

Tuberculosis: interferon gamma tests for the diagnosis of latent tuberculosis (partial update)

Short clinical guideline

Draft for consultation, July 2010

This short clinical guideline was developed following the NICE short clinical guideline process. It partially updates the recommendations in 'Tuberculosis' (NICE clinical guideline 33) and replaces section 5.1 of the full version of the guideline.

During consultation, this short clinical guideline should be reviewed in conjunction with the full version of 'Tuberculosis' (NICE clinical guideline 33), which is available at <http://guidance.nice.org.uk/CG33>

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This guidance is a partial update of NICE clinical guideline 33 (published 2006).

New recommendations have been added on interferon-gamma immunological testing for diagnosing latent TB.

Where recommendations are shaded in grey and end [2006] the evidence has not been updated since the original guideline. You are invited to comment on the new and updated recommendations in this guideline only. These are marked as [2010] if the evidence has been reviewed but no change has been made to the recommendation or [new 2010] if the evidence has been reviewed and the recommendation has been updated or added.

Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their

duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Introduction

As part of the review process for 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' (NICE clinical guideline 33), concern about the appropriateness of interferon-gamma testing in current clinical practice was raised.

The Department of Health formally requested the National Institute for Health and Clinical Excellence to produce a short clinical guideline on interferon-gamma immunological testing for diagnosing latent TB (partial review of CG33).

The following population subgroups were considered:

- Adults and children at increased risk of infection by *M. tuberculosis* complex (*M. tuberculosis*, *M. africanum*, *M. bovis*), specifically if they:
 - have arrived or returned from high-prevalence countries within the last 5 years
 - were born in high prevalence countries
 - live with people diagnosed with active TB
 - have close contact with people diagnosed with active TB, for example at school or work
 - are homeless and/or problem drug users
 - are, or have a recently been, a prisoner.
- Adults and children who are immunocompromised because of:
 - prolonged steroid use (equivalent to 15 mg prednisolone daily for at least 1 month)
 - TNF- α antagonists like infliximab and etanercept
 - anti-rejection therapy such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine

- the use of immunosuppression-causing medication
- comorbid states that affect the immune system, for example HIV, chronic renal disease, many haematological and solid cancers, and diabetes.

Patient-centred care

This guideline offers best practice advice on using interferon gamma tests for the diagnosis of latent tuberculosis (TB) in people at risk of infection.

Treatment and care should take into account people's needs and preferences. People at risk of latent TB should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If people do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

If the person is under 16, healthcare professionals should follow the guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the person's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people at risk of latent TB. Diagnosis and management should be reviewed throughout the transition process, and to ensure continuity of care there should be clarity about who is the lead clinician.

1 Summary

1.1 *List of all recommendations*

R1 To diagnose latent TB in:

Offer Mantoux testing in line with the Green Book²¹ (Department of health. Immunisation against infectious diseases-the 'Green Book' London DOH, 2006) to diagnose latent TB in:

- household contacts 5 years and older
- non-household contacts and
- adult contacts. **[new 2010]**

Those with positive results (or in whom Mantoux testing may be less reliable) should then be considered for interferon-gamma immunological testing **[2010]**

If Mantoux testing is inconclusive or positive, refer the person to a TB specialist. **[2010]**

Recent arrivals from highly prevalent countries

In people 5 – 34 offer a mantoux test followed by an IGT test if positive. In those 16 and above, an IGT test alone can be used. (refer to other sections for other groups eg immunocompromised) **[new 2010]**

For under 5's use Mantoux (2TU) as initial diagnostic tests for latent tb infection. If the initial test is positive taking into account the BCG history (Green Book), then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI. **[new 2010]**

Household contacts, under 5 years of age

Use Mantoux (2TU) as initial diagnostic tests for latent tb infection. If the initial test is positive taking into account the BCG history (Green Book), then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI.

[new 2010]

If the initial Mantoux is negative then in those who are contacts of sputum smear positive disease, an IGT test should be performed after an interval of six weeks as well as repeat the Mantoux test to increase the sensitivity. If either test is positive assess and treat as above. Children under 2 years who meet the criteria in previous guideline cross reference to the algorithm on page 146 Figure 8. **[new 2010]**

Contacts

In an outbreak situation among children 5 years and older where large numbers of individuals may need to be screened a single IGT test is appropriate. **[new 2010]**

Immunocompromised

For patients with HIV and CD4 counts of less than 200 perform both an IGT test and a TST. If either test is positive assess for active TB. Consider treatment of LTBI if active disease is excluded. **[new 2010]**

For patients with HIV and CD4 counts of 200 – 500 perform an IGT test alone or an IGT 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. **[new 2010]**

For other categories of immunocompromised patients perform an IGT test alone or an IGT test with a concurrent TST. If either test is positive assess for active TB. Consider treatment of LTBI if active disease is excluded. **[new 2010]**

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 in recommendation for recent arrivals from highly prevalent countries. **[new 2010]**

Test other healthcare workers in contact with patients or clinical materials, who have not had BCG (for example, without scar, other documentation or reliable history) for latent TB infection with either Mantoux testing or interferon-gamma immunological testing. **[new 2010]**

Healthcare workers who have CD4 counts of 200–500 should be screened as in recommendation for the immunocompromised population **[new 2010]**

No further evidence has been reviewed for other groups such as:

Prisoners/prison staff - But the tests will perform as with any other adults

In hard to reach populations a single IGT test will be the most appropriate **[new 2010]**

1.2 Overview

1.2.1 Diagnosing latent TB

In asymptomatic people, exposure to, and potential infection with, tuberculosis is demonstrated by a positive skin test, or more recently from a positive blood-based immunological (interferon-gamma) test. Those with a strongly positive skin test are then regarded as having been infected with tuberculosis. Of these people presumed infected, there is a 10–15% chance of developing clinical disease at some point in their lives. If a comorbidity develops which reduces the strength of the immune system, that risk is increased. The majority of exposed people will kill off the inhaled bacteria, and be left only with a positive skin test as a marker of exposure. About half of those who develop the clinical disease will do so within five years of the initial infection. In cases where a long period elapses between infection and development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can 'reactivate' in favourable circumstances for the organism.

Until recently, only skin tests (Mantoux and Heaf tests) were available to give evidence of exposure. The tuberculin skin tests (TST) had the advantage of being cheap and relatively easy to perform, but suffered from a number of problems. The test results have to be interpreted within a certain timescale, and patients who do not return, or delay returning, will have either no result or a possibly inaccurate one. False positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or opportunist environmental mycobacteria. False negative results can occur due to anything reducing immunity, particularly co-infection with HIV, but also treatments such as cytotoxics, or immunosuppression. Extensive tuberculosis (pulmonary or miliary) can itself also temporarily depress immunity, and can lead to a paradoxically negative TST.

More recently, interferon-gamma tests (IGT) have been developed using the tuberculosis antigens 'early secretion antigen target 6' (ESAT-6) and 'culture filtrate protein 10' (CFP-10), which are not present in BCG, and are found in only a few species of environmental mycobacteria. These can be done on either cells or cell products derived from whole blood tests. These tests aim to be more specific by removing false positive results, and to be better correlated with latent infection or dormant organisms.

There are currently two interferon-gamma immunological tests commercially available for use in the UK: QuantiFERON-TB Gold and T-SPOT.TB. QuantiFERON-TB Gold measures the release of interferon-gamma in whole blood in response to stimulation by ESAT-6 and CFP-10 which are not present in BCG vaccine strains or the vast majority of non-TB mycobacteria. In the T-SPOT.TB test, individual activated ESAT-6 and CFP-10 specific T cells are enumerated using ELISPOT methodology.

There is no gold-standard test for latent tuberculosis. Diagnosis has in the past been reliant on the TST but this has poor specificity if there has been BCG vaccination or environmental mycobacterial exposure, which can lead to false positive results. In the absence of a gold-standard reference test, it is not possible to measure directly the sensitivity and specificity of a new test for latent tuberculosis.

There is a lack of evidence available on the use of these tests in those who are HIV positive, in other immunocompromised individuals and in younger children. Furthermore, there is an issue of the generalisability of non-UK studies. This short clinical guideline aims to improve the care of people at risk of latent TB by making evidence-based recommendations on interferon gamma tests for diagnosis and partially updates recommendations made in 'Tuberculosis' (NICE clinical guideline 33).

1.2.2 Who this guideline is for

This document is intended to be relevant to healthcare professionals working in primary, secondary and tertiary care settings. The target population is people at risk of latent TB infection.

2 How this guideline was developed

2.1 Introduction

'Tuberculosis: interferon gamma tests for the diagnosis of latent tuberculosis' (NICE clinical guideline [XX]) is a NICE short clinical guideline. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual

Review questions were framed according to population groups as described above. Children were treated as a separate population because they have a less developed immune system than adults. Results from the included studies are presented in GRADE profiles and evidence statements. The GRADE profiles were developed based on the outcome measures, discordance, concordance, positive and negative predictive values, odds ratios and the ratio of odds ratios. For questions for children and contact tracing it was possible to pool the ratio of odds ratios and to perform a meta analysis. The studies for which the results were pooled were heterogeneous for exposure to active tuberculosis. Grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type).

