1 Appendix O: CG33 & CG117 Deleted sections and appendices

2 Background

2.1 Preface - 2006

Tuberculosis, or TB, is one of man’s oldest foes and for centuries among the most feared. One of the triumphs of modern medicine has been the development of vaccination and medication capable of combating this ancient disease, and it now rarely troubles the thoughts of those born into modern Western society. Yet TB remains capable of exciting occasional major concern, for example when reports of local outbreaks emerge, and this continuing wariness is appropriate. Although TB notifications fell steadily for most of the twentieth century, this fall was not maintained in the last decade. Some racial groups have much higher TB incidence than others and, irrespective of ethnicity, the disease is more common in those in deprived social circumstances. Moreover, there are huge reservoirs of TB elsewhere in the world, with the additional spectre of growing pockets of infection resistant to available treatment. For all these reasons it is still necessary to focus attention on the optimum management of TB, and that is the purpose of this guideline.

The guideline has been commissioned by NICE as a successor to the British Thoracic Society’s TB guidelines, which have been used with great benefit for many years as the principal source of advice on TB management in the UK. The scope of the guideline is unusually wide, and we were obliged to divide the work between two separate guideline development groups, one covering diagnosis and management, the other prevention and control. Both groups used what has become our standard methodology, first identifying the key aspects of the disease and then searching out and appraising the bestother sources, in particular advice from the Joint Committee on Vaccination and Immunisation.

Although TB will not affect the majority of the UK population, some of the recommendations in the guideline will do so. For years, all secondary school children have been given Bacille Calmette-Guèrin (BCG) vaccination through the schools programme. The current epidemiology of TB in the UK suggests that this is inappropriate and that vaccination efforts should be targeted towards those most at risk, with a change in emphasis towards offering BCG to neonates. This will bring challenges for implementation, and this is not the only recommendation in the guideline which will do so. Directly observed therapy is not necessary as a routine, but is appropriate in those unlikely to adhere to the required treatment regime. This will necessitate careful risk assessment. The guideline also recommends that all people with TB should have a key worker to help educate and promote treatment adherence. These measures are important to the individuals with TB and to the wider community since effective management of patients and contacts is critical to avoiding the development and spread of drug-resistant TB.

The two guideline development groups have each had to meet their own challenges in the development of this document. Their sincere desire to get the best for patients with TB has been evident to those of us involved in the administration of the project, and we are grateful to them for this commitment as well as their expertise. Particular thanks are due to the clinical advisor, Peter Ormerod, who sat on both groups. I believe their efforts have resulted in a comprehensive and authoritative guideline, which should serve the NHS well in the short and medium term and provide a firm basis for future development and improvement in TB management.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

2.2 Preface – 2011

The 2006 guideline was reviewed for update in 2009, leading to a partial update that resulted in new recommendations for the diagnosis of latent TB (chapter 5).

In 2006 there was a lack of evidence available on the diagnostic utility of interferon-gamma tests (IGTs) and it was noted that there would need to be a partial update of the guideline to make recommendations on the use of IGTs for diagnosis of latent TB once additional evidence came available. The perception in 2006 was that this additional scientific evidence would have emerged by the time the guideline was due for review. There was also a concern that practice would have moved on and was then not in line with the recommended strategies. NICE concluded that because IGT is now commonly used the guideline should be updated but be only in the section(s) relevant to the use of IGT in the diagnosis of latent TB. Therefore, in October 2009 the Department of Health formally asked NICE to produce a short clinical guideline on interferon-gamma immunological testing for diagnosing latent TB (partial review of CG33).

3 Related NICE guidance

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.

3.1 Key messages of the guideline

3.2 Key priorities for implementation

A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB[1] in:

- adults not known to be HIV positive A
- adults who are HIV positive B
- children. B

This regimen is referred to as the 'standard recommended regimen' in this guideline.

Patients with active meningeal TB should be offered:

- a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP)
- a glucocorticoid at the normal dose range
  – adults: equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg A
  – children: equivalent to prednisolone 1–2 mg/kg, maximum 40 mg D(GPP)

[1] TB affecting the lungs, pleural cavity, mediastinal lymph nodes or larynx.

with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation.

Use of directly observed therapy (DOT) is not usually necessary in the management of most cases of active TB. A

All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

- street- or shelter-dwelling homeless people with active TB B
- patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)

The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)

New entrants[2] should be identified for TB screening from the following information:

- port of arrival reports D(GPP)
- new registrations with primary care B
- entry to education (including universities) D(GPP)
- links with statutory and voluntary groups working with new entrants. D(GPP)

Neonatal Bacille Calmette-Guèrin (BCG) vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. D(GPP)

Primary care organisations with a high incidence of TB[3] should consider vaccinating all neonates soon after birth. D(GPP)

[2] New entrants are defined as people who have recently arrived in or returned to the UK from high-incidence countries, with an incidence of more than 40 per 100,000 per year, as listed by the Health Protection Agency (go to www.hpa.org.uk and search for 'WHO country data TB').

3.3 Algorithms

In line with NICE's digitalisation strategy, the algorithms in the full version of the guideline and in the NICE quick reference guide supporting the updated guideline have now been replaced by a NICE pathway. The pathway is an interactive web-based tool for health and social care professionals providing fast access to the NICE guidance and associated products.

[3] Incidence of more than 40 per 100,000, as listed by the Health Protection Agency; go to www.hpa.org.uk and search for 'tTB rate bands'

Audit criteria

Table 4: Audit criteria

• **Key priority for implementation**	• **Criteria**	• **Exception**
A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in: • adults not known to be HIV positive A • adults who are HIV positive B • children. B This regimen is referred to as 'standard recommended regimen' in this guideline.	a) Process measure: percentage of patients with active TB receiving rifampicin, isoniazid, pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Outcome measure: percent cure and completion rate.	Contraindications, meningeal TB, CNS involvement, drug resistance.
Patients with active meningeal TB should be offered:	a) Process measure: percentage of patients with meningeal TB receiving rifampicin, isoniazid,	Contraindications, drug resistance.

• a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP) • a glucocorticoid at the normal dose range • adults – equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg A • children – equivalent to prednisolone 1–2 mg/kg, maximum 40 mg D(GPP) with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation.	pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Process measure: percent receiving/having received glucocorticoids. c) Outcome measure: percent cure and completion rate (12 months).	

Use of DOT is not usually necessary in the management of most cases of active TB. A All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular: a) street- or shelter-dwelling homeless people with active TB B b) patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)	Process measure: percentage of patients with active TB who are treated with DOT.	
The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)	Process measure: percentage of TB patients in possession of current correct key worker's details.	Hospital inpatients.

New entrants should be identified for TB screening from the following information: • port of arrival reports D(GPP) • new registrations with primary care B • entry to education (including universities) D(GPP) • links with statutory and voluntary groups working with new entrants. D(GPP)	a) Process measure: percentage of new entrants referred or recorded who are contacted for screening. b) Process measure: percent of new entrants contacted for screening, who complete the screening. c) Process measure: percent of new entrants contacted for screening, who are referred to secondary care TB teams.	a) Any people sought but not found b) Any people sought but not found Loss to follow-up, including not returning for Mantoux test to be read, chest X-ray to be taken, treatment for latent TB infection to be started, etc.

Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. D(GPP) Primary care organisations with a high incidence of TB[4] should consider vaccinating all neonates soon after birth. D(GPP)	a) Process measure: percentage of neonates vaccinated with BCG. b) Process measure: percentage of eligible neonates vaccinated with BCG.	Informed refusal, HIV.	

[4] As defined by the Health Protection Agency; go to www.hpa.org.uk and search for 'tuberculosis rate bands'

4 Aims and principles of tuberculosis care

In 2005, the Chief Medical Officer's TB Action Plan, *Stopping tuberculosis in England,*{2} set out essential tasks for reversing the increase in tuberculosis incidence and ensuring high-quality care and public health. The very first task in the action plan is the production and wide availability of information and educational materials on tuberculosis, and it specifies that they should be 'multi-lingual and culturally appropriate'. The GDG enthusiastically support this, and therefore this guideline recommends the availability of such information and materials throughout the NHS, tailored to meet the needs of different languages and cultures.

As part of the action for 'excellence in clinical care', the action plan calls for a named key worker assigned to every patient, and that they should work closely with other agencies such as housing and social services to achieve improved outcomes. The GDG acknowledged the great importance of achieving a care plan which makes the successful completion of treatment of active or latent TB as easy as possible for the person receiving the treatment, and so this guideline has provided recommendations to support these aims and those of the Chief Medical Officer.

Where scientific evidence supports it, the parts of this guideline addressing prevention and control (chapters 11–13) include recommendations for aspects of service organisation as well as for individual teams of healthcare professionals. The guideline attempts to focus NHS resources where they will effectively combat the spread of TB, and in some sections deals with high- and low-incidence areas separately.

