufacturer's instructions		
Bocchino et al (2008)[110] Italy	Diagnostic accuracy Prospective Consecutive subject selection	Patients undergoing screening before anti-TNF therapy	69	2 /69 (2.8)	QTF-GIT	Manufacturer's recommendations	5 IU of PPD	≥5 mm
					T.SPOT®-TB	Manufacturer's recommendations		
Bruzzese et al (2009)[111] Italy	Diagnostic accuracy Prospective Consecutive subject selection	HIV negative immune-compromised children	80	0/80 (0.0)	QTF-GIT	Manufacturer's instructions	Details not reported	>5 mm
					T.SPOT®-TB	Manufacturer's instructions		
Casas et al (2009)[112]	Diagnostic accuracy Prospective Subject selection not consecutive	HCWs undergoing routine examination	147	23/147 (15.6)	QTF-GIT	IFN-γ ≥0.35 IU/ml regardless of the result of the mitogen control	2 TU of PPD RT23	<u>BCG unvaccinated</u> ≥5 mm <u>BCG vaccinated</u> ≥15 mm
					T.SPOT®-TB	≥6 SFCs more than the nil control well and at least twice the number of the nil control well		
Connell et al	Diagnostic accuracy	Children at high risk of	101 (87)	48/87 (55)	QTF-GIT	Manufacturer's recommendations	10 IU of	<u>Moderate risk factors</u>

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
(2008)[113] Australia	Prospective Subject selection method not reported	latent TB			T.SPOT®-TB	Manufacturer's recommendations	PPD	≥10 mm ≥15 mm (BCG within five years) High risk factors[b] ≥5 mm ≥10 mm (BCG within five years)
Dominguez et al (2008)[114] Spain	Diagnostic accuracy Prospective Subject selection method not reported	Patients attending a hospital for contact tracing or screening for LTBI	626 270 (contact tracing) 314 (screening)	128/270 (47.4) 136/314 (43.3)	QTF-GIT T.SPOT®-TB	Manufacturer's instructions Manufacturer's instructions	2 TU of PPD RT23	≥5 mm
Lucas et al (2010)[115] Australia	Diagnostic accuracy Prospective Consecutive enrolment	African and ethnic Burmese children (from refugee families)	523 (239)	361/523 (69) African: 275/411 (67) Burmese: 86/112 (77)	QTF-GIT T.SPOT®-TB	Manufacturers' protocol Manufacturers' instructions	5 TU PPD	≥10 mm ≥15 mm (<5 years old and BCG vaccinated) Household contacts >1year of age ≥5 mm ≥10 mm (<5 years old and BCG vaccinated)
Kik et al (2010)[35] The Netherlands	Diagnostic accuracy Prospective Subject selection method not reported	Immigrant close contacts	812 (339)	274/339 (80.8)	QTF-GIT T.SPOT®-TB	Manufacturer's instructions Manufacturer's instructions	2 TU of PPD RT23	≥5 mm
Richeldi et al (2009)[116] Italy	Diagnostic accuracy Prospective Consecutive subject selection	Immunocompromised patients (LTCs, patients with HIV infection, or HMs)	369 (331)	12/331 (3.6)	QTF-GIT T.SPOT®-TB	Manufacturer's instructions Manufacturer's instructions	5 IU PPD	HIV infection ≥5 mm LTC and HM patients ≥10 mm
Rivas et al (2009)[117] Spain	Diagnostic accuracy Prospective Subject selection reported as "patients admitted between February 2006 and May 2007were included"	Patients undergoing drug and alcohol detoxification (high risk)	135 (100)	NR	QTF-GIT T.SPOT®-TB	IFN-γ ≥0.35 IU/ml above negative control ≥6 spots above the negative control in any well	2 TU of PPD RT23	HIV positive ≥5 mm HIV negative ≥10 mm
Stefan et al	Diagnostic accuracy	Paediatric oncology	34	99% (estimated	QTF-GIT	Manufacturers' instructions	2 TU PPD	≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
(2010)[118] South Africa	Prospective Subject selection: "all children"	patients[b]	(29 QTF-GIT; 23 T.SPOT®-TB)	from neonatal vaccination coverage)	T.SPOT®-TB	Manufacturers' instructions	RT23	
Talati et al (2009)[119] USA	Diagnostic accuracy Prospective Cross sectional Subject selection method not reported Technicians blinded to TST and IGRA results	HIV-infected	336 (278)	25/336 (7.4)	QTF-GIT T.SPOT®-TB	IFN-γ minus the negative control ≥ 0.35 IU/ml and > 25% of the negative control response to either the ESAT 6 or CFP10 minus the negative control ≥ 6 spot forming cells, or > 2 x the negative control	5 TU PPD	≥5 mm
Triverio et al (2009)[120] Switzerland	Diagnostic accuracy Prospective Subject selection method not reported	Patients undergoing haemodialysis for end-stage renal disease for at least 3 months	62[c]	14/62 (23)	QTF-GIT T.SPOT®-TB	IFN-γ ≥0.35 IU/ml above the negative control tube SFU in either antigen well >6 spots above negative control	2 TU of PPD RT23	>5 mm