The spreadsheets used to calculate and determine the risk categories as defined by level of exposure to active tuberculosis are given in appendix 4.

The key clinical questions considered were:

- Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults and children who are recent arrivals from highly prevalent countries?
- Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in children?
- Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults and children (children considered as a separate population) who have been in close contact with patients with active tuberculosis?
- Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients? What is the effectiveness of screening using IGT for healthcare workers?

The review protocol is included in appendix 2.

A search strategy was used which aimed to identify relevant studies for all the review questions. The following databases were searched Cochrane database of systematic reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health technology assessment (HTA) database, Medline, Embase, Cinahl, NHS Economic Evaluation database (NHS EED). Trial registers such as Cochrane central register of controlled trials (CENTRAL), UKCRN Portfolio database, current controlled trials, clinicaltrials.gov. Websites of relevant organizations were also searched. No methodology search filters or publication date filters were used. A total of 5270 studies were identified for the whole review. 467 studies were selected after sifting by abstract. 56, 70, 69 and 153 were selected for questions 1 to 4 respectively.

Studies were excluded if they

- did not compare TST with IGT
- evaluated IGT based on purified protein derivative
- did not focus on latent tuberculosis

- focused on treatment of tuberculosis
- focused on non commercial IGT or in house IGT.

The detailed evidence tables for the included studies and list of excluded papers and reasons for exclusion are given in appendix 4 and 5.

There were methodological issues with the included papers. For example, active TB was not always excluded (either through investigation or simply not reported), there was repeated testing of both TST and IGT, the threshold for positive TST varied, and it was not clear whether the use of cut offs were always age appropriate. Where identified, these issues were used to downgrade the quality of the evidence in the GRADE tables.

The main aim of this work was diagnosis using tests for which there is no ideal reference standard for comparison. One important objective was to identify appropriate measures of effect to assess the diagnostic utility of the tests. Different approaches were taken to address this objective.

- Discordance and concordance between the IGT and TST were measured in some of the papers. There were few prospective studies to identify participants who would either develop active tuberculosis following a positive test result or stay healthy following a negative test result. These studies are designed to determine positive and negative predictive values. For diagnosis of latent tuberculosis this type of design would give the most accurate prognosis predicting those who will get active tuberculosis and those who would not.
- In other studies the odds of a positive test associated with graded exposure to an active tuberculosis case(s) were measured. In these cases a proxy measure of effect, the ratio of odds ratios could be calculated from where figures of positive test results of study participants were clearly stated, and where the exposure status of those participants had been identified. The ratio of odds ratios is a measure of effect which reflects test performance and provides an approach to evaluating tests in the absence of a gold standard. The odds ratio (OR) is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically

OR = [sensitivity/(1-specificity)]/[(1-sensitivity)/specificity]. The main disadvantage of this proxy measure is that it fails to identify whether the good performance of a test compared with another is due to either better sensitivity, specificity or both. It is impossible therefore to determine the false positive and false negative rates of a particular test.

2.2 *Diagnosis of latent TB in people who are recent arrivals from countries where TB is highly prevalent*

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults and children who are recent arrivals from highly prevalent countries?

Evidence review

Of the 11 studies included:

- three were conducted in Germany (Diel et al. 2006; Diel et al. 2008;(Nienhaus, Schablon, and Diel e2665)
- three in the Netherlands (Franken et al. 2007; Kik et al. 2009; Kik et al follow-up study 2009)
- two in the United States (Brodie et al. 2008; (Porsa et al. 53-58)
- one in Italy (Carvalho et al. 2007)
- one in Norway ((Winje et al. 65))
- one in Switzerland ((Janssens et al. 585-93)).

All studies looked at participants from high prevalence countries from places such as sub Saharan Africa, Central and South America, Eastern Europe and Asia.

The main measures of effect used were:

- concordance and discordance between tests
- agreement between the tests as measured by kappa values
- odds ratios

Table 1 Diagnosis of latent TB infection in foreign-born people and in people arriving from high-prevalence

Study ¹	Population group (by prevalence or place of birth or racial group)	Odds ratio (TST ≥ 5 mm)	Odds ratio (TST ≥ 10 mm)	Odds ratio (TST ≥ 15 mm)	Odds ratio (IGT)	ROR	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Janssens et al (2008)	< 50 per 100,000	1	1	–	1	–	Y	Y	N	N	N	Low
	50–99 per 100,000	2.58 (1.26 to 5.27)	2.22 (1.15 to 4.27)	–	2.17 (1.13 to 4.15)	0.98						
	> 100 per 100,000	3.67 (1.40 to 9.60)	3.84 (1.61 to 9.20)	–	2.62 (1.18 to 5.82)	0.68						
Diel et al (2008)	Germany	1	1	–	1	–	Y	N	N	N	N	Low
	Not Germany	5.81 (3.6 to 9.1)	5.2 (3.2 to 8.4)	–	2.28 (1.3 to 3.9)	0.438						
Nienhaus et al (2008)	Germany (< 6 per 100,000)	–	1	–	1	–	N	N	N	N	N	Low
	Not Germany (> 20 per 100,000)	–	4.6 (3.21 to 6.53)	–	2.6 (1.71 to 4.09)	0.565						
Diel R et al (2006)	Germany (< 6 per 100,000)	1	1	–	1	–	Y	N	N	N	N	Low
	Not Germany (> 20 per 100,000)	5.4 (2.7 to 10.6)	7.3 (3.7 to 14.3)	–	4.7 (2.1 to 10.5)	0.644						
Porsa et al (2006)	USA (<10 per 100,000)	–	1	–	1	–	Y	N	N	N	N	Low
	Not USA (25–300 per 100,000)	–	20.20 (4.21 to 79.02)	–	2.86 (0.67 to 12.15)	0.141						

Study ¹	Population group (by prevalence or place of birth or racial group)	Odds ratio (95%CI) TST ≥ 5 mm	Odds ratio (95%CI) TST ≥ 10 mm	Odds ratio (95%CI) TST ≥ 15 mm	Odds ratio (95%CI) IGT	ROR	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Kik et al (2009)	Asia		1		1		Y	N	Y	N	N	Low
	Europe, North America		1.69 (0.44 to 6.45)		QFT = 0.48(0.17 to 1.36); TSPOT = 0.35(0.13 to 0.99)							
	Sub-Saharan Africa		6.00 (1.32 to 27.24)		QFT = 2.97 (1.40 to 6.27); TSPOT 2.40 (1.13 to 5.10)							
Winje et al (2008)	Asia			1	1		Y	N	Y	N	N	Low
	Europe			2.7 (1.5 to 4.9)	1.0 (0.6 to 1.6)							
	Africa			3.8 (2.4 to 5.8)	3.1 (2.2 to 4.2)	0.82						
Porsa et al (2006)	CaucasianWhite		1		1		Y	N	N	N	N	Low
	African-Caribbean		4.97 (1.58 to 15.68)		5.57 (1.16 to 26.74)	1.12						

¹ Outcomes were diagnostic utility and threshold value for a positive diagnosis of latent TB.

² Odds Ratio for a positive test in people who are foreign-born or from high endemic areas adjusted for BCG vaccination, age, gender and exposure time.

Limitations were the lack of a gold standard means the measures of effect of sensitivity and specificity cannot be determined. Inconsistencies were different studies used different types of TST.

CI = confidence interval. TST = tuberculin skin test. IGT = interferon gamma test. ROR = ratio of odds ratios. QFT = QuantiFERON-TB interferon gamma test. TSPOT = T-SPOT.TB interferon gamma test

2.3 *Diagnosis of latent TB in children*

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB infection in children?

Evidence review

Of the 11 studies included:

- four were conducted in Asia (Chun et al. 2008; Higuchi et al. 2007; Higuchi et al. 2009; Okada et al. 2008), three in Europe (Brock et al. 2004; Hansted et al. 2009; Winje et al. 2008b), two in North America (Lighter et al. 2009; Tsiouris et al. 2006) and two in Australasia (Connell et al. 2006; Connell et al. 2008)
- ages ranged from 0–19 years
- grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type).

The studies also looked at other factors such as BCG vaccination and country of birth.