The GDG acknowledge the importance of honest and positive communication concerning TB in overcoming stigma, poor concordance and misinformation about the condition and recognising socio-economic factors. Healthcare teams caring for people with, or at risk from, TB will need to work with non-NHS agencies to ensure a seamless service that promotes detection, concordance and cure.

4.1 Current service organisation

The review of current services (see Appendix G for more details) identified four basic service models in use.

1. Centralised

In this model TB nurses are based in a central unit, usually the health protection unit (HPU), and are responsible for all TB services including contact tracing and screening in a defined area. This model is used in areas with high and low incidence. It allows all TB services in the area to be coordinated and standardised. A variant which resembles the specialist hospital-based model (see below) is seen in some low-incidence small geographical areas, where a few nurses based in local hospitals or community clinics can achieve high volumes of specialisation.

2. Central with satellites

This is a variation of the first model; there are nurses at HPU level and other clinics alongside such as specialist new entrant and screening clinics. It may include generalist clinics in hospitals. In some cases the HPU nurse may coordinate all TB services, including contact tracing using satellite clinics. In this model, the HPU nurse may identify and send individuals for contact tracing to non-specialist health visitors in the community. It allows for coordination of services in areas of large geographical distance.

3. General hospital/community model

General respiratory nurses see people with TB in this model, sometimes with an additional nurse led clinic for contact tracing, BCG or new entrant screening. This model is used in areas of lowest incidence. Nurses may also be based in the community, and may run screening clinics.

4. Specialist hospital-based model

TB nurses are based in clinics in local hospitals or specialist community screening units but have functions for the surrounding community. There may a larger HPU-based network connecting these nurses. This model is seen in London and other areas with a relatively high TB incidence.

5. *Staffing levels*

The review aggregated staffing levels across HPUs to account for apparent imbalances between different types of clinic within each local area. The scatter plot of notifications against whole time equivalent (WTE) nursing staff (Figure 1) shows a clear correlation (Spearman's ρ =0.85), which is perhaps an indication that services are now in line with the British Thoracic Society (BTS) code of practice's{6} recommendations. These stated that nursing staff should be maintained at one WTE nurse (or health visitor) per 50 notifications per year outside London, and 40 per year in London. The review reflects a development in TB services since the audit conducted in 1999.{7} However, notification rates continue to increase in England and Wales, and it would seem that the challenge for those planning TB services is to see this increase in resources targeted effectively at those activities for which the evidence demonstrates benefit. This guideline aims to inform those decisions wherever possible.

Across HPUs, the WTE rate is roughly 1 per 40 notifications. London HPUs have the highest caseload and hence the highest WTE.

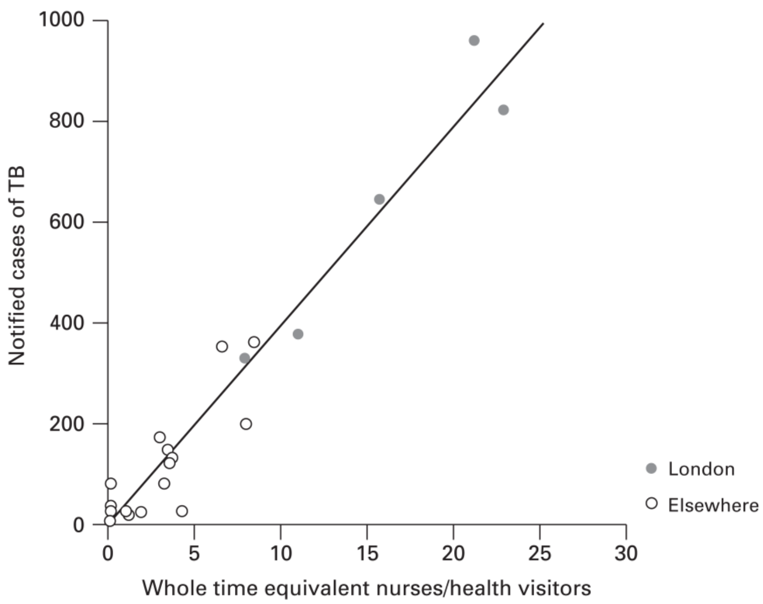


Figure 1: Staffing levels of nurses/health visitors vs notified cases of TB. The line represents one whole time equivalent per 40 cases

6. Other information on current services

The following aspects of the review of current services are reported in this guideline (details of the methods employed are given in Appendix G):

- dedicated TB clinics (section 6.1)
- nurse-led follow-up clinics (section 6.1)
- specialist HIV/TB clinics (section 6.1)
- specialist paediatric TB clinics (section 6.1)
- directly Observed Therapy (DOT) (section 8.2)
- free prescriptions (section 8.3)
- measures to improve adherence (section 8.3)
- outreach (section 8.3)
- incentives for attending clinic (section 8.3)
- treatment of latent TB infection (sections 10.2 and 12.2)
- negative pressure facilities (section 9.3)
- BCG clinics (section 11)
- neonatal BCG (section 11.1)
- high risk group screening (section 12)
- contact tracing clinics (section 12.2)
- *Mycobacterium bovis* (section 12.3)
- specialist new entrants clinics (section 12.7)
- prison services (section 13.3).

4.2 Communication and patient information

During the development of the guideline, patient and carer representatives on the GDG highlighted these suggestions:

- a single national source of high-quality TB information in relevant languages, and formats for vision- or hearing-impaired people
- TB services to assess local language and other communication needs, and accordingly make information from the national source available locally

- clear discussion between healthcare professionals, people with (or at risk from) TB and their carers about tests, treatment, contact tracing and infection control measures, to enable understanding
- people with both HIV and TB to be provided with information about the different specialties who may provide care during and after their treatment for TB
- contact tracing explained and handled sensitively to avoid misunderstanding and stigma
- information set out so as not to medicalise the patient
- TB services providing each patient completing anti-tuberculosis treatment with clear 'inform and advise' information

The first task for improving TB services to be named in the Chief Medical Officer's TB Action Plan{2} is to 'produce multilingual and culturally appropriate public information and education materials for national and local use and make them widely available'. See also section 2.5 above, for details of the National Knowledge Service.

Communication and information provision are an important part of efforts to successfully reverse the increase in TB incidence in England and Wales. Information resources for TB address the following aims:

- achieving earlier diagnosis through general public awareness of symptoms
- combating stigma and myths, which may delay presentation and impede contact tracing
- helping to achieve concordance and treatment completion through awareness of different treatment options, awareness of side effects, and the importance of adhering to the treatment regimen
- relieving anxiety about infection control measures in healthcare settings, family life and the workplace.

Recommendations are therefore given under section 6.2.

4.3 HIV co-infection

This guideline discusses risk assessments for HIV, and gives recommendations for treatment of active and latent TB in co-infected people. However, the specialised guidelines in the UK, at the time of going to press, are those from the British HIV Association,{8} and readers should be aware of these when considering care of any patient who is known to be, or is possibly, co-infected.

5 The Guideline: Diagnosis and Treatment

5.1 Diagnosis

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 TB in adults and children who are recent arrivals from highly prevalent countries?

Evidence review

Of the ten studies included:

- three were conducted in Germany (Diel et al. 2006; Diel et al. 2008; (Anon)
- two in the Netherlands (Franken et al. 2007; Kik et al. 2009)
- two in the United States (Brodie et al. 2008; Porsa et al. 2006)
- one in Italy (Carvalho et al. 2007)
- one in Norway (Winje et al. 2008)
- one in Switzerland (Janssens et al. 2008).

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

- ratio of odds ratios (ROR). In this guideline ROR is mathematically defined as (odds of positive IGT in a high-risk area divided by the odds of a positive test in a low-risk area) divided by (odds of a positive Mantoux test in a high-risk area divided by a positive Mantoux test in a low-risk area)

Table 5 Diagnosis of latent TB infection in foreign-born people and in people arriving from high-prevalence countries

Study[1]	Population group (by prevalence or place of birth or racial group)	Odds ratio (Mantoux test ≥ 5 mm)	Odds ratio (Mantoux test ≥ 10 mm)	Odds ratio (Mantoux test ≥ 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	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	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	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	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	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) Mantoux test ≥ 5 mm	Odds ratio (95%CI) Mantoux test ≥ 10 mm	Odds ratio (95%CI) Mantoux test ≥ 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	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	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	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 reference test means the measures of effect of sensitivity and specificity cannot be determined. Inconsistencies were different studies used different types of Mantoux test. Imprecision was not measurable.