BCG = Bacillus Calmette-Guérin; HCWs = healthcare workers; HIV = human immunodeficiency virus; HMs = hematologic malignancies; IFN-γ = interferon gamma; IGRA = interferon gamma release assay; IU = international units; LTC = liver transplantation candidates; n = number; NR = not reported; PPD = Purified protein derivative; QTF-GIT = QuantiFERON®-TB Gold In-Tube; SFC = spot-forming cells; SFUs = spot-forming units; TB = tuberculosis; TNF-α = tumour necrosis factor-alpha; TST = tuberculin skin test; TU = tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Includes 4 children who had previously been treated for TB.

c Includes 8 patients with chest x-rays suggestive of TB and 13 defined as LTBI [chest X-ray suggestive of prior TB and/or prior 'at risk' contact].

Table 33: Study profiles of included studies on diagnostic accuracy of QTF-GIT and ELISPOT

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Peptides	Cut-off for positive index test	TST	Cut-off for positive TST
Adetifa et al (2007)[121] The Gambia	Diagnostic accuracy Prospective Household contacts were selected using an "even consecutive balanced sampling frame"	Household contacts ≥15 years of age	194 (175)	92/194 (47.4)	QTF-GIT	NA	IFN-γ ≥0.35 IU/ml above negative control. There was no positive control tube.	2 TU of PPD RT23	≥10 mm
					ELISPOT	ESAT-6 CFP-10	≥8 SFUs/well/2 x 105 PBMCs more than negative control well.		
Leyten et al (2007)[122] The Netherlands	Diagnostic accuracy Prospective Subject selection method not reported	Individuals with documented TST conversion during contact investigations or screening and controls	40[b]	16/40 (40.0)	QTF-GIT	ESAT-6 CFP-10 TB7.7	IFN-γ ≥ 0.35 IU/ml	2 TU of PPD RT23	≥10 mm
					ELISPOT	ESAT-6 CFP-10 TB7.7	≥5 SFCs per well (negative wells subtracted) and at least twice the background value		

BCG = Bacillus Calmette-Guèrin; CFP-10 = culture filtrate antigen-10; ELISPOT = enzyme-linked immunosorbent assay; ESAT-6 = early secretory antigenic target-6; IFN-γ = Interferon gamma; IGRA = interferon gamma release assay; IU = International units; n = number; NA = not applicable; NR = Not reported; PBMCs = peripheral blood mononuclear cells; PPD = Purified protein derivative; QTF-GIT = QuantiFERON®-TB Gold In-Tube; SFC = spot-forming cells; SFU = spot-forming units; TST = tuberculin skin test.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Includes 27 with TST conversion [8 of which had been treated with ING prophylaxis]; 4 with previously treated TB [1.5 to 50 years prior]; and 9 controls.