Exposure was measured in several ways:

- Duration of contact
 - Hours/day
 - Hours/week
- Sleeping proximity
 - Same or different house
 - Same or different room
- Type of contact
 - Household/close
 - Non-household
 - Unknown
 - School contact

- Casual contact

The following measures of effect were used:

- concordance between tests
- agreement between tests measured by kappa value
- risk factors for positive test result.
- odds Ratios

Risk of development of active TB

Meta analysis of the results of a positive test associated with graded exposure to active was performed from six studies(Brock et al. 65-69;Chun et al. 389-94;Hansted et al. 41;Okada et al. 1179-87;Higuchi et al. 352-57;Lighter et al. 30-37)

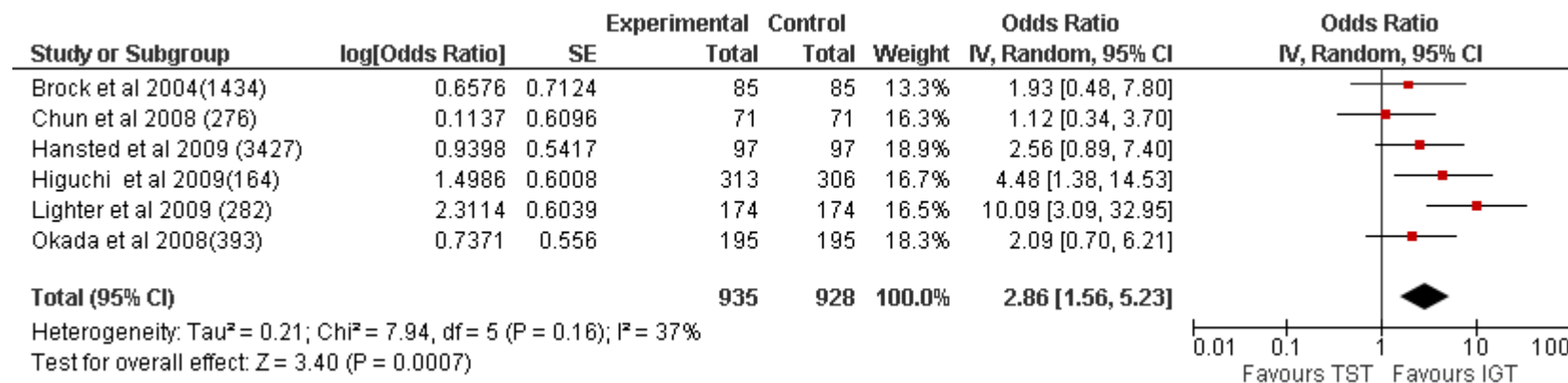
There were two longitudinal studies (Higuchi et al. 88-92;Higuchi et al. 352-57) that followed up participants to investigate the development of active tuberculosis.

Five studies (Connell et al. 616-20;Connell et al. e2624;Brock et al. 65-69;Chun et al. 389-94;Okada et al. 1179-87) looked at the concordance between IGT and TST.

Table 2 Diagnosis of latent TB in children

Study	Results ¹ (IGT versus TST in children aged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Meta-analysis (6 studies) (Brock et al. 65-69;Chun et al. 389-94;Hansted et al. 41;Okada et al. 1179-87;Higuchi et al. 352-57;Lighter et al. 30-37)	ROR ranged from 0.70 to 10.09. The overall ROR value was 2.86 (95% CI 1.56 to 5.23). A value greater than 1 in this case means that IGT was more strongly associated with TB exposure than was TST.	Y	Y	N	N	N	Low
<p>¹ Outcomes were associations between graded exposure and positive test.</p> <p>Limitations were the lack of a gold standard means the measures of effect of sensitivity and specificity cannot be determined. Inconsistencies were grading of exposure differed between studies (for example sleeping proximity, duration of exposure, contact type).</p> <p>IGT = interferon gamma testing. TST = tuberculin skin testing. ROR = ratio of odds ratios. CI = confidence interval</p>							

Figure 1 Forest plot of meta-analysis of IGT and TST results based on high-risk and low-risk exposure



Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a gold standard. OR is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically $OR = \frac{\text{sensitivity}/(1-\text{specificity})}{(1-\text{sensitivity})/\text{specificity}}$

SE = standard error. CI = confidence interval. OR = odds ratio

Table 3 Diagnosing latent TB in children (predicting development of active TB)

Study	Results ¹ (IGT versus TST in children aged 8–16 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Two studies (Higuchi et al. 88-92; Higuchi et al. 352-57)	281 children with negative IGT but positive TST were followed-up for a total of 888.5 person-years. None developed active TB. Mean duration of follow up was 3 years. 99% of participants were BCG-vaccinated. Negative predictive value = 100%	N	N	N	Y	N	Moderate
<p>¹ Outcome was prognostic value of IGT in predicting the subsequent development of potential active tuberculosis. Imprecision was number of participants too few and follow-up too short for precise result to be determined. IGT = interferon gamma test. TST = tuberculin skin test</p>							

Table 4 Diagnosis of latent TB in children (agreement between tests)

Study	Results (IGT versus TST in children aged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Five studies (Connell et al. 616-20; Connell et al. e2624; Brock et al. 65-69; Chun et al. 389-94; Okada et al. 1179-87)	Concordance between IGT and TST as measured by kappa values ranged from 0.19 to 0.866	Y	Y	N	–	N	Low
<p>Outcome was concordance between TST and IGT. Limitations were the lack of a gold standard therefore sensitivity and specificity could not be determined. Inconsistencies were grading of exposure differed between studies (for example sleeping proximity, duration of exposure, contact type). Imprecision was not measurable. IGT = interferon gamma test. TST = tuberculin skin test</p>							

2.4 *Diagnosis of latent TB in adults and children who have been in close contact*

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults and children who have been in close contact with patients with active tuberculosis?

Evidence review

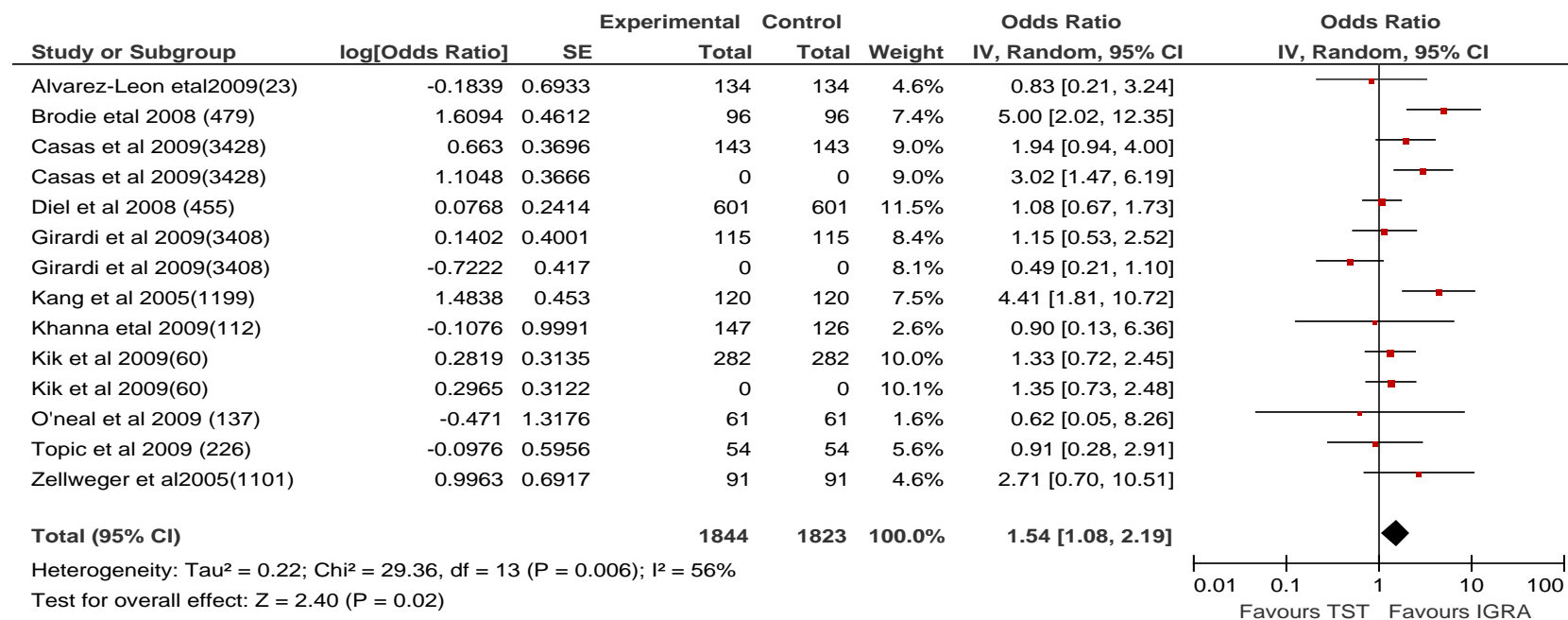
Of the 27 papers selected:

- TST thresholds ranged from 5 mm to 30 mm
- 11 papers graded TB exposure, risk and proximal contact and it was possible to pool the results (Alvarez-Leon et al. 876-83; Brodie et al. 869-74; Casas et al. e6686; Diel et al. 1164-70; Girardi et al. 2009; Kang et al. 2756-61; Khanna et al. 581-84; Kik et al. 820-28; O'Neal et al. 662-64; Topic, Dodig, and Zoricic-Letoja 103-08; Zellweger et al. 1242-47)
- 16 papers (Kang et al. 2756-61; Mirtskhulava et al. 513-19; Tripodi et al. 30; Pai et al. 2746-55; Casas et al. e6686; Topic, Dodig, and Zoricic-Letoja 103-08; Vinton et al. 215-21; Alvarez-Leon et al. 876-83; Hesselning et al. 840-46; Adetifa et al. 122; Brodie et al. 869-74; Porsa, Cheng, and Graviss 714-19; Kik et al. 820-28; Zellweger et al. 1242-47; Arend et al. 618-27; Diel et al. 1010-18) analysed the degree of concordance between TST and IGT
- there were two longitudinal studies (Diel et al. 1164-70) which followed up participants to investigate the development of active tuberculosis.