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

	OVERALL						BCG VACCINATED						NON BCG VACCINATED											
	Induration						Induration						Induration											
Studies	5 mm		10 mm		15 mm		5 mm		10 mm		15 mm		5 mm		10 mm		15 mm		Limitations	Inconsistensy	Indirectness	Imprecision	Other Considerations	Quality
	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa						
Porsa et al. 2006	90 %(87–93 %)	0.25(0.1–0.41)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	very low
Franken et al. 2007	ND	ND	82%	0.19	92.30 %	0.24	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	very low
Carvalho et al. 2007	ND	ND	71%	0.37	ND	ND	ND	ND	0.28(0.10–0.77)a OR	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	Low
Brodie et al. 2008	64 %(54–74 %)	0.33 (0.19–0.48)	ND	ND	ND	ND	56% (43–68)	0.22 (0.06–0.37)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	Y	-	Y	very low

Janssens et al. 2008	60.70%	0.24(0.14–0.33)	63.60%	0.27(0.16–0.38)	63.90%	0.19(0.09–0.30)	ND	ND	ND	ND	ND	ND	78.40%	0.47(0.20–0.74)	76.50%	0.41(0.14–0.68)	78.40%	0.28(0.03–0.54)	N	N	N	-	Y	Low
Nienhaus et al. 2008	74.80%	0.26	84.20%	0.37	89.80%	0.33	ND	0.12	ND	0.28	ND	ND	ND	0.5	ND	0.54	ND	0.3	N	N	N	-	Y	Low
Diel et al. 2006	ND	ND	ND	ND	ND	ND	38.90%	0.08	77.10%	0.35	ND	ND	89.50%	0.58	94.10%	0.68	ND	ND	N	N	N	-	Y	Low
Winje et al. 2008	72%	0.43(0.37–0.49)	79%	0.51(0.45–0.57)	78%	0.39(0.32–0.47)	ND	ND	ND	0.45(0.37–0.52)	ND	ND	ND	ND	ND	0.66(0.56–0.77)	ND	ND	Y	N	N	-	Y	Low
Diel et al. 2008	69.20%	0.276	ND	ND	ND	ND	44.20%	0.119	ND	ND	ND	ND	90.70%	0.616	ND	ND	ND	ND	Y	N	N	-	Y	low

Table 6 Degree of concordance between Mantoux tests and IGT and corresponding threshold for Mantoux test

Evidence statements

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

Low quality evidence from three studies with 2351 participants showed that BCG vaccination decreased both concordance and agreement between the assay results of IGT and Mantoux tests.

Low quality evidence from one study showed IGTs were more likely to detect progression to active TB than Mantoux tests 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 Mantoux tests were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for Mantoux test thresholds of 10 mm and 15 mm and 2.8% and 3.3% for QFT and T-SPOT. Negative predictive values for the Mantoux test thresholds of 10 mm and 15 mm, and QFT and TSPOT were 100%, 99.3%, 98% and 98.3% respectively.

Very low quality evidence from four studies with 1636 participants showed very low levels of concordance between the Mantoux and IGTs in BCG-vaccinated populations

Health economics – diagnosing latent TB in adults and children who are recent arrivals from high prevalence countries

The published reviews of test accuracy identified were Pai et al. (2008) and Diel et al. (2010). Both use active TB as a proxy for the calculation of sensitivities and specificities. Because there was no differentiation between IGTs, midpoints were used for the accuracy estimates.

The base-case analysis is shown in table 7. It used a prevalence of 30% for latent TB in the cohort group. These results demonstrate that Mantoux tests/IGT and IGT are associated with ICERs which are just under £30,000 per QALY. These estimates are within a range that means NICE requires further consideration of the various input parameters before a decision can be made.

Table 7 Cost-effectiveness results for new entrants from high prevalence countries

Strategy	Cost	Effect (QALY loss)	ICER per QALY gained compared with no test	Net monetary benefit (£20,000 per QALY)
Pai et al. 2008				
No test	£316	9.98686	-	-
Mantoux test/IGT	£403	9.99015	£26,641	−£22
IGT	£452	9.99156	£29,043	−£43
Mantoux test	£458	9.99107	Dominated	Dominated
Diel et al. 2010				
No test	£316	9.98686	-	-
Mantoux test/IGT	£387	9.98925	Extended dominance	Extended dominance
IGT	£451	9.98994	£29,211.57	−£43
Mantoux test	£442	9.99150	Extended dominance	Extended dominance
ICER = incremental cost-effectiveness ratio IGT = interferon gamma test. QALY = quality-adjusted life year.				

A number of sensitivity analyses were run and are presented in appendix L. The prevalence of latent TB in this population and the transformation rate of latent TB to active TB are presented in tables 8 and 9 because the GDG considered them to be two of the key parameters in the model. The net monetary results at £20,000 per QALY are presented in table 8.

Table 8 Net monetary benefits at £20,000 per QALY gained for different prevalence rates and test accuracy sources for screening people from high prevalence countries

Prevalence	Mantoux test/IGT	IGT	Mantoux test
Pai et al. 2008			
0.01	−34	−73	Dominated
0.05	−32	−69	Dominated
0.1	−30	−64	Dominated
0.15	−28	−58	Dominated
0.2	−26	−53	Dominated
0.25	−24	−48	Dominated
0.3	−22	−43	Dominated
Diel et al. 2010			
0.01	−34	−74	Dominated
0.05	−33	−69	Dominated
0.1	−31	−64	Dominated
0.15	−30	−60	Dominated
0.2	−27	−53	Dominated
0.25	Extended Dominated	−48	Extended Dominated
0.3	Extended Dominated	−43	Extended Dominated
IGT = interferon gamma test. QALY = quality-adjusted life year.			

Table 9 Net monetary benefits at £20,000 per QALY gained for different transformation rates and test accuracy sources for screening people from high prevalence countries

Latent TB to active TB	Mantoux test/IGT	IGT	Mantoux test
Pai et al 2008			
0.01	-60	-97	Dominated
0.05	-9	-24	Dominated
0.1	55	66	Dominated
0.15	119	157	Dominated
0.2	183	247	Dominated
0.25	247	338	Dominated
0.3	311	428	Dominated
Diel et al 2010			
0.01	Extended dominance	-97	Extended dominance
0.05	Extended dominance	-15	Extended dominance
0.1	Extended dominance	67	Extended dominance
0.15	Extended dominance	149	Extended dominance
0.2	Extended	231	Extended

	dominance		dominance
0.25	Extended dominance	334	Extended dominance
0.3	Extended dominance	416	Extended dominance
IGT = interferon gamma test. QALY = quality-adjusted life year. TB = tuberculosis.			

These results suggest that as the prevalence of TB and the conversion rate of TB increase the tests (Mantoux test/IGT and IGT alone) will be cost effective. IGT appears to be the optimum choice based on cost effectiveness. However, the results indicate that relatively small differences in either the prevalence or the transformation rate could result in Mantoux test/IGT being the optimum choice. In addition, the deterministic ICER per QALY gained for Mantoux test/IGT suggests it is a cost-effective option.

Evidence to recommendations

The issue of generalisability of the studies to the UK population was raised as well as how the results could be applied to a UK setting. It was agreed that the studies had similar settings and prevalence figures to the UK. The GDG noted that IGT was being used in certain UK practices. The evidence presented was of low quality but it showed how a previous BCG vaccination would confound the Mantoux test results and not affect the IGT results. The GDG felt that good quality evidence to predict active TB in the future was required.

Evidence to recommendations – health economics (people who have arrived from high-prevalence countries)

Health economic analysis indicated that none of the tests were associated with ICERs of below £20,000 per QALY gained. However the GDG considered that the mean rate of transformation from latent TB to active TB was an underestimate and that the true rate was closer to 16% over 15 years; evidence from Kik et al. (2010) suggested equivalent rates of close to 3% over 2 years. At estimates this high, IGT alone is the most cost-effective option, followed by the Mantoux test/IGT dual strategy. The GDG considered that while IGT alone appeared to be the most cost-effective option, the dual strategy should remain as an alternative because there was significant uncertainty in the point estimates, it was a less expensive strategy that would be more effective in low incidence areas and, in particular, there were still issues over the operation of the tests and intersubject variability.

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 to 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
  - casual.

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 TB was performed from six studies (Brock et al. 2004; Chun et al. 2008; Hansted et al. 2009; Higuchi et al. 2009; Lighter et al. 2009; Okada et al. 2008).

There were two longitudinal studies (Higuchi et al. 2007; Higuchi et al. 2009) that followed up participants to investigate the development of active TB.

Five studies (Anon ; Brock et al. 2004; Chun et al. 2008; Connell et al. 2006; Okada et al. 2008) looked at the concordance between IGTs and Mantoux tests.

Evidence statements

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

Low quality evidence from two studies that followed 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 with a Mantoux test 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 a low-to-moderate level of concordance between IGTs and Mantoux tests 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 IGTs and Mantoux tests (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.

Evidence to recommendations

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 children aged under 5 years.This could lead to disability or death depending on the location of the infection. The GDG observed that the evidence presented that determined the negative predictive values of the tests was of very low quality. It also felt that the generalisability of those studies could be an issue especially with regard to the BCG vaccination program in Japan. It was agreed that most paediatricians would choose to treat a high-risk child if they had a positive Mantoux test and negative IGT because there was very limited evidence to suggest that a negative IGT could completely exclude infection. The difficulty of phlebotomy and obtaining enough blood in children was discussed, generally in those under five years of age and especially when they are under two years. Indeterminate IGT results occur more frequently in younger children. The GDG was of the view that IGTs perform less well in younger children. The group also agreed that careful consideration should be given to high-risk young children, especially those aged under 5 years because false-negative results could have substantial implications.