Table 34: Study profiles of included studies on diagnostic accuracy of QTF-G and T.SPOT®-TB

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
Hesseling et al (2008)[123] South Africa	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts	82 (29 children aged 0-5 years; 53 adults aged ≥15 years)	29/29 children (100) (adults not reported)	QTF-G	Manufacturers' recommendations	2 TU of PPD RT23	≥10 mm
					T.SPOT®-TB	Manufacturers' recommendations		
Lee et al (2006)[124] South Korea	Diagnostic accuracy Prospective Subject selection method not reported	High school students (aged 15-16 years)	131	131/131 (100)	QTF-G	IFN-γ ≥ 0.35 IU/ml above control	2 TU of PPD RT23	≥10 mm
					T.SPOT®-TB	≥5 spots more than negative control		
Lee et al (2009)[34] Taiwan	Diagnostic accuracy Prospective Subject selection method not reported	ESRD patients on hemodialysis	32 ESRD patients 32 control patients	53/64 (82.8) 23/32 (71.9) 28/32 (87.5)	QTF-G	As per manufacturer's instructions	Two step 2TU tuberculin RT-23	ESRD/BCG unvaccinated ≥10 mm BCG vaccinated ≥15 mm
					T.SPOT®.TB	As per manufacturer's instructions		
Mandalakas et al (2008)[125] South Africa	Diagnostic accuracy Prospective Consecutive subject selection	HIV positive adults and children	43 23 children 20 adults	35/43 (81.4) 21/23 (91.3) 14/20 (70.0)	QTF-G	IFN-γ ≥ 0.35 IU/ml above control	2 TU of PPD RT23	≥5 mm
					T.SPOT®-TB	If negative well 0-5 spots, ≥6 spots more than negative control If negative control well had ≥6 spots, ≥2 x negative well		
Pollock et al (2008)[126] USA	Diagnostic accuracy Prospective Subject selection method not reported	Healthcare workers	143 (143) 143 (36)	133/143 (93) 36/36 (100)	QTF-G (TST positive subjects only)	IFN-γ ≥ 0.35 IU/ml above control	5 TU Two-step when indicated	≥10 mm
					T.SPOT®-TB	Manufacturers' recommendations		
Rangaka et al (2006)[127] South Africa	Diagnostic accuracy Prospective Consecutive subject selection	Adults attending voluntary testing and counselling for HIV infection	160 - 74 HIV infected - 86 HIV uninfected	92/150 (61.3) 36/71 (51) 56/79 (71)	QTF-G	Manufacturers' recommendations	2 TU of PPD RT23	≥5 mm, >10mm, and >15 mm analysed.
					T.SPOT®-TB	Manufacturers' recommendations		
Soysal et al (2008b)[128] Turkey	Diagnostic accuracy Prospective Subject selection method not reported	Healthy controls	47 (46)	39/47 (83)	QTF-G	IFN-γ ≥ 0.35 IU/ml above control	5 TU of PPD Tuberculin Tween 80	≥10 mm
					T.SPOT®-TB	If negative well 0-5 spots, ≥6 SFUs more than negative control If negative control well had ≥6 SFUs, ≥2 x negative well		

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
Stephan et al (2008)[129]	Diagnostic accuracy Prospective Subject selection method not reported	HIV positive patients	286 (275) (29 [10.1%] with a history of active TB)	19/286 (6.64)	QTF-G	IFN-γ ≥ 0.35 IU/ml	2 TU of PPD RT23	≥5 mm
					T.SPOT®-TB	≥6 SFU in either of the antigen wells or SFU (antigen well) >2 x SFU (negative well) if the negative control result = 6-9 SFU		

BCG = bacillus Calmette-Guérin; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; IFN-γ = Interferon gamma; IU = International units; n = number; PPD = purified protein derivative; QTF-G = QuantiFERON®-TB Gold; SFUs = spot-forming units; TB = tuberculosis; TST = tuberculin skin test; TU = tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

Table 35: Study profiles of included studies on diagnostic accuracy of QTF-G and ELISPOT.