Table 5 Diagnosing latent TB in adults and children who have been in close contact with patients with active TB.

Study	Results IGT versus TST)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
11 studies: Alvarez-Leon et al (2009); Brodie et al (2008); Casas et al (2009); Diel et al (2008); Girardi et al (2009); Kang et al (2005); Khanna et al (2009); Kik et al (2009); O'Neal et al (2009); Topic et al (2009); Zellweger et al (2005)	Greater than 1 in this case means that IGT was more strongly associated with TB exposure than was TST. The overall ROR value was 1.54 (1.08 to 2.19)The overall ROR value was 1.54(1.08-2.19)		Y	N	N	N	Low
<p>Children were considered as a separate population. Outcome was diagnosis of latent TB in contacts from meta-analysis of ROR for IGT versus TST. Limitations were the lack of a gold standard means the measures of effect of sensitivity and specificity could not be determined. Inconsistencies were grading of exposure differed between studies (for example sleeping proximity, duration of exposure, contact type)</p> <p>IGT = Interferon gamma test. TST = Tuberculin skin test. ROR = ratio of odds ratios</p>							

Figure 2 Forest plot of meta-analysis of interferon gamma test and tuberculin skin test results based on high-risk and low-risk exposure to active tuberculosis

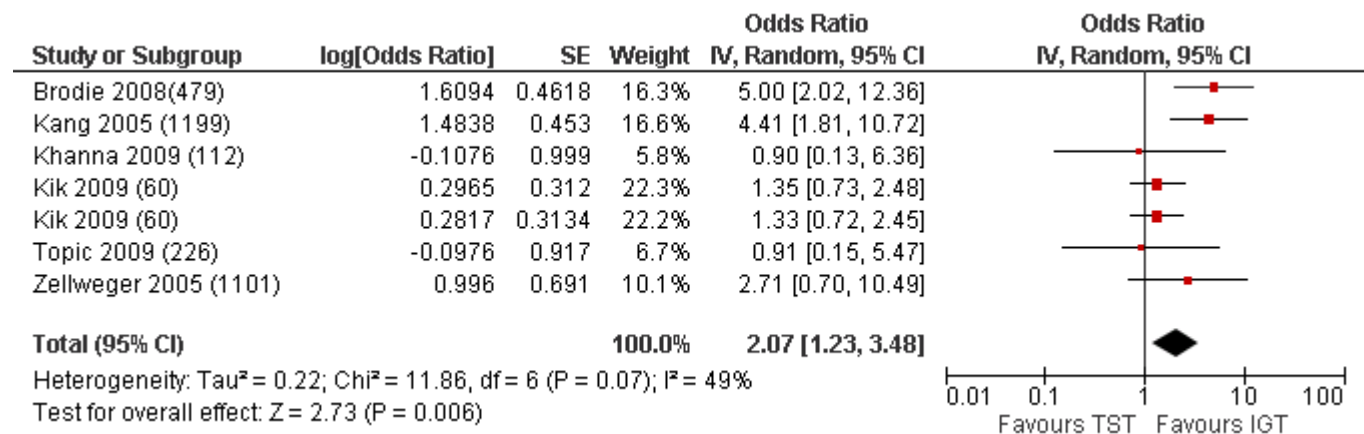


Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a gold standard. OR is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically $OR = \frac{\text{sensitivity} / (1 - \text{specificity})}{[(1 - \text{sensitivity}) / \text{specificity}]}$.

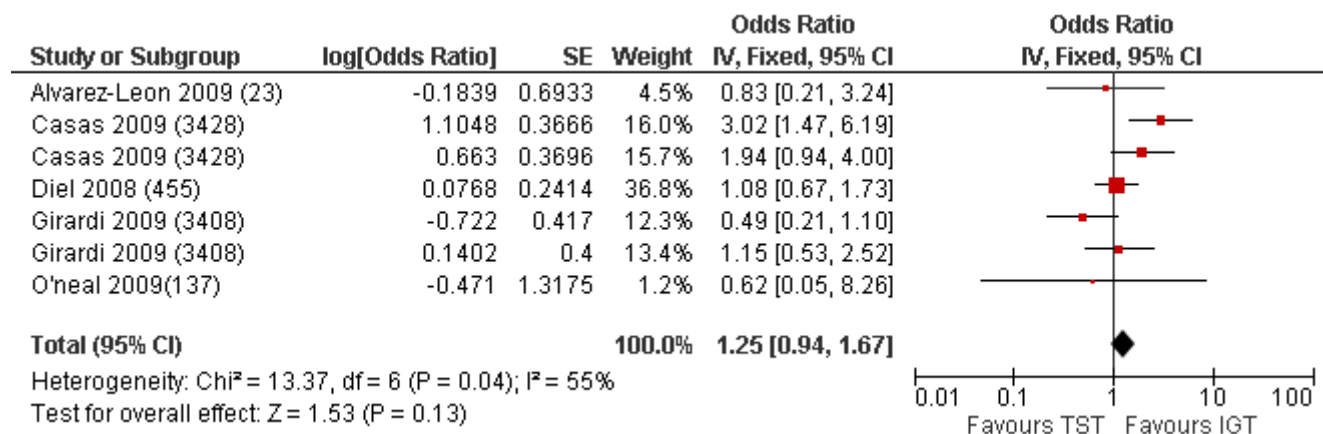
OR = odds ratio. ROR = ratio of odds ratios

Figure 3 Forest plot of meta-analysis of interferon gamma test and tuberculin skin test results based on high-risk and low-risk exposure to active TB stratified by BCG vaccination rates

>50% BCG-vaccinated



<50% BCG-vaccinated



SE =standard error. CI = confidence

interval

Table 6 Diagnosis of latent TB in adults and children who have been in close contact with patients with active tuberculosis (concordance between results) Children are considered as a separate population in this case.

Study	Results (IGT versus TST)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Sixteen studies ¹ (Kang et al. 2756-61;Mirtskhulava et al. 513-19;Tripodi et al. 30;Pai et al. 2746-55;Casas et al. e6686;Topic, Dodig, and Zoricic-Letoja 103-08;Vinton et al. 215-21;Alvarez-Leon et al. 876-83;Hesseling et al. 840-46;Adetifa et al. 122;Brodie et al. 869-74;Porsa, Cheng, and Graviss 714-19;Kik et al. 820-28;Zellweger et al. 1242-47;Arend et al. 618-27;Diel et al. 1010-18)	Overall agreement ranged was 46.6–94%. Kappa values were 0.11–0.85	Y	N	Y	–	N	Low
Diel et al (2008) ²	None of the 25 patients who were IGT positive and started treatment had developed active TB. Six of 41 patients (14.6%) who were IGT positive but refused treatment later developed active TB. Five of 219 patients (2.3%) who were TST positive and were not treated later developed active TB. These patients were followed-up for 2 years	N	N	N	Y	N	Low

Kik et al (2009) ²	Positive predictive values were TST ≥ 10 mm = 3.1%; TST ≥ 15 mm = 3.8%; QFT = 2.8% ; T-SPOT = 3.3% Negative predictive values were TST ≥ 10 mm = 100%; TST ≥ 15 mm = 99.3%; QFT = 98%; T-SPOT = 98.3% These patients were followed-up for median of 1.83 years	N	N	N	Y	N	Low
<p>Children were considered as a separate population.</p> <p>¹ Outcome was diagnosis of latent TB in contacts and degree of concordance between TST and IGT results.</p> <p>² Outcome was diagnosis of TB in children and the prognostic value of IGT in predicting the subsequent development of potential active tuberculosis.</p> <p>Imprecision was that studies had too few participants and too short a follow-up</p> <p>TST = tuberculin skin test. IGT = interferon gamma test. QFT = QuantiFERON-TB interferon gamma test. TSPOT = T-SPOT.TB interferon gamma test</p>							

2.5 *Diagnosis of latent TB in adults and children who are immunocompromised*

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients?