Table 10 Diagnosis of latent TB in children

Study	Results[1] (IGT versus Mantoux tests in children aged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Meta-analysis (six studies) (Brock et al. 65–9;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 Mantoux test.	Y	Y	N	-	N	Low

[1] Outcomes were associations between graded exposure and positive test.

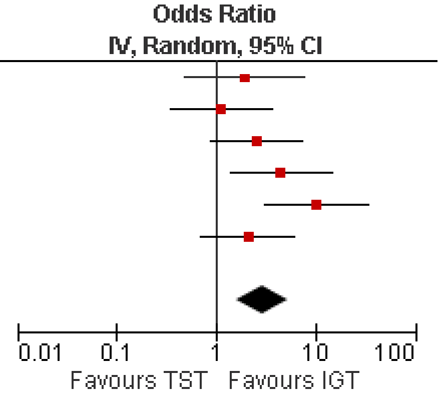
Limitation was the lack of a reference test meaning the measures of effect of sensitivity and specificity could not be determined. Inconsistency was the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable.

CI = confidence interval. IGT = interferon gamma test. ROR = ratio of odds ratios.

Figure 2 **Forest plot of meta-analysis of IGT and Mantoux test results based on high-risk and low-risk exposure**

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Brock et al 2004(1434)	0.6576	0.7124	85	85	13.3%	1.93 [0.48, 7.80]
Chun et al 2008 (276)	0.1137	0.6096	71	71	16.3%	1.12 [0.34, 3.70]
Hansted et al 2009 (3427)	0.9398	0.5417	97	97	18.9%	2.56 [0.89, 7.40]
Higuchi et al 2009(164)	1.4986	0.6008	313	306	16.7%	4.48 [1.38, 14.53]
Lighter et al 2009 (282)	2.3114	0.6039	174	174	16.5%	10.09 [3.09, 32.95]
Okada et al 2008(393)	0.7371	0.556	195	195	18.3%	2.09 [0.70, 6.21]
Total (95% CI)			**935**	**928**	**100.0%**	**2.86 [1.56, 5.23]**

Heterogeneity: Tau² = 0.21; Chi² = 7.94, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 3.40 (P = 0.0007)



Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a reference test. 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]

CI = confidence interval. IGT = interferon gamma test. OR = odds ratio. ROR = ratio of odds ratios. SE = standard error. See appendix L for definitions of high and low risk.

Table 11Diagnosing latent TB in children (predicting development of active TB)

Study	Results[1] (IGT versus Mantoux test in children aged 8–16 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Two studies (Higuchi et al. 88–92;Higuchi et al. 352–7)	281 children with negative IGT but positive Mantoux test 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%	Y	N	N	-	N	Moderate
[1] Outcome was prognostic value of IGT in predicting the subsequent development of potential active TB. Imprecision was not measurable. Limitations were defined as number of participants too few and follow-up too short for a precise result to be determined. BCG = Bacille Calmette-Guerin. IGT = interferon gamma test; TB = tuberculosis.							

Table 12 Diagnosis of latent TB in children (agreement between tests)

Study	Results (IGT versus Mantoux test in childrenaged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Five studies (Connell et al. 616–20;Connell et al. e2624;Brock et al. 65–9;Chun et al. 389–94;Okada et al. 1179–87)	Concordance between IGT and Mantoux tests as measured by kappa values ranged from 0.19 to 0.866	Y	Y	N	–	N	Low
Outcome was concordance between Mantoux test and IGT. Limitation was the lack of a reference test therefore sensitivity and specificity could not be determined. Inconsistency was that the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable. IGT = interferon gamma test. TB = tuberculosis.							

Diagnosis of latent TB in people who are immunocompromised

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB in people who are immunocompromised?

Evidence review

Of the 16 papers selected:

- five papers (Balcells et al. 2008; Jones et al. 2007; Luetkemeyer et al. 2007; Mandalakas et al. 2008; Talati et al. 2009) looked at people with HIV. The paper by Mandalakas et al. (2008) also had a children's population.
- seven papers (Bartalesi et al. 2009; Cobanoglu et al. 2007; Matulis et al. 2008; Ponce de et al. 2008; Shovman et al. 2009; Soborg et al. 2009; Vassilopoulos et al. 2008) looked at participants who had rheumatoid arthritis, or rheumatic or inflammatory disease
- one study (Richeldi et al. 2009) combined people with HIV, who have had a liver transplant and who have haematological malignancy
- one paper (Manuel et al. 2007) looked at participants with chronic liver disease
- one paper (Piana et al. 2006) investigated patients in the haematology department who were immunosuppressed
- one (Schoepfer et al. 2008) looked at people with Crohn's disease and ulcerative colitis

Table 15 Diagnosis of latent TB in patients who are immunocompromised

Study	Results (discordance between Mantoux test 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. 1190–5;Mandalakas et al. 417–23)	Overall discordance 0– 29.7%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 1.8–28.6%						
	Mantoux test negative:IGT positive discordance 0–29.7%						

Limitations: The lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not 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 difficult because the performance of the tests depended on the immunocompetence of the participants.

IGT = interferon gamma test TB = tuberculosis.

Table 16 Diagnosis of latent TB in children who are immunocompromised

Study	Results (discordance between Mantoux test and IGT in 23 children with HIV and mean age 4.4 years (range 1.1–11.1 years)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
One study Mandalakas et al. 417–23	Overall discordance 0–39.1%	Y	N	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 13–25%						
	Mantoux test negative:IGT positive discordance 0– 39.1%						

Limitations were that the lack of a reference test meant 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 difficult because the performance of the tests depends on the immunocompetence of the participants.

IGT = interferon gamma test. TB = tuberculosis.

Table 17 Diagnosis of latent TB in people who are immunocompromised (indeterminate results)

Study	Results (indeterminate IGT results in people with HIV)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Three studies Luetkemeyer et al. 737–42;Talati et al. 15;Jones et al. 1190–95	1.83–17.87%	Y	Y	N	–	Y	Low
	Odds ratio for indeterminate results adjusted for CD4 count: below 100 cells /mm³ 4.8 (95% CI 1.55 to 4.75), 34.81 (95% CI 7.98 to 151.89) below 200 cells/mm³ 3.6 (95% CI 1.9 to 6.8), 47.58 (95% CI 5.89 to 384.5)	Y	Y	N	-	Y	Low
Limitations were that the lack of a reference test 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 difficult because the performance of the tests depends on the immunocompetence of the participants. CI = confidence interval. IGT = interferon gamma test. TB = tuberculosis.							

Table 18 Diagnosis of latent TB in people with rheumatoid arthritis who are immunocompromised

Study	Results (discordance between IGT and Mantoux test in 1121 people)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Seven studies in people with rheumatoid arthritis (Vassilopoulos et al. 1271–6;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%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 5.9–47.5%						
	Mantoux test negative, IGT positive discordance 1.6–23.7%						
Limitations were that the lack of a reference test 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. TB = tuberculosis.							

Table 19 Diagnosis of latent TB in people who are immunocompromised (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 Mantoux test 0.74 (95% CI 0.32 to 1.72); RR with Mantoux test 0.4(95% CI 0.1 to1.0)	Y	Y	N	-	Y	Low
	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 Mantoux test 0.75 (95% CI 0.32 to 1.77); RR with Mantoux test 1.3 (95% CI 0.7 to 2.3) RR Mantoux test = 1.5 (95% CI 0.7 to 2.9)						
Limitations were that the lack of a reference test 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. CI = confidence interval. IGT = interferon gamma test. OR = odds ratio. RR = relative risk. TB = tuberculosis							

Table 20 Diagnosis of latent TB in people with haematological conditions who are immunocompromised

No of studies	Results (discordance between IGT and Mantoux test in 380 people with haematological conditions)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
3 studies (Piana et al. 31–4;Manuel et al. 2797–801; Richeldi 2009 et al. 198–204)	Overall discordance 9–32.2%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 2.6–8.5%						
	Mantoux test negative:IGT positive discordance 6.4–29.6%						

Limitations were that the lack of a reference test 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.

IGT = interferon gamma test. TB = tuberculosis.

Evidence Statement

Low quality evidence from five studies showed that the level of discordance between IGTs and Mantoux tests in 973 adults with HIV ranged from 0% to 29.7% for negative Mantoux tests/positive IGTs and 1.8% to 28.6% for positive Mantoux tests/negative IGTs.

Low quality evidence from one study showed that in 23 children with HIV (mean age of 4 years) the positive Mantoux tests/negative IGTs discordance ranged from 13% to 25% and negative Mantoux tests/positive IGTs discordance ranged from 0 to 39.1% similar overall discordance

Low quality evidence from three studies showed that the rate of indeterminate results from an IGT test in 837 people with HIV ranged from 1.83% to 17.87%. The rate of indeterminate results was significantly higher in those with a CD4 count below 200cells/mm^3.