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Cut-off for positive index test	TST	Cut-off for positive TST
Winthrop et al (2008)[130] USA	Diagnostic accuracy Prospective Subject selection reported as "attempted to enrol all dialysis patients" Lab personnel blinded	Contact tracing of patients with ESRD	100 (94 QTF-G) (97 ELISPOT)	NR	QTF-G	As per manufacturer's instructions. Repeated 16 wks later and reported as positive if either test returned a positive result	5 TU of Tubersol	≥5 mm Repeated 16 wks later if initial TST negative
					ELISPOT	≥10 spots above the control. Repeated 16 wks later and reported as positive if either test returned a positive result		

BCG = bacillus Calmette-Guérin; ELISPOT = enzyme-linked immunosorbent assay; ESRD = end-stage renal disease; n = number; NR = Not reported; QTF-G = QuantiFERON®-TB Gold; TST = tuberculin skin test; TU = Tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported

.

Table 36: Study profiles of included studies on diagnostic accuracy of T.SPOT®.TB and ELISPOT

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Peptides	Cut-off for positive index test	TST	Cut-off for positive TST
Mantegani (2006)[131] Italy	Diagnostic accuracy Prospective Consecutive subject selection	Surveillance program of high risk individuals	86	38/86 (44.2)	T.SPOT®.TB[b]	NA	Manufacturer's recommendation	5 TU of PPD	≥5 mm
					ELISPOT	ESAT-6 CFP-10	>mean number of SFCs than the mean number plus 2 SDs in the negative control and ≥20 SFCs per million PBMCs in the stimulated wells		

BCG = bacillus Calmette-Guérin; ELISPOT = enzyme-linked immunosorbent assay; n = number; NA = not applicable; PPD = purified protein derivative; SDs = standard deviations; SFC = spot-forming cells; TST = tuberculin skin test; TU = tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Results of T.SPOT®.TB compared to TST not reported.

Table 37: Study profiles of included studies on safety and effectiveness of ELISPOT

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Peptides	Cut-off for positive index test	TST	Cut-off for positive TST
Chapman et al (2002)[132] Zambia	Diagnostic accuracy Prospective Subject selection method not reported	Population with a high burden of HIV	75	57/75 (76.0)	ELISPOT	ESAT-6 CFP-10	Individual peptide wells: ≥5 (and at least twice as many) SFC more than negative well. NOTE: a cut-off of ≥10 SFC more than negative control well was used for rESAT-6	5 TU of PPD RT23	≥10 mm
Codecasa et al (2006)[133] Italy	Diagnostic accuracy Prospective Consecutive subject recruitment	Household contacts	119	67/119 (56.3)	ELISPOT	ESAT-6 CFP-10	Higher mean number of SFCs than the mean number plus 2 SDs in the negative control wells	5 TU of PPD	≥5 mm
Hill et al (2004)[134] The Gambia	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts	856 (735)	282/629[b] (45)	ELISPOT	ESAT-6 CFP-10	≥10 SFUs more than, and at least twice as many as, negative control wells. For a positive ESAT-6/CFP-10 result, it was necessary for ≥1 pools of overlapping peptides to be positive.	2 TU PPD RT23	≥10 mm
Hill et al (2006)[135] The Gambia	Diagnostic accuracy Prospective Consecutive subject recruitment	Household contacts (aged >6 months) Community controls	775 119	260/615 (42) 61/105 (59)	ELISPOT	ESAT-6 CFP-10	≥10 SFCs more than, and at least twice as many as, negative control wells	2 TU of PPD RT23	≥10 mm
Hill et al (2006b)[136] The Gambia	Diagnostic accuracy Prospective Subject selection method not reported	Child contacts (aged >6 months, <15 years)	917	313/718 (43.6)	ELISPOT	ESAT-6 CFP-10	Wells containing ≥8 SFUs than the negative control wells. For a positive ESAT-6/CFP-10 result, ≥1 overlapping peptides must be positive	2 TU of PPD RT23	≥10 mm
Hill et al (2007)[31] The Gambia	Diagnostic accuracy Prospective Consecutive subject recruitment	Household contacts	740 (558)	NR	ELISPOT	ESAT-6 CFP-10	≥8 SFUs than the negative control well.	2 TU of PPD RT23	≥10 mm
Hill et al (2008)[32] The Gambia	Diagnostic accuracy Prospective Maximum 12 contacts had an ELISPOT per day, the rest randomly excluded	Household contacts	2348 (1648)	981/2348 (41.8)	ELISPOT	ESAT-6 CFP-10	≥8 SFUs than the negative control well.	2 TU of PPD RT23	≥10 mm
Jackson-Sillah et al (2007)[137]	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts	1656	NR	ELISPOT	ESAT-6 CFP-10	≥10 SFCs more than, and at least twice as many as, negative control wells	2 TU of PPD RT23	≥10 mm