Evidence review

Of the 16 papers selected:

- five papers (Balcells et al. 645-52;Luetkemeyer et al. 737-42;Talati et al. 15;Jones et al. 1190-95;Mandalakas et al. 417-23) looked at HIV-positive participants. The paper by Mandalakas et al. also had a children's population.
- seven papers (Vassilopoulos et al. 1271-76;Ponce de et al. 776-81;Bartalesi et al. 586-93;Cobanoglu et al. 1177-82;Soborg et al. 1876-84;Matulis et al. 84-90;Matulis et al. 84-90;Shovman et al. 1427-32) looked at participants who had rheumatoid arthritis/ rheumatic or inflammatory disease
- one study (Richeldi et al. 198-204) combined HIV+, liver transplant and haematological malignancy patients
- one paper (Manuel et al. 2797-801) looked at participants with chronic liver disease
- one paper (Piana et al. 31-34) investigated immunosuppressed haematology patients
- one (Schoepfer et al. 2799-806) looked at people with Crohn's disease and ulcerative colitis

Table 7 Diagnosis of latent TB in immunocompromised patients?

Study	Results (discordance between TST and IGT in 973 people with HIV)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Five studies (Balcells et al. 645-52;Luetkemeyer et al. 737-42;Talati et al. 15;Jones et al. 1190-95;Mandalakas et al. 417-23)	Overall discordance = 0– 29.7% TST positive:IGT negative discordance = 1.8–28.6% TST negative:IGT positive discordance = 0–29.7%	Y	Y	N	–	Y	Low
<p>Limitations: The lack of a gold standard means the crucial measures of effect of sensitivity and specificity cannot be determined. Inconsistencies were noted in study designs: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some studies seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants.</p> <p>TST = tuberculin skin test. IGT = interferon gamma test</p>							

Table 8 Diagnosis of latent TB in immunocompromised children?

Study	Results (discordance between TST and IGT in 23 children with HIV and mean age 4.4years (range 1.1–11.1years))	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
One study Mandalakas et al. 417-23	Overall discordance = 0–39.1%	Y	N	N	–	Y	Low
	TST positive:IGT negative discordance = 13–25%						
	TST negative:IGT positive discordance = 0– 39.1%						
<p>Limitations were that the lack of a gold standard means the crucial measures of effect of sensitivity and specificity could not be determined.: Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants. TST = tuberculin skin test. IGT = interferon gamma test</p>							

Table 9 Diagnosis of latent TB in immunocompromised people (indeterminate results)

Study	Results (indeterminate IGT results in people with HIV)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Three studies	1.83–17.87%	Y	Y	N	–	Y	Low
Luetkemeyer et al. 737-42; Talati et al. 15; Jones et al. 1190-95	Odds ratio for indeterminate results adjusted for CD4 count: below 100 cells/mm ³ = 4.8 (95% CI 1.55 to 4.75), 34.81 (95% CI 7.98 to 151.89) below 200 cells/mm ³ = 3.6 (95% CI 1.9 to 6.8), 47.58 (95% CI 5.89 to 384.5)	Y	Y	N	Y	Y	Low
<p>Limitations were that the lack of a gold standard meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants.</p> <p>IGT = interferon gamma test</p>							

Table 10 Diagnosis of latent TB in immunocompromised people with rheumatoid arthritis

Study	Results (discordance between IGT AND TST in 1121 people)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Seven studies in people with rheumatoid arthritis (Vassilopoulos et al. 1271-76; Ponce de et al. 776-81; Bartalesi et al. 586-93; Cobanoglu et al. 1177-82; Soborg et al. 1876-84; Matulis et al. 84-90; Shovman et al. 1427-32)	Overall discordance = 12.2–44.3% TST positive:IGT negative discordance = 5.9–47.5% TST negative, IGT positive discordance = 1.6–23.7%	Y	Y	N	–	Y	Low
Limitations were that the lack of a gold standard meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants. IGT = interferon gamma test							

Table 11 Diagnosis of latent TB in immunocompromised patients (association between risk factors and positive test)

Study	Results (people with rheumatoid arthritis)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Two studies Soborg et al. 1876-84;Matulis et al. 84-90	Corticosteroid treatment: OR with IGT = 1.11 (95% CI 0.30 to 4.14); RR with IGT = 0.5 (95% CI 0.1 to 1.6) No Corticosteroid treatment: OR with TST = 0.74 (95% CI 0.32 to 1.72); RR with TST = 0.4(95% CI 0.1 to1.0) <hr/> Disease-modifying antirheumatic drug treatment: OR with IGT = 2.34 (95% CI 0.52 to 10.6); RR with IGT = 0.7 (95% CI 0.3 to 1.7) No disease-modifying antirheumatic drug treatment: OR with TST = 0.75 (95% CI 0.32 to 1.77); RR with TST = 1.3 (95% CI 0.7 to 2.3) RR TST = 1.5 (95% CI 0.7 to 2.9)	Y	Y	N	Y	Y	Low
Limitations were that the lack of a gold standard meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was present because the confidence intervals did not statistical significance.. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants. OR = odds ratio. IGT = interferon gamma test. RR = relative risk. TST = tuberculin skin test							

Table 12 Diagnosis of latent TB in immunocompromised people with haematological conditions

No of studies	Results (discordance between IGT and TST in 291 people with haematological conditions)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
2 studies (Piana et al. 31-34;Manuel et al. 2797-801)	Overall discordance = 14.9–32.2%	Y	Y	N	–	Y	Low
TST positive:IGT negative discordance = 2.6–8.5%	TST negative:IGT positive discordance 6.4–29.6%						
<p>Limitations were that the lack of a gold standard meant the measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design and others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge since the performance of the tests depends on the immunocompetence of the participants.</p> <p>IGT = interferon gamma test. TST = tuberculin skin test</p>							

2.6 Screening for latent tuberculosis in healthcare workers

Key clinical question

What is the effectiveness of screening using IGT for healthcare workers?

Evidence review

Even though studies which included healthcare workers had been analysed as part of the contact tracing question, the GDG advised that screening in healthcare workers be specifically looked at.

Five studies were selected for critical appraisal. Of these:

- two (Alvarez-Leon et al. 876-83;Harada et al. 442-48) looked at existing employees
- two (Cummings et al. 1123-26;Hotta et al.) looked newly hired workers
- two (Hotta et al.;Harada et al. 442-48) studies had participants of whom most were BCG vaccinated
- concordance and discordance were determined in three studies(Zhao et al. 678-86;Hotta et al.;Alvarez-Leon et al. 876-83).

There are no GRADE tables for this question but there is an evidence summary in appendix. This is because it was not practical to make any GRADE profiles for these papers.

2.7 Evidence statements

Test results and TB exposure

In a UK study¹⁷ of healthy adults in a contact tracing clinic, IGT (ESAT-6 ELISPOT assay) results had a strong positive relationship with increasing intensity of contact exposure (OR 9.0 per unit increase in exposure, 95%CI 2.6 to 31.6, $p=0.001$), whereas TST results had a weaker relationship with exposure (OR 1.9, 95%CI 1.0 to 3.5, $p=0.05$). (2)

In a study¹¹ of students aged 11–15 years in the UK from the same school as an index case, the odds of a test result being positive for each increase across four stratified exposure groups increased by a factor of 2.78 (95%CI 2.22 to 3.48, $p<0.0001$) for the interferon-gamma test (ESAT-6/CFP10 ELISPOT assay) and 2.33 (95%CI 1.88 to 2.88, $p<0.0001$) for the TST. The interferon-gamma test correlated significantly better with increasing exposure across the four groups than the TST ($p=0.03$). The odds of a positive interferon-gamma test result increased by a factor of 2.51 (95%CI 1.58 to 3.99, $p<0.0001$) with each week of direct exposure, which was significantly higher ($p=0.007$) than that for the TST (OR 1.30, 95%CI 1.10 to 1.54, $p=0.002$). (2)

In contacts of index cases in the Gambia,¹³ with increasing *M. tuberculosis* exposure, the percentage of participants who were tuberculin positive and interferon gamma test (ESAT6/CFP-10 ELISPOT assay) negative increased from 11% of those sleeping in a different house from the index case to 32% of those sleeping in the same room ($p<0.001$). (3)

In contacts of an index case on an Italian maternity unit,¹⁹ the odds for a test result being positive for each increase across four stratified exposure groups (from no discernible contact to household contacts) increased by 1.93 (95%CI 1.11 to 3.35, $p=0.020$) for the IGT (ESAT-6/CFP-10 ELISPOT assay) but there was no significant correlation for TST. (3)

In Korea where BCG vaccination is mandatory,¹⁵ a study found that the odds of a positive test result per unit increase in exposure across four groups,

increased by a factor of 5.31 (95%CI 3.62 to 7.79) for the IGT (QuantiFERON-TB Gold) and by a factor of 1.52 (95%CI 1.2 to 1.91) for the TST ($p < 0.001$). (2)

Test results and BCG status

Healthy adults in a contact tracing clinic in the UK,¹⁷ had IGT (ESAT-6 ELISPOT assay) results which were not correlated with BCG vaccination status whereas TST results were significantly more likely to be positive in BCG vaccinated contacts (OR 12.1, 95%CI 1.3 to 115.7, $p = 0.03$). (2)

Students aged 11–15 years from the same school as an index case in the UK¹¹ had IGT (ESAT-6/CFP-10 ELISPOT assays) which showed no significant relation with BCG vaccination status, however, BCG vaccinated children were significantly more likely to have higher Heaf grades than unvaccinated children ($p = 0.002$). (2)