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

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 negative Mantoux tests/positive IGTs, and 2.6% and 8.5% for positive Mantoux tests/negative IGTs.

Evidence to recommendations

The GDG pointed out that it was important to differentiate the groups of people who were immunocompromised. The group agreed that the degree and type of immunosuppression was 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, but in general IGTs may identify more truly positive latent TB infections than Mantoux tests but the value of such tests varies with the nature and the degree of immunosuppression. 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/mm^3 was significantly associated with an indeterminate result. The group also strongly felt that people with HIV who have a CD4 count of 500cells/mm^3 or more should be tested in the same way as people who are immunocompetent because the tests would perform in a similar way in these two groups of people. Evidence that looked at the effect specific anti-TNFalpha medications had on the diagnosis of latent TB was not identified.

Evidence to recommendations – Health economics (immunosuppresion)
No health economic modelling was conducted in this patient group. However the modelling for contacts and people from high prevalence countries indicated that high rates of transformation from latent TB to active TB and worse outcomes would all result in improved cost-effectiveness estimates for the testing strategies.

5.2 Diagnosing active tuberculosis

Signs and symptoms of non-respiratory TB
Tuberculosis can affect nearly every non-respiratory site, sometimes with a combination of respiratory and non-respiratory sites, or single or multiple non-respiratory sites.{22} As with respiratory tuberculosis, there can be systemic and site-specific symptoms. Weight loss is particularly associated with disseminated (including miliary) and gastrointestinal tuberculosis. Fever and night sweats are common in some non-respiratory sites of disease (disseminated, including miliary, and gastrointestinal TB), but are not common in others (peripheral lymph nodes, skin, bone and joint, genitourinary TB). Tuberculosis has to be considered in the differential diagnosis of an unexplained fever, particularly in those born abroad and/or in ethnic minority groups.

Because of the multiplicity of potential sites of non-respiratory TB, suggestive symptoms are considered site by site.

Signs and symptoms of lymph node TB
Nearly half of all non-respiratory TB in England and Wales occurs in peripheral lymph nodes, mainly cervical.{26},{27} The nodal enlargement in TB is usually gradual and painless, but can be painful if rapid. The usual absence of erythema and warmth makes the classical 'cold abscess'. The nodes originally are discrete and firm, but may later mat together and become fluctuant as necrosis develops, which can discharge through the skin with sinus formation and superficial ulceration.

Persistent lymphadenopathy of over four weeks duration in people other than white UK-born should be regarded as TB until proven otherwise and investigated appropriately.

Signs and symptoms of bone and joint TB

Bone and joint TB accounts for some 10–15% of non-respiratory disease, with approximately 50% in the spine, and 50% in a wide range of other bones and joints.{28},{29}

With spinal disease pain is the commonest symptom, and may be accompanied by local tenderness or slight kyphosis. Grosser kyphosis occurs when disease has progressed. Paraspinal abscesses can develop and may present as a loin mass, or as a psoas abscess pointing below the groin or causing psoas spasm with hip flexion. Compression on spinal nerve roots can mimic abdominal pathology. Extradural abscess or spinal collapse and subluxation can lead to sensory and motor symptoms involving the legs and sphincters due to spinal cord compression. Back pain and/or neurological signs should have an infective process in the differential diagnosis, particularly in ethnic minority groups.

A wide range of other joints can be involved. TB should be included in the differential diagnosis of unusual bone and joint lesions, particularly of an isolated lesion or a mono-arthritis in an ethnic minority group.

Signs and symptoms of gastrointestinal TB

This form of disease, as with nearly all other non-respiratory sites, is much commoner in ethnic minority groups. The gastrointestinal tract can be involved anywhere along its length, but peri-anal and upper gastrointestinal sites are uncommon (3% of gastrointestinal TB).{30} Series in both the developing{31} and developed world{32} show approximately one third of cases present acutely simulating abdominal emergencies and two thirds with a more gradual onset. Of the cases with an acute onset, approximately one half have right iliac fossa pain simulating acute appendicitis and the other half acute intestinal obstruction. Of those with a more gradual onset of symptoms, fever and malaise, abdominal pain and weight loss are the commonest described symptoms,{32} being found in 72%, 60% and 58% of cases respectively in another series.{33} Abdominal distension, usually due to ascites, is reported in between 10%{32} and 65%{34} of cases. There may be right iliac fossa tenderness simulating appendicitis, or a right iliac fossa mass simulating appendix abscess or carcinoma. The ileocaecal area is the commonest site of disease. With bowel involvement there may be acute or sub-acute small bowel obstruction with vomiting and abdominal distension; there may also be palpable mass. The colon distal to the caecum is involved in up to 10% of cases{32} and is a cause of gastrointestinal bleeding.{35}

Signs and symptoms of genitourinary TB

Genitourinary TB is one of the commoner sites of non-respiratory TB in white UK-born people. For example, in 1993 it accounted for 17% of non-respiratory cases in the white UK-born ethnic group, compared with 4% in people of Indian (subcontinent) origin.{27} In white cases renal tract lesions predominate but female genital disease predominates in the Indian sub-continent ethnic group.{36}

Renal tuberculosis is often a 'silent' disease with insidious progression which can lead to total unilateral renal destruction. Systemic features such as weight loss, fever and night sweats are not common. As disease progresses, dysuria, haematuria, nocturia and pain either in the loin or anteriorly may occur. Renal disease can lead to ureteric and then bladder involvement by tubercle bacilli seeding distally. Bladder involvement initially leads to cystitis symptoms with frequency and dysuria, but as bladder wall inflammation with associated fibrosis worsens, bladder capacity falls and can be greatly reduced, the so-called 'thimble bladder' leading to marked frequency and nocturia due to a tiny bladder capacity. The urine with renal and ureteric disease, but particularly with bladder disease, shows proteinuria and haematuria on dipstick testing, and pus cells on microscopy but is sterile on standard culture. The finding of sterile pyuria should lead to the routine sending of three early morning urines for TB culture. A cold perinephric abscess can occur pointing in either the loin or like a psoas abscess in the groin. Prostatic, epididymal and testicular TB are less common. Testicular TB can present as a mass simulating testicular tumour.

Female genital TB is due to either haematogenous spread or direct spread from intra-abdominal disease. As with urological TB, systemic symptoms are uncommon unless there is associated abdominal tuberculosis. Infertility, either primary or secondary, is the commonest presentation of tubal and endometrial TB.{37} Most have no associated symptoms, but menorrhagia is reported in 20–25%, with much lower proportions having amenorrhoea or post menopausal bleeding.{37}

Signs and symptoms of disseminated (including miliary) TB

Disseminated TB occurs when tubercle bacilli are spread acutely though the blood stream. The symptoms are insidious at the onset with malaise, fever, anorexia and weight loss. In addition, headache from associated TB meningitis can occur with disseminated TB.

Signs and symptoms of central nervous system TB

Although only forming 5% of non-respiratory TB,{36} TB of the CNS is of disproportionate importance because of its significant morbidity and mortality. Early symptoms are non-specific with anorexia, malaise, headache, vomiting and altered behaviour. In children these can be poor feeding, irritability, altered behaviour, drowsiness or seizures. The prodromal phase can last from two weeks to two months, then focal neurological signs or decreasing level of consciousness occur. If cranial nerve palsies are present, 3rd and 6th nerve palsies are commoner than 7th and 8th nerve palsies. Internuclear ophthalmoplegia or lateral gaze palsies are less common but more serious because of midbrain or brainstem involvement.{37} Other neurological signs can develop depending on the site of endarteritis or infarction, including cerebellar signs, extrapyramidal movements such as choreoathetosis, hemiparesis or monoparesis.

Signs and symptoms of skin TB

Skin involvement can be due to disease of underlying structures, usually lymph node, bone or urogenital tract, with discharge through the skin, with sinus formation, so-called 'scrofuloderma'. Lupus vulgaris is a slowly destructive local skin form with dull red or violaceous edges. The tuberculides are forms of skin disease thought to be a manifestation of TB elsewhere in the body. Panniculitis, erythema induratum (Bazin's disease), and papular and papulo-necrotic forms are described and TB is in the differential diagnosis of such lesions, particularly in ethnic minority groups.{38}

Signs and symptoms of pericardial TB

TB can cause either pericardial effusion or constrictive pericarditis, particularly in ethnic minority groups. Fever, malaise, sweats, cough and weight loss can occur. The signs of pericardial effusion are oedema, pulsus paradoxus, a raised venous pressure, and hypotension with a narrow pulse pressure. With constrictive pericarditis, oedema, abdominal distension and breathlessness are the major signs and symptoms. A lymphocytic exudate on pericardial aspirate should be regarded as TB until proven otherwise.

Signs and symptoms of TB at other sites

TB should be considered in the differential diagnosis of adrenal deficiency, liver abscess, pancreatic mass in young adults with fever, and for isolated 'cold' abscesses wherever found, particularly in ethnic minority individuals.