Study	Study design	Population	N (n analysed)[a]	BCG vaccinated n/N (%)	Index test	Peptides	Cut-off for positive index test	TST	Cut-off for positive TST
Karam et al (2008)[138] Senegal	Diagnostic accuracy Prospective Subject selection method not reported	HIV-infected	285	207/285 (72.6)	ELISPOT	CFP-10 ESAT-6	>20 SFC/10^6 PBMC after negative control well SFC subtraction	2 TU PPD RT23	>5 mm
Krummel et al (2010)[139]	Diagnostic accuracy Prospective Subject selection method not reported	Contact tracing	274 (83)	18/172[c] (10.5)	ELISPOT	ESAT-6 CFP-10	>5 spots and had at least twice the number of spots than the negative control well	2 TU PPD RT23	≥5 mm
Murakami et al (2009)[140] Japan	Diagnostic accuracy Prospective Subject selection method not reported	RA patients considered for anti-TNF therapy	71	71/71 (100)	ELISPOT	ESAT-6 CFP-10	Determined by ROC curves	3 TU of PPD	CDC guidelines ≥5 mm Japanese guidelines >20 mm
Mutsvangwa et al (2010)[141] Zimbabwe	Diagnostic accuracy Prospective Subject selection method not reported	Household contacts (aged >10 years) 222 Controls contacts 176		NR	ELISPOT	ESAT-6 CFP-10	Mean of at least 5 SFCs more than, and at least twice as many as, the mean of negative control wells	2 TU of PPD RT23	≥10 mm (two step performed if first test <10 mm)
Richeldi et al (2004)[142]	Diagnostic accuracy Prospective Subject selection reported as "all"	Contact investigation (maternity unit)	92n(51 adults; 41 newborn babies)	9 (9.8)	ELISPOT	ESAT-6 CFP-10	Mean of at least 5 SFCs more than, and at least twice as many as, the mean of negative control wells	5 IU of PPD-S	≥5 mm
Shams et al (2005)[143]	Diagnostic accuracy Prospective Subject selection method not reported	Contact investigation	416	204/413 (49.4)	ELISPOT	ESAT-6 CFP-10	Any well at least 7 more spots than the mean of the negative control wells	5 TU of Tubersol	≥5 mm
Wu et al (2009)[33] China	Diagnostic accuracy Prospective Subject selection method not reported	Army recruits	100	45/100 (45)	ELISPOT	ESAT-6 rCFP-10	Mean of at least 7 SFCs more than, and at least twice as many as, the mean of negative control wells	0.1 mL of 5 IU PPD	>5 mm