In a UK study¹⁶ of healthy household contacts and healthy unexposed controls, ESAT-6 peptide-specific interferon-gamma-secreting cells were detected in 85% of the healthy household contacts who were tuberculin positive. None of the healthy control subjects without a history of TB exposure, responded to this IGT even though all unexposed control subjects were BCG vaccinated. (3)

TST negative Australian born medical students (or those born in another low TB prevalence country),¹⁴ with no prior BCG, and no known exposure to TB, were BCG vaccinated and then tested again at five months. ESAT-6 stimulated interferon-gamma levels (using ESAT-6 QuantiFERON) were very low or undetectable in all students both before and after BCG vaccination. Of these students, 46% had TST responses of 0 to 4 mm and 54% had responses of ≥ 5 mm. Thirteen percent had TST results of ≥ 10 mm. Under current Australian guidelines, one student with a 16 mm result was defined as having a TST result suggestive of *M. tuberculosis* infection. (3)

High school contacts in a TB outbreak in Denmark⁹ who had high exposure to an index case and were not BCG vaccinated, had agreement between TST

and IGT (QuantiFERON-TB Gold) results of 93% (95%CI 86 to 100%). This was 95% (95%CI 88 to 102%) in the low exposure group and an overall agreement between the two tests of 94% (95%CI 89 to 99%) in all subjects tested. The kappa value was 0.866, indicating high agreement between the two tests. (3)

In an Italian study¹⁹ of contacts of an index case on a maternity unit, IGT (ESAT-6/CFP-10 ELISPOT assay) results were independent of BCG vaccination status. (3)

IGTs were prescribed by hospital physicians for inpatients or outpatients in an Italian study with no influence from the study investigators.¹² After excluding indeterminate results, the agreement between IGT (QuantiFERON-TB Gold) and TST results was significantly lower among BCG-vaccinated individuals than in non-vaccinated individuals (41.5% vs. 80.3%, $p < 0.0001$). (3)

In a study of healthcare workers conducted in India¹⁸ (where non-tuberculous mycobacteria are highly prevalent), previous BCG vaccination was not associated with TST or IGT (QuantiFERON-TB Gold) positivity. (3)

Indeterminate test results

An Italian study¹² found that indeterminate IGT results (QuantiFERON-TB Gold) were significantly over-represented in patients with a negative TST (28.6% vs. 6.6% in tuberculin positive patients, $p < 0.001$) and were more frequent in patients receiving immunosuppressive therapies than in those who were not receiving such treatments (OR 3.35, 95%CI 1.84 to 6.08, $p < 0.0001$). Immunosuppressive therapy was defined as cancer chemotherapy, systemic steroids, or anti-tumour necrosis factor alfa agents at the time of testing. (3)

Diagnosing latent tuberculosis in adults and children who are recent arrivals from highly prevalent countries

Moderate quality evidence from four studies with 2646 participants showed that there was a higher level of concordance and agreement between IGT and TST when both tests were used in non BCG-vaccinated populations than in populations who were BCG vaccinated.

Moderate quality evidence from three studies with 2351 participants showed that BCG vaccination decreases both concordance and agreement between the assay results of IGT and TST.

Low quality evidence from one study showed IGT was more likely to detect progression to active TB than TST over a 2-year period. Positive predictive values were 14.6% and 2.3% respectively.

Low quality evidence from one study following up 339 immigrant contacts for a median of 1.83 years showed that IGT and TST were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for TST thresholds 10 mm and 15 mm respectively and 2.8% and 3.3% for QFT and T-SPOT respectively. Negative predictive values were 10 mm and 15 mm TST, QFT and TSPOT 100%, 99.3%, 98% and 98.3% respectively.

Diagnosing latent tuberculosis in children

Moderate quality evidence from 6 studies with 935 children aged 0–18 years showed that IGT was more strongly associated with increasing TB exposure than TST (Ratio of odds ratio = 2.86 [95% CI 1.56 to 5.23]).

Low quality evidence from two studies following up 281 children aged 8–16 years who had a negative IGT test found that none had developed active TB within 888.5 person–years. Each child had been followed up for an average of just over 3 years. All the children had tested positive for TST but 99% were BCG vaccinated. The studies were from the same group in Japan.

Moderate quality evidence from two studies with 110 children found that there was low to moderate level of concordance between IGT and TST but a high level of concordance between the two commercial IGTs.

Low quality evidence from five studies with 461 children aged 0–18 years showed a wide variation in concordance between IGT and TST, kappa values ranging from 0.19 to 0.866. These studies were conducted in very diverse populations with different rates of BCG vaccinations and wide age ranges.

Diagnosing latent TB in adults and children who have been in close

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contact with patients with active TB

Low quality evidence from 11 studies with 1844 participants showed that IGT was more strongly associated with increasing TB exposure than TST. (Ratio of odds ratio = 1.54 [95% CI 1.08 to 2.19]). In those studies with the proportion of BCG-vaccinated patients under 50% the ratio of odds ratio was 1.25 (95% CI 0.94 to 1.67), whereas those over 50% it was 2.07 ((95% CI 1.23 to 3.48).

Low quality evidence from 16 studies showed that the degree of concordance between TST and IGT results as measured by kappa values were between 0.11 and 0.85.

Low quality evidence from one study showed IGT was more likely to detect progression to active TB than TST over a 2-year period. Positive predictive values were 14.6% and 2.3% respectively.

Low quality evidence from one study following up 339 immigrant contacts for a median of 1.83 years showed that IGT and TST were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for TST thresholds 10 mm and 15 mm respectively and 2.8% and 3.3% for QFT and T-SPOT respectively. Negative predictive values were TST 100%, 99.3%, 98% and 98.3% respectively.

Diagnosing latent tuberculosis in immunocompromised patients

Low quality evidence from five studies showed that the level of discordance between IGT and TST in 973 HIV-infected adults ranged from 0% to 29.7% for TST negative, and IGT positive and 1.8% to 28.6% for TST positive and IGT negative.

Low quality evidence from one study showed that in 23 HIV-infected children with a mean age of 4years showed that the TST positive IGT negative discordance was 13% to 25% and TST negative IGT positive discordance was 0-39.1%similar overall discordance

Low quality evidence from three studies showed that the rate of indeterminate results from an IGT test in 837 HIV-infected individuals ranged from 1.83% to TB (partial update) short clinical guideline DRAFT (July 2010)

17.87%. The rate of indeterminate results was significantly higher in those with a CD4 count below 200cells/mm³

Low quality evidence from seven studies showed that in 1121 individuals with rheumatoid arthritis, the overall discordance between IGT and TST was between 5.9% and 47.5% for TST positive and IGT negative, and 1.6% to 23.7% for TST negative and IGT positive.

Low quality evidence from two studies showed that the level of discordance in patients with diseases including, chronic liver disease, non-Hodgkin's lymphoma, multiple myeloma, acute myeloid leukaemia, and chronic myeloma was between 6.4% and 29.6% for TST negative and IGT positive, 2.6% and 8.5% for TST positive and IGT negative.

Screening healthcare workers

Evidence from three poor quality papers showed that there was more discordance between TST positive and IGT negative results than TST negative and IGT positive results in 381 healthcare workers. TST negative IGT positive discordance was very low (at less than 2%). Some of the healthcare workers were newly employed. Coverage and timing of BCG vaccination was variable. In two other studies discordance figures were not quantified

5.1.4 Health economics

A decision model was used to compare the expected cost-effectiveness of four strategies of testing for latent infection in the context of a contact tracing programme in England and Wales. The strategies compared were:

- TST
- IGT
- TST followed by IGT for patients with a positive TST
- no test (inform and advise only).

It was assumed that treatment followed current policy: with appropriate therapy for people diagnosed with active TB or testing positive for latent

infection, and BCG when appropriate for others. The analysis did not compare different types of skin tests or different types of IGT.

The model is a decision tree, which does not account for the dynamics of disease transmission within the population. Instead, for simplicity, it was assumed that each primary case of active disease is associated with a fixed number of secondary cases. This is probably a reasonable assumption when comparing tests with similar sensitivity, since the absolute difference in false negatives, and hence in opportunities for transmission within the community, will be small. However, estimates of the relative cost effectiveness of contact tracing *per se* are less robust and should be treated with caution.

Various assumptions were made about the epidemiology and likely concordance with testing and treatment programmes. However, it should be noted that these factors will vary with the context of contact tracing. There is also considerable uncertainty over the relative accuracy of the TST and IGT, as well as over some of the other model parameters. Whenever possible input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and GDG.

Cost-effectiveness of testing strategies in contact tracing

The base-case economic analysis suggests that the two-stage strategy (TST/IGT) is within the range usually considered cost effective, at around £26,000 per quality-adjusted life-year (QALY) gained. Compared with this, IGT is not cost effective (over £150,000 per QALY gained). TST is both less effective and more expensive than all of the other options (it is 'dominated').