Diagnosing active respiratory TB

The diagnosis of TB is suspected from a combination of context, symptoms, clinical signs and investigations. The diagnosis is rarely made from a single piece of evidence, and the sensitivity and specificity of individual tests may not reflect the strength of multiple tests or data. Most of the data on the utility of individual tests comes from studies in patients with proven tuberculosis by positive culture. Certain clinical settings are highly suggestive of tuberculosis in ethnic minority groups or recent TB contacts. These are: a pleural effusion which is a lymphocytic exudate, or isolated mediastinal lymphadenopathy, either supported by a positive skin tuberculin test (or IGT). These scenarios should be regarded as tuberculosis until proved otherwise and investigated accordingly.

A significant minority of respiratory TB cases however are not bacteriologically confirmed, but are treated on suspicion and regarded as probable cases because of response to specific anti-tuberculosis medication. The guideline aims to advise clinicians on which tests may help if cultures have been, or are subsequently shown to be, negative.

In children, who often have no culture confirmation, scoring systems have been developed to help diagnosis based on context, symptoms, X-ray appearances and other investigations. Some scoring systems are better validated than others.{39}

Diagnosing active non-respiratory TB

Most forms of non-respiratory tuberculosis have a lower bacterial load than for pulmonary disease, being so-called pauci-bacillary forms. A relatively very low proportion of cases have positive microscopy for acid-fast bacilli (AFB), and with the lower bacterial loads, even with rapid culture (see section 5.4) it takes longer to obtain positive cultures. With many of the non-respiratory sites, biopsy histology, or, in the case of lymph node disease, needle aspiration cytology, is available well before bacteriology. The finding of caseating granulomas, or granulomas with Langhan's giant cells on histology or cytology, is very highly suggestive of tuberculosis. A number of other conditions however can cause non-caseating granuloma formation. In the absence of caseation or Langhan's giant cells, additional tests such as a tuberculin skin test or IGT may be needed to assist in diagnosis. Obtaining a sample for culture is important as this confirms the diagnosis and provides the drug susceptibility profile of the organism. One caution is that in children aged under five, particularly if they are of white UK-born origin, granulomatous lymphadenitis is much more likely to be *M. avium* complex (MAC) than *M. tuberculosis*. To confirm this, samples are sent for culture, management for *M. avium* being completely different from *M. tuberculosis* in this context.{40}

The yield of histology/cytology depends on tissue sample size, which is much smaller with aspiration cytology than biopsy, and on the level of immune response which generates the histological appearances. In HIV-positive individuals the histological response depends on the level of immunosuppression. With levels of CD4 lymphocytes above 200/μl typical TB histology is the rule, but as the CD4 cell count falls, particularly below 100/μl, less and less granuloma formation occurs, and with profound immunosuppression there may be no cellular histological response at all. In these circumstances however there is an increased likelihood of AFB being seen microscopically. The differential diagnosis in such very immunosuppressed individuals is usually between *M. tuberculosis* and MAC infection. Polymerase chain reaction (PCR) techniques may help in distinguishing between these infections on AFB microscopy-positive samples (see section 5.3). A similar diagnostic problem can occur when patients with a very low CD4 count are started on highly active antiretroviral therapy (HAART). The rapid fall in HIV viral load and rise in CD4 count allows an immune response to be mounted to either of these organisms, which was not previously possible. Enlargement of cervical and intra-abdominal lymph nodes in particular are described in this context, which is known as the immune reconstitution or IRIS syndrome.

In some cases of non-respiratory tuberculosis, the diagnosis of TB is not entertained in the differential diagnosis, and the doctor, usually a surgeon, does not send any material for culture, instead placing the entire sample in formalin. This then completely precludes any attempt at bacterial culture, although if AFB are seen histologically it still allows PCR-based techniques to be used (see section 5.3). The same histological and cytological criteria apply as in Table 27. Tuberculin skin tests or whole blood interferon-gamma based tests may be needed to assist with histological appearances that are not fully diagnostic.

Methodological introduction

Diagnosing active respiratory TB: testing while awaiting culture results

Studies were identified which calculated the sensitivity, specificity or predictive value of plain X-ray, sputum smear microscopy and gastric washings when compared with culture as the gold standard for the diagnosis of respiratory TB. Studies on sputum smear microscopy were excluded from review if they were conducted in non-Organisation for Economic Co-operation and Development countries as it was thought that in terms of background levels of mycobacteria and laboratory standards they might not be representative of the UK.

Eight studies examined the diagnostic accuracy of sputum smear microscopy in comparison with culture. Two US studies were excluded for methodological reasons.{41},{42}

Of the six remaining sputum microscopy studies, five were conducted in the US{43–47} and one in Turkey.{48} Three of these studies reported results for HIV-positive patients or those with AIDS.{43},{44},{47}

Four studies were identified which considered the diagnostic accuracy of chest X-ray in predicting culture results. One Danish study included all patients who had a respiratory sample examined for *M. tuberculosis* during a specified time period,{49} a South African study was of paediatric patients suspected of having TB{50} whilst two US studies{51},{52} considered diagnostic accuracy of chest X-ray in those with AIDS/HIV.

Three studies considered the diagnostic accuracy of gastric washings in children.{53–55} Two of the studies were performed more than ten years ago in developing countries in populations with a high proportion of malnourished children, thus their applicability to the UK today is highly questionable. A more recent study performed in Cape Town, South Africa{55} compared gastric lavage and induced sputum samples from children in terms of their diagnostic yield, reporting how many cases were culture positive, smear positive or both.

Methodological considerations include the following:

- In terms of sputum smear microscopy, serial testing of sputum samples will increase the sensitivity and specificity of the test.

- Sensitivity and specificity values are calculated in different ways, either on a patient basis or a specimen basis.
- Methods used for processing the sputum specimen (including the minimum volume of sputum required and whether the specimen is expectorated or induced) or the method of isolating cultures may differ in various settings.

Diagnosing active respiratory TB if culture results are negative

Two studies{56},{57} addressed the issue of what other test results might support a positive diagnosis in those with a negative culture for TB but with suspected respiratory TB. In a South African study a group of black male goldmine employees with small lesions in the lung apices on chest X-ray, and a positive skin test but negative sputum culture, were followed up.{56} A diagnosis of TB was made if the smear became positive, if the culture yielded *M. tuberculosis* or if a histological diagnosis was made. A Hong Kong study had a subgroup of patients who had TB diagnosed on the basis of chest X-ray but had negative culture results.{57} This group were followed up for future confirmation of TB by culture of *M. tuberculosis* from sputum, or by radiographic or clinical deterioration.

Methodological issues for consideration are that the gold standard against which diagnostic tests for TB are usually compared is microbiological identification of TB by culture. This is not a perfect gold standard and culture might be negative in TB cases due to 'pauci-bacillary disease' (only a small number of *M. tuberculosis* organisms are present), sampling error or technical problems. In these cases where culture is negative, the standard against which a diagnostic test might be compared could be response to treatment, clinical features or a positive culture in the future. A TB diagnosis in this population would probably be achieved on a case-by-case basis and this has thus not been the subject of many studies.

Diagnosing active non-respiratory TB: testing while awaiting culture results

Studies were searched for which considered the sensitivity and/or specificity of histology from biopsy when compared with culture as the gold standard for the diagnosis of non-respiratory TB. Biopsies could be obtained during surgical procedures or by fine needle aspiration.

Four studies were identified where sensitivity of histology was calculated or it was possible to calculate sensitivity from the results reported. These studies were performed in India,{58} Malawi,{59} the USA{60} and the UK.{61} Two studies reported results in HIV-positive patients.{59},{60}

Due to the recognition that non-respiratory TB can have low positive culture rates, studies often base a firm TB diagnosis on histology or culture. A positive histology result is thus not necessarily considered to be inaccurate in the presence of a negative culture. For this reason, there are few studies which consider the sensitivity of histology from biopsy compared to culture alone as the reference standard. Studies merely report the numbers positive on each test. This is not useful for calculating the sensitivity of histology as it is necessary to know the results for each patient on both tests.

These studies were not blinded, mostly because they were retrospective analyses. The majority of specimens used in these studies were lymph nodes and little information is available concerning whether sensitivity and/or specificity may differ when using specimens from other sites.

Although the diagnostic accuracy of individual tests was considered in isolation, in reality test results would not be considered in isolation but would contribute to the overall evidence on which a diagnosis is made.

Diagnosing active non-respiratory TB if culture results are negative

Studies of patients with suspected non-respiratory TB where the results of histology from biopsy or tuberculin skin test were used to support a positive diagnosis in those with a negative culture for TB were searched for.

As with respiratory TB, culture is not a perfect gold standard and may be negative in TB cases for several reasons. In particular in non-respiratory TB, this may be due to pauci-bacillary disease.

No studies were identified in culture-negative populations where the results of histology from biopsy or tuberculin skin tests were used to support a positive diagnosis.