BCG = bacillus Calmette-Guérin; ELISPOT = enzyme-linked immunosorbent assay; HIV = human immunodeficiency virus; IU = international units; n = number; NR = not reported; PPD = purified protein derivative; RA = rheumatoid arthritis; ROC = receiver operating characteristics; SD = standard deviation; SFC = spot-forming cells; TB = tuberculosis; TNF-α = tumour necrosis factor-alpha; TST = tuberculin skin test; TU = Tuberculin units.

a Number of participants in which intervention and reference test results were available for analysis and reported.

b Data only available for 629 persons.

c Data only available for 172 persons.

Appendix E Excluded studies

Reason for exclusion	Study
Irrelevant outcomes	Bruzzese et al (2009)[144]
	Chen et al (2008)[145]
	Del Corral et al (2009)[146]
	Demissie et al (2006)[147]
	Dyrhol-Riise et al (2010)[148]
	Franken et al (2007)[149]
	Franken et al (2008)[150]
	Gennaro et al (2007)[151]
	Goletti et al (2007)[152]
	Harstad etl al (2010)[153]
	Herrmann et al (2009)[154]
	Herrmann et al (2009b)[155]
	Laffitte et al (2009)[156]
	Marques et al (2009)[157]
	Nsutebu et al (2008)[158]
	Ordway et al (2004)[159]
	Pai et al (2006)[160]
	Perry et al (2008)[161]
	Rabahi et al (2007)[162]
	Van Brummelen et al (2010)[163]
	Whalen et al (2006)[164]
	Zhang et al (2010)[165]
Incorrect study design	Yoshiyama et al (2010)[166]
Letter/comment	Belknap et al (2008)[167]
	Hernandez-Garduno (2008)[168]
Not in English, and not of a higher level of evidence than the English language literature	Fukazawa (2007)[169]
	Okamba et al (2008)[170]
	Ravn et al (2009)[171]

Glossary and abbreviations

ACT	Australian Capital Territory
AS	Ankylosing spondylitis
BCG	Bacille Calmette-Guérin
CFP-10	Culture filtrate protein-10
CDC	Centers for Disease Control and Prevention
CDNA	Communicable Diseases Network Australia
CH	Children
CMI	Cellular mediated immune
CO2	Carbon dioxide
DTH	delayed-type hypersensitivity
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent assay
ESAT-6	Early secretory antigenic target-6
ESRD	End stage renal disease
FDA	Food and Drug Administration
HCWs	healthcare workers
HI	Healthy individuals
HIV	Human immunodeficiency virus
HP	Hospital patients
HRP	Horseradish peroxidise
IC	Immunocompromised
IFN-γ	Interferon gamma
IGRA	Interferon gamma release assay
IMID	Immune-mediated inflammatory disease
INH	Isoniazid
IU	International unit
JI	Jail inmates
LTBI	latent tuberculosis infection
mL	Millilitre

mm	Millimetre
MBS	Medicare Benefits Scheme
MP	Medical practitioner
MP	Military personnel
MSAC	Medical Services Advisory Committee
MTBC	Mycobacterium tuberculosis complex
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NP	Nurse practitioner
NSW	New South Wales
NT	Northern Territory
NTAC	National Tuberculosis Advisory Committee
°C	Degrees celisus
OD	Optical density
PBMC	Peripheral blood mononuclear cells
PBS	Pharmaceutical Benefits Scheme
PHA	Phytohaemagglutinin
PPD	Purified protein derivative
QLD	Queensland
QTF	QuantiFERON®-TB
QTF-G	QuantiFERON®-TB Gold
QTF-GIT	QuantiFERON®-TB Gold In-tube
RA	Rheumatoid arthritis
RI	Recent immigrants
SA	South Australia
TAS	Tasmania
TB	Tuberculosis
TGA	Therapeutic Goods Administration
TST	tuberculin skin test
VIC	Victoria
WA	Western Australia

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