Variation in optimal strategy with context of contact tracing

The results of the economic analysis were highly dependent on the context of the contact tracing scheme – with a higher-risk cohort of contacts, the expected benefits of early diagnosis of active cases, treatment of latent infection, and vaccination will be greater. Below a prevalence of about 10%, none of the testing strategies is cost effective. At intermediate levels of prevalence (between about 10% and 40%), the two-stage TST/IGT strategy is cost effective. Above 40%, IGT on its own is the most cost-effective option.

Table 13 Cost-effectiveness of diagnostic strategies

Prevalence of infection	Strategy	Cost (£)	Effect (QALYs lost)	ICER (£ per QALY gained)
0	No test	31	0.00409	–
	TST/IGT	58	0.00394	178,835
	IGT	102	0.00394	Dominated
	TST	139	0.00404	Dominated
10%	No test	191	0.02533	–
	TST/IGT	240	0.02323	23,351
	IGT	282	0.02290	126,813
	TST	314	0.02310	Dominated
20%	No test	351	0.04658	–
	TST/IGT	423	0.04252	17,575
	IGT	463	0.04185	60,073
	TST	489	0.04217	Dominated
30%	No test	512	0.06782	–
	TST/IGT	605	0.06182	15,553
	IGT	643	0.06081	38,081
	TST	664	0.06123	Dominated
40%	No test	672	0.08907	–
	TST/IGT	788	0.08111	14,522
	IGT	824	0.07976	27,132
	TST	838	0.08029	Dominated
50%	No test	832	0.11031	–
	TST/IGT	970	0.10040	13,898
	IGT	1005	0.09872	20,578
	TST	1013	0.09936	Dominated

QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. TST = tuberculin skin test. IGT = interferon gamma test

Uncertainty over optimal testing strategy for contact tracing

The results of the economic analysis were subject to a high degree of uncertainty. The results were very sensitive to assumptions about the relative accuracy of the two types of test, the risk of current and future TB in the cohort, the level of transmission to the wider population, and also to the expected net benefit of avoiding each active case of TB.

The following sections outline the updated modelling for a number of populations. However, due to an absence of evidence the following populations were not analysed: children and screening new NHS employees. For children, the almost complete absence of sensitivity and specificity information and quality of life data meant that a useful analysis could not be produced. For screening new NHS employees, there was no new data on prevalence or on the potential outcomes from latent TB resulting so any new analysis would add very little value.

Diagnosing latent tuberculosis in adults and children who are recent arrivals from highly prevalent countries

A search for cost-effectiveness studies identified five relevant papers that examined the use of IGT in this cohort of patients suspected with latent tuberculosis infection. No suitable papers were identified.

A decision model based on the previous guideline was used to compare the expected cost effectiveness of four strategies of testing for latent infection in the context of a contact tracing programme in England and Wales for adults from high prevalent countries. The strategies compared were:

- TST
- IGT
 - QFT
 - T-SPOT.TB
- TST followed by IGT (both tests)
- No test (inform and advice only)

In the model, treatment follows current policy: with appropriate therapy for people diagnosed with active TB and latent tuberculosis. The analysis did not compare different types of skin tests.

The assumptions made in the initial guideline are still applicable unless stated otherwise. One parameter that was not considered here was the age cut-off; the rationale for excluding this parameter is noted in the appendix. Whenever possible, input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and Guideline Development Group (GDG). The model considers the QALYs lost due to infection, adverse events and so on. Therefore, the interventions with the smallest QALY loss are the most effective. Throughout the analysis ICERs will either be compared to the next best option (incremental) or to a common base line (usually no test).

Using a prevalence of 30% for latent tuberculosis in the cohort group, the base case analysis is shown in Table XX. This shows that the dual strategy (TST/QFT) is within the range usually considered cost effective since the incremental cost-effectiveness ratio (ICER) is around £20,000 to 30,000 per QALY gained.

Table 14 Cost effectiveness results for new entrants from high prevalence countries

Strategy	Cost (£)	Effect (QALY loss)	ICER compared with no test (£)	ICER – incremental analysis (£)
No test	159.9	0.03334		
TST/QFT	289.8	0.02856	27,175.73	27,147.33
TST/TSPOT	316.1	0.02773	27,843.14	31,783.74
QFT	341.2	0.02684	27,892.31	28,130.62
TSPOT	386.5	0.02571	29,698.56	40,199.28
TST	457.7	0.02726	48,980.26	Dominated

QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. TST = tuberculin skin test. QFT = QuantiFERON-TB interferon gamma test. TSPOT = T-SPOT.TB interferon gamma test. IGT = interferon gamma test

Using a 'no test' strategy as the baseline for calculating the ICER for all the other strategies, we have a scenario that still results in the dual-strategy being the most cost-effective. However, all the tests are cost effective apart from the TST-alone strategy.

Contact tracing for healthcare workers

A search for cost-effectiveness studies identified one relevant paper that examined the use of IGT in the cohort of patients with suspected latent tuberculosis infection. This paper was reviewed with a quality checklist to assess its applicability and limitations. A completed checklist is available in appendix xx. Other cost-effectiveness papers were used to explore approaches to modelling strategies and to inform the structure of the model.

The economic model uses the same structure, costs and health related quality of life values as those in the adults from high prevalence countries. However, the difference is in the estimates of the test accuracy and the prevalence of LTBI in this cohort. The treatment regimen is the same. We have also assumed that diagnosing and screening for latent tuberculosis is done in an outpatient setting and therefore, costs associated with logistical challenges are not considered as well as indirect costs associated with forgone productivity. The rationale for this approach is in keeping with the NICE reference case which stipulates the use of only direct costs.

Diagnostic accuracy

The sensitivity and specificity values for this population cohort were obtained from the following study (Girardi et al. 2009) - see appendix for more details.

Table 15 Cost-effectiveness of testing strategies for contacts

Strategy	Cost (£)	Effect (QALY loss)	ICER – incremental analysis (£)	ICER from no test (£)
No test	379.9	0.0607	–	–
TST/QFT	466.5	0.0531	11,447	11,447
TST/TSPOT	496.1	0.0512	15,327	12,231
QFT	499.3	0.0527	Dominated	14,925
TSPOT	566.5	0.0507	132,616	18,660
TST	616.7	0.051	Dominated	24,412

QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. TST = tuberculin skin test. QFT = QuantiFERON-TB interferon gamma test. TSPOT = T-SPOT.TB interferon gamma test. IGT = interferon gamma test

The modelling approach is very similar to that in adults from high prevalence countries. There are many limitations to this analysis. First is the inherent dependence on the quality and estimate values for test accuracy are based on a single study (Girardi et al. 2009) with a small sample size, however, the statistical analysis (Latent Class Analysis) to estimate the diagnostic accuracy is appropriate for consideration in the analysis. In addition, because there are few studies that have addressed the diagnostic accuracy from settings that have low incidence of TB, this study was considered appropriate to generalize its applicability to this guideline. The other assumptions and limitations are similar to those in the economic model for the adults from high prevalence countries.

Immunosuppression

A search for cost-effectiveness studies identified no relevant paper that examined the use of IGT in this cohort of patients suspected with latent tuberculosis infection.

The economic model uses a similar structure to that in the 'adults from high prevalence countries' analysis. However, the difference is in the estimates of the test accuracy and the prevalence of latent TB infections in this cohort. The treatment regimen is different because of the drug interaction of TB medication especially rifampicin with antiretroviral therapy. It is clinical practice that HIV-infected patients on antiretroviral therapy with suspected

latent tuberculosis are given 6 months of isoniazid therapy.

Diagnostic accuracy

There are very few studies addressing the diagnostic accuracy of the tests in this population. Those that address the diagnostic accuracy have focused on a population based in high incidence of TB with a high prevalence of HIV (Chapman A et al. 2285-8893). Because of the lack of data on the estimates of test accuracy, assumptions were made on the most plausible values by the GDG members (see appendix for further details). These values were to reflect HIV patients with CD4 levels of ≥ 500 cells/microL. No studies were identified that have assessed the diagnostic accuracy of these tests in a HIV cohort group of 200-499 cells/microL and <200 cells/microL.

Cost effectiveness of the testing strategies

The proportion of indeterminate results associated with immunosuppression was included in the analysis. Recent studies have shown that the proportion of indeterminate results in HIV patients is highly variable (Richeldi et al. 198-204; Luetkemeyer et al. 737-42; Jones et al. 1190-95). A mean estimate of 5% was chosen to reflect the most plausible value from these studies and a sensitivity analysis assessed with a range from 1% to 10%. However, a major limitation in using these estimates is the lack of stratification in the proportion of indeterminate results with CD4 count levels.

Table 16 Cost effectiveness results in immunosuppressed patients

Strategy	Cost (£)	Effect (QALY loss)	ICER – incremental analysis (£)	ICER compared with no test (£)
No test	434	0.0864	0	0
TST/IGT	523	0.0788	11,780	11,780
IGT	622	0.0759	34,749	17,914
TST	660	0.0766	Dominated	23,061

QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. TST = tuberculin skin test. IGT = interferon gamma test

The dual strategy is still cost effective; however these results are based on assumptions of the sensitivity and specificity without supporting evidence from any studies and therefore, should be treated with the highest caution.