Evidence statements: diagnosing active respiratory TB while awaiting culture results

Sputum microscopy

In a comparison in the USA{45} of direct and concentrated specimens, results were analysed for the first three sputum specimens received from patients who were culture-positive for *M. tuberculosis* and from whom three or more specimens were received. The cumulative proportion of positive smears for each of the three smears for concentrated specimens were 74%, 83% and 91% and this was 57%, 76% and 81% for direct smears. (**2**)

Sensitivity of smears (all smears, not per patient) using more than or equal to 5 ml of sputum volume in a study in the USA{46} was 92%. This was significantly greater than a sensitivity of 72.5% in a previous period when all specimens were processed regardless of volume. In both periods the specificity of acid-fast smear for *M. tuberculosis* was comparable at 98%. (**2**)

A Turkish study{48} compared Ziehl-Neelsen (ZN) and fluorescence microscopy (FM) staining of sputum smears. Where only one specimen was submitted the sensitivities of ZN and FM stains were found to be 61% and 83% respectively. When two were submitted the sensitivities were 66% and 83% and where three or more were submitted sensitivities were 80% and 92%. (**3**)

In a US study{43} of expectorated sputum specimens that were culture positive for TB, 55% of specimens from both patients with and without AIDS (mean 2.4 specimens per patient for both groups) were smear positive. (**3**)

In a group of non-HIV infected, culture-positive TB patients in the USA,{47} 57% had positive acid-fast smears compared with 60% of the HIV-infected patients with culture-positive TB (all had at least three specimens tested). Among the TB culture-positive HIV-infected patients, no significant differences were found in the frequency of positive acid-fast sputum smears between groups stratified by CD4 cell counts (in those with a CD4 count of <50, 58% had positive smears, with a CD4 count of 50–200, 60% had positive smears and with a count of >200, 56% had positive smears). (**3**)

In a USA study,{44} 70% of all HIV-infected culture-positive TB patients and 71% of all non-HIV infected culture-positive TB patients had at least one positive smear (up to three were performed). The sensitivity for the diagnosis of TB dropped to 55% and 64% respectively when only the first smear was considered. (**3**)

Chest X-ray

According to X-ray category in a Danish study,{49} positive predictive values and sensitivity for TB were 61% and 67% respectively with X-ray changes thought to be due to TB. These values were 20% and 19% with X-ray changes compatible with TB; 14% and 9% with previous TB and radiographically active TB; 2% and 3% with previous TB but not radiographically active TB and 1% and 2% with X-ray changes thought to be due to other disease. None of the patients with normal chest X-rays were culture positive. (**1**)

In a South African study{50} of the diagnostic accuracy of X-ray in children, the results yield a sensitivity of 38.8% and a specificity of 74.4% compared to culture for the diagnosis of pulmonary TB using standard radiographs. (**3**)

In a group of culture-positive adult AIDS patients a US study{51} found 36% of patients had a primary *M. tuberculosis* pattern, 28% had a post-primary *M. tuberculosis* pattern, 14% had normal radiographs, 13% had atypical infiltrates, 5% had minimal radiographic changes and 3% had a miliary pattern. Normal chest radiographs were seen for 10 (21%) of 48 patients with less than 200 T-cells per microlitre and one (5%) of 20 patients with more than 200 T-cells per microlitre ($p<0.05$). (**2**)

In a US study{52} of TB culture-positive adults, 78% of HIV-negative patients' radiographs were consistent with post-primary pattern TB versus 26% of patients who were HIV positive ($p<0.001$). Only 11% of 18 significantly immunosuppressed HIV-positive patients (CD4 counts <200) had X-rays consistent with post-primary pattern TB, while all four patients with CD4 counts >200 had typical post-primary pattern chest radiographs ($p<0.005$). Of the 16 significantly immunosuppressed HIV positive patients the predominant chest X-ray finding was diffuse or multilobar infiltrates without an upper lobe predominance (N=8) followed by normal chest X-ray (N=3). (**3**)

Gastric washings

In a study of Haitian children{54} the sensitivity, specificity and predictive value of positive fluorescence microscopy of gastric washings compared with culture were 58%, 95% and 81% respectively from 536 specimens (median three specimens per patient). Among 49 children with at least one positive fluorescence microscopy of gastric washings, pulmonary TB was bacteriologically confirmed in 85%. Specimens were more frequently positive in far-advanced and miliary disease (82%) than in less severe disease (32%) ($p<0.001$). (**3**)

Culture was grown in 16 gastric washings samples in a study of Indian children{53} and smears for AFB were positive in only three samples, thus sensitivity was 3/16 or 19% (most children had only one sample taken). (**3**)

A South African study{55} of children with suspected TB found that sensitivity of gastric lavage compared with culture was 39%, specificity was 99%, positive predictive value was 88% and negative predictive value was 90% (based on three gastric lavage samples). Similar results were found for induced sputum specimens, however the yield of culture positive cases from each method was 88% from induced sputum and 66% from gastric lavage. (**2**)

Evidence statements: diagnosing active respiratory TB if culture results are negative

In South African black male goldmine employees with small lesions in the lung apices on chest X-ray and positive skin tests but negative sputum culture, TB was subsequently diagnosed in 88 (58%) of the 152 men. A diagnosis of TB was made if the smear became positive or the culture yielded *M. tuberculosis* or if a histological diagnosis was made. Active TB developed in these men from three to 58 months after entering the study, with a mean of 19.8 months.{56} (**2**)

A study performed in Hong Kong of patients with TB diagnosed on the basis of chest X-ray, but with negative culture results, obtained eventual confirmation of active disease requiring treatment in 99 (57%) of 173 patients. During the first 12 months 43% had a confirmed diagnosis. Confirmation of TB was by culture of *M. tuberculosis* from sputum, or by radiographic or clinical deterioration. There was bacteriological confirmation in 41%. (**3**)

Evidence statements: diagnosing active non-respiratory TB while awaiting culture results

In patients who presented with lymphadenopathy in one or more extra-inguinal sites in Malawi{59} and who did not respond to general antibiotics, it could be calculated that the sensitivity of histology compared to culture was 70%, the specificity was 59%, the positive predictive value was 52% and the negative predictive value was 67%. (**2**)

In a US study{60} of lymph node specimens where the cytology report was compared with culture results, the sensitivity of cytology was calculated to be 72%. (**2**)

The sensitivity of histology (using a variety of specimens although most frequently lymph nodes) compared with culture in an East London population was 97% with a positive predictive value of 69%.{61} (**2**)

Where culture was the gold standard, an Indian study,{58} calculated that in clinically suspected cases of tuberculous lymphadenitis, sensitivity, specificity and positive predictive values for cytology were 78.5%, 73% and 76.7% respectively. (**1**)

HIV-positive

In a study in Malawi{59} in HIV-negative patients with TB lymphadenitis (diagnosed on the basis of a positive culture or histology result), 100% had positive histology results and 83% had positive culture results. These figures were 78% and 56% for those who were HIV positive. Thus the HIV status of the TB lymphadenitis patients suggests a negative influence of HIV infection on the possibility of both histology and culture being indicative of TB (OR 0.10, 95%CI 0 to 1.17, p=0.06). (**2**)

In a US study{60} of lymph node specimens where the cytology report was compared with culture results the sensitivity of cytology in those who were HIV negative was 76% and it was 69% in those who were HIV positive. (**2**)

From evidence to recommendations

The Chief Medical Officer's TB Action Plan{2} calls for primary and community care staff to be aware of 'the signs and symptoms of the disease, local TB services and local arrangements for referring patients with suspected TB'. As this guideline is aimed at generalist clinicians as well as those working regularly with people with tuberculosis, recommendations include signs, symptoms and potentially helpful imaging techniques. NICE guidelines generally do not include service guidance (although exceptions have been made elsewhere in this guideline), and so recommendations for local referral are not given.

The GDG were aware of the General Medical Council's advice{62} on gaining consent for testing for 'serious communicable diseases', but noted that this advice was reprinted from prior guidance specific to HIV and did not feel that routine clinical practice supported it in TB, and that it was at variance with the Public Health Act.{63}

Testing for active respiratory TB while awaiting culture results

Microscopy on gastric washings has some utility in children, but a recent comparative study in children showed a single induced sputum (by hypertonic saline) to be superior to three gastric washings. Chest X-ray changes are less specific in children and HIV-positive individuals, particularly if the CD4 count is under 200 cells/μl.

Testing for active respiratory TB if culture results are negative

The evidence does not assess the adequacy of the respiratory samples sent for culture; a negative culture result can reflect no growth at that time, while a positive result may be obtained later. Chest X-ray appearances consistent with TB were noted to show progression to culture-proven disease in over 50% of subjects in the studies analysed from South Africa and Hong Kong. The decision whether to start TB treatment will be a clinical one based on experience, context and appraisal of all the individual's results. Further culture samples are sometimes needed after treatment has begun, and will remain viable for a few days, though growth may be slower; the GDG agreed a threshold of one week in this regard.