5.1.5 From evidence to recommendations

Interferon-gamma tests showed little evidence of being affected by prior BCG vaccination, and showed stronger correlation with exposure categories than did TST. This was shown in low prevalence groups, in household contacts, and in outbreak situations. The specificity of interferon-gamma tests seemed better, and there was less potential for false positive results. It is not possible to determine, for either TST or IGT, the rate of false negative results. Some people with false negative results will go on to develop active TB and thus reduce the cost-effectiveness of vaccination and treatment of latent TB infection.

Prospective studies in people with latent TB (as judged by positive interferon-gamma tests) found at TB contact tracing and new entrant screening, have not yet been performed to find what proportion of such persons went on to develop clinical disease.

Economic modelling was undertaken with various strategies from no action to a two-step strategy with either TST followed by interferon-gamma testing, or serial interferon-gamma tests. Of these options, the model provided most support, on grounds of cost-effectiveness, for a two-step approach with an initial TST, followed by an interferon-gamma test to confirm positivity. The GDG members also supported this because of clinical utility and feasibility.

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in Adults and children who are recent arrivals from highly prevalent countries?

The issue of generalisability of the studies to the UK population was raised and how the results could be applied to a UK setting. Evidence presented showed how a previous BCG vaccination would confound the TST results and not affect the IGT results. Health economic analysis suggested that the dual strategy was the most cost effective.

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in children?

Because of their underdeveloped immune system, children would be more

likely to develop active and more serious disease if they had latent infection. This risk is greater in the under 5's. This could lead to disability or death depending on the location of the infection. It was agreed that most paediatricians would choose to treat a high risk child if they had TST positive and IGT negative since there was no evidence to suggest that a negative IGT could completely exclude infection. The difficulty of phlebotomy and obtaining sufficient blood in children was discussed especially in the very young. Indeterminate IGT results occur more frequently in younger children. The GDG was of the view that there is increasing evidence IGT perform less well in younger children. The group also agreed that careful consideration should be given to high risk young children especially those under 5 years of age since false negative results could have substantial implications.

Which diagnostic strategy is most accurate in diagnosing latent TB in adults and children who have been in close contact with patients with active TB?

The GDG was presented with evidence showing the meta analysis of ROR for comparing IGT with TST. This was stratified by percentage BCG vaccination. Having adjusted for BCG vaccination, IGT showed a better ROR than TST. The GDG felt that although IGT seemed better from ROR the evidence was of poor quality and that recommendations should ideally be based on longitudinal studies aiming to determine positive and negative predictive values of developing active tuberculosis. The health economic analysis indicated that again the dual test was the most cost effective strategy, however, that the IGT tests were also cost effective compared to no test. Therefore, if a dual strategy is not implementable the single IGT test is appropriate.

Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients?

The GDG pointed out that it was important to differentiate the different groups of immunocompromised people as described in the full guideline¹. The group

¹ See pXX of 'Tuberculosis' (NICE clinical guideline 33). Available at www.nice.org.uk/guidance/CG33

agreed that the degree and type of immunosuppression is also important. There was general agreement that the evidence was of low quality. There was a lot of discordance between the tests in the immunocompromised population. The group discussed the stratification of some of the HIV studies by CD4 count and agreed on the basis of the evidence presented that a CD4 count below 200cells/mm³ was significantly associated with an indeterminate result. Health economic analysis indicated that all the testing strategies appeared cost effective compared to no test. However, given the challenges of conducting TST tests in immunocompromised population, the single or dual strategy testing were considered appropriate.

Summary

In the studies evaluated, IGT show a stronger correlation with exposure than TST. Much of the discordance between a positive TST and a negative IGT can be accounted for by prior BCG vaccination. The GDG agreed that in the absence of good quality longitudinal studies the relative benefit of IGT over TST in determining the need for treatment of latent infection is not certain. However the they made recommendations in populations where they considered IGT to be of clear benefit especially in cases where IGT would reduce the uncertain diagnosis of TST.

RECOMMENDATIONS

R1 To diagnose latent TB in:

Offer Mantoux testing in line with the Green Book²¹ (Department of health. Immunisation against infectious diseases-the 'Green Book' London DOH, 2006) to diagnose latent TB in:

- household contacts 5 years and older
- non-household contacts and
- adult contacts. **[new 2010]**

Those with positive results (or in whom Mantoux testing may be less reliable) should then be considered for interferon-gamma immunological testing **[2010]**

If Mantoux testing is inconclusive or positive, refer the person to a TB specialist.

[2010]

Recent arrivals from highly prevalent countries

In people 5 – 34 offer a mantoux test followed by an IGT test if positive. In those 16 and above, an IGT test alone can be used. (refer to other sections for other groups eg immunocompromised) **[new 2010]**

For under 5's use Mantoux (2TU) as initial diagnostic tests for latent tb infection. If the initial test is positive taking into account the BCG history (Green Book), then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI. **[new 2010]**

Household contacts, under 5 years of age

Use Mantoux (2TU) as initial diagnostic tests for latent tb infection. If the initial test is positive taking into account the BCG history (Green Book), then clinical assessment should be undertaken to exclude active disease and consider treatment of LTBI.

[new 2010]

If the initial Mantoux is negative then in those who are contacts of sputum smear positive disease, an IGT test should be performed after an interval of six weeks as well as repeat the Mantoux test to increase the sensitivity. If either test is positive assess and treat as above. Children under 2 years who meet the criteria in previous guideline cross reference to the algorithm on page 146 Figure 8. **[new 2010]**

Contacts

In an outbreak situation among children 5 years and older where large numbers of individuals may need to be screened a single IGT test is appropriate. **[new 2010]**

Immunocompromised

For patients with HIV and CD4 counts of less than 200 perform both an IGT test and a TST. If either test is positive assess for active TB. Consider treatment of LTBI if active disease is excluded. **[new 2010]**

For patients with HIV and CD4 counts of 200 – 500 perform an IGT test alone or an IGT 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. **[new 2010]**

For other categories of immunocompromised patients perform an IGT test alone or an IGT test with a concurrent TST. If either test is positive assess for active TB. Consider treatment of LTBI if active disease is excluded. **[new 2010]**

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 in recommendation for recent arrivals from highly prevalent countries. **[new 2010]**

Test other healthcare workers in contact with patients or clinical materials, who have not had BCG (for example, without scar, other documentation or reliable history) for latent TB infection with either Mantoux testing or interferon-gamma immunological testing. **[new 2010]**

Healthcare workers who have CD4 counts of 200–500 should be screened as in recommendation for the immunocompromised population **[new 2010]**

No further evidence has been reviewed for other groups such as:

Prisoners/prison staff - But the tests will perform as with any other adults

In hard to reach populations a single IGT test will be the most appropriate **[new 2010]**

Cross-referring: For details of people more likely to develop active TB, see section 10.2. For people with negative tuberculin skin test results, see BCG vaccination under chapter 11. For people with latent TB, see treatment of latent TB infection under section 10.1. (available at <http://guidance.nice.org.uk/CG33>)

3 Research recommendations

We have made the following recommendations for research, based on our review of evidence, to improve NICE guidance and patient care in the future.

3.1 [Topic of research question]

[Type the full question here - keep as brief as possible]

Why this is important

[Type up to 150 words explaining why the proposed research is important]

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website ([www.nice.org.uk/CG\[XX\]/FullGuideline](http://www.nice.org.uk/CG[XX]/FullGuideline)). **[Note: these details will apply to the published full guideline.]**

Quick reference guide

A quick reference guide for healthcare professionals is available from [www.nice.org.uk/CG\[XX\]/QuickRefGuide](http://www.nice.org.uk/CG[XX]/QuickRefGuide)

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from [www.nice.org.uk/CG\[XX\]/PublicInfo](http://www.nice.org.uk/CG[XX]/PublicInfo)

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about diagnosing latent TB.

5 Related NICE guidance

Published

- Tuberculosis. NICE clinical guideline 33 (2006). Available from www.nice.org.uk/CG36

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Tuberculosis: hard-to-reach groups. NICE public health guidance. Publication expected March 2012.

6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

7 References, glossary and abbreviations**7.1 References****7.2 CG33 references**

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7.4 Glossary

[Keep the use of abbreviations to a minimum, and don't include any term in the glossary or abbreviations list that does not appear in the main body of the document, and that is not specific to the topic of the guideline. Cross

reference may be made to the NICE glossary if necessary for other terms. Any necessary definitions that are not guideline specific and are not covered by the NICE glossary should be defined in the appendices rather than here. Please use definitions from the standard NICE list wherever possible.]

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8.2 *The short clinical guidelines technical team*

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

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8.5 *The Guideline Review Panel*

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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8.6 *Declarations of interest*

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

8.7 *Authorship and citation*

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

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