IGTs may also have a role in ruling out infection with *M. tuberculosis*; this area is developing rapidly and may need to be updated ahead of the rest of the guideline in 2008.

Testing for active non-respiratory TB while awaiting culture results

Microscopy can be strongly suggestive of TB with certain patterns, and this is often confirmed by a positive culture if material has been sent. Although the data were entirely for peripheral lymph nodes, the GDG thought that this was likely also to apply to other non-respiratory sites.

The decision to biopsy should not be influenced by concerns about sinus formation, as there is no evidence to support this with modern chemotherapy.

Patient preferences are an important consideration in choosing biopsy or needle aspiration.

Posterior–anterior chest X-rays in people with suspected non-respiratory disease are helpful through detecting any coexisting respiratory disease, which will aid or confirm the diagnosis, and be another potential source of bacteriological confirmation. The GDG also agreed a range of other potential tests and imaging techniques.

Testing for active non-respiratory TB if culture results are negative

Although there was no evidence in this area, the GDG noted that continuous enhanced surveillance by the Health Protection Agency (HPA) shows that only some 55% of cases of TB are culture confirmed, and that this is often because no samples have been obtained, with the diagnosis being entirely histological. (However, other reasons include failures in the reporting system and limitations of the matching between Enhanced Tuberculosis Surveillance and MycobNet systems.) To raise the proportion of TB cases diagnosed, particularly at non-respiratory sites, more samples from common TB sites should be sent for TB bacteriology, which requires the education of those sending samples such as general, ENT and orthopaedic surgeons and radiologists performing biopsies.

IGTs may also have a role in ruling out infection with *M. tuberculosis*; this area is developing rapidly and may need to be updated ahead of the rest of the guideline in 2008.

RECOMMENDATIONS

R19 To diagnose active respiratory TB:

- a posterior–anterior chest X-ray should be taken; chest X-ray appearances suggestive of TB should lead to further diagnostic investigation C(DS)
- multiple sputum samples (at least three, with one early morning sample) should be sent for TB microscopy and culture for suspected respiratory TB before starting treatment if possible or, failing that, within seven days of starting C(DS)
- spontaneously produced sputum should be obtained if possible; otherwise induction of sputum or bronchoscopy and lavage should be used B(DS)
- in children unable to expectorate sputum, induction of sputum should be considered if it can be done safely, with gastric washings considered as third line B(DS)
- if there are clinical signs and symptoms consistent with a diagnosis of TB, treatment should be started without waiting for culture results (see section 6.1 for details) D(GPP)

- the standard recommended regimen should be continued in patients whose subsequent culture results are negative D(GPP)
- samples should be sent for TB culture from autopsy samples if respiratory TB is a possibility. D(GPP)

R20 To diagnose active non-respiratory TB:

- advantages and disadvantages of both biopsy and needle aspiration should be discussed with the patient, with the aim of obtaining adequate material for diagnosis B(DS)
- if non-respiratory TB is a possibility, part or all of any of the following samples should be placed in a dry pot (and not all placed in formalin) and sent for TB culture: D(GPP)
  - lymph node biopsy
  - pus aspirated from lymph nodes
  - pleural biopsy
  - any surgical sample sent for routine culture
  - any radiological sample sent for routine culture
  - histology sample
  - aspiration sample
  - autopsy sample
- microbiology staff should routinely perform TB culture on the above samples (even if it is not requested) D(GPP)
- the appropriate treatment regimen should be started without waiting for culture results if the histology and clinical picture are consistent with a diagnosis of TB (see chapters 6 and 7) C(DS)
- all patients with non-respiratory TB should have a chest X-ray to exclude or confirm coexisting respiratory TB; in addition, tests as described in Table 27 should be considered D(GPP)
- the appropriate drug regimen (see chapters 6, 7 and 9) should be continued even if subsequent culture results are negative. D(GPP)

Table 27: Suggested site-specific investigations in the diagnosis and assessment of non-respiratory TB

• Site	• Imagin	• Biops	• Cultur

	g	y	e
Lymph node		• Node	• Node or aspirate
Bone/joint	• Plain X-ray and computed tomography (CT) • Magnetic resonance imaging (MRI)	• Site of disease	• Biopsy or para-spinal abscess • Site or joint fluid
Gastrointestinal	• Ultrasound • CT abdomen	• Omentum • Bowel	• Biopsy • Ascites
Genitourinary	• Intravenous urography • Ultrasound	• Site of disease	• Early morning urine • Site of disease • Endometrial curettings
Disseminated	• High resolution CT thorax • Ultrasound abdomen	• Lung • Liver • Bone marrow	• Bronchial wash • Liver • Bone marrow • Blood
Central nervous system	• CT brain • MRI	• Tuberculoma	• Cerebrospinal fluid (CSF)
Skin		• Site of disease	• Site of disease
Pericardium	• Echocardiogra m	• Pericardium	• Pericardial fluid

Cold/liver abscess	• Ultrasound	• Site of disease	• Site of disease

Cross-referring:

For details of rapid diagnostic tests, see sections 5.3 and 5.4.

For people with active TB, see treatment under chapters 6, 7 and 9.

For details of contact tracing, see section 12.2.

For details of notification and enhanced surveillance, see chapter 14.

Rapid diagnostic tests: molecular methods

Clinical introduction

Molecular probes for diagnosis

A number of methods have been developed which target and amplify specific regions of mycobacterial DNA, thus allowing a rapid result. However, such tests can result in false negative and false positive findings. Although rare, false positive results may occur due to contamination of the sample with environmental mycobacteria causing non-specific binding to the probe. More commonly, false negative results may occur due to low organism numbers or, in some sample types, for example CSF, to the presence of inhibitors. The specificity and sensitivity of the tests has been compared with culture proven disease. However, since 20–30% of pulmonary cases, and a higher proportion of non-pulmonary cases are not culture proven, the performance of molecular tests in these settings is difficult to assess.

Molecular probes for species confirmation

Species identification may sometimes be possible directly from the specimen using the techniques referred to above. Most usually, this will be possible only for *M. tuberculosis* complex organisms (*M. tuberculosis*, *M. bovis*, *M. africanum*). However, these methods may allow early differentiation between these organisms and environmental mycobacteria. These tests are most effective when applied to samples in which mycobacteria have been detected microscopically. Their use is currently recommended, to confirm true tuberculosis (ie transmissible disease) before a large contact tracing exercise, for example in a school or hospital, is carried out.{6}

When a sample yields a positive culture, rapid identification of several commonly encountered species may be possible. This may be done by the application of an expanded range of DNA amplification-based assays or by the use of non-amplified hybridisation probes. Both of these approaches are effective since the high numbers of organisms present in a positive culture overcome the problems associated with low bacterial counts and inhibition in the primary sample. The Mycobacterium Reference Service of the HPA now routinely confirms to clinicians whether a positive culture received is from the *M. tuberculosis* complex or not.

Molecular probes for rifampicin resistance

The incidence of multi-drug resistant strains of *M. tuberculosis* (MDR TB) in the UK is low (~1%) (see Appendix G). However, in some areas of the country and in some population groups the incidence is much higher. Whilst it should be noted that mono-resistance to rifampicin is found in approximately 5% of rifampicin-resistant strains, a high proportion of rifampicin resistance is associated with concurrent resistance to isoniazid (~95%). Thus the detection of resistance to rifampicin can be used as a marker for MDR TB with a high level of accuracy.

Rifampicin resistance is commonly due to one or more of several possible mutations of the *rpo*B gene and these can be detected using a PCR-based technique. A positive result from such a test should lead to the implementation of infection control measures and drug treatment for MDR TB until the results of standard drug susceptibility tests are available. Risk factors for MDR TB, which should lead to such tests for rifampicin resistance, are listed in section 9.1. Clinicians should be aware that there is a small (<5%) false negative rate for these tests as a few mutations conferring rifampicin resistance are not at the *rpo*B gene tested for.{64},{65}

Molecular typing of M. tuberculosis isolates

In the past the typing of *M. tuberculosis* strains has been principally to detect previous events. This was largely due to the comparatively slow techniques available (for example, restriction fragment length polymorphisms). Newer methods based on the detection of variable numbers of tandem repeat sequences within the *M. tuberculosis* genome (variable number of tandem repeats (VNTR)/mycobacterial interspersed repetitive unit (MIRU) typing) are amenable to automation. As a result rapid, high-throughput typing systems have become available. These systems also have the advantage of digitised data which allow much easier computerised storage and analysis than previous typing methods. If this rapidity of method is used to type strains as they are isolated, then potential links between patients may be detected early enough to interrupt the disease transmission process. Thus an epidemiological tool may make an impact on diagnosis and transmission.

Methodological introduction

In consideration of the use of molecular methods for rapid diagnosis of TB, the review being developed by the NHS Heath Technology Assessment Programme{66} has been adopted. This aims to conduct a systematic review of the effectiveness of available diagnostic tests to identify mycobacteria. The review is not yet published.

The draft review of nucleic acid amplification tests (NAAT) found 163 studies which compared NAAT with a reference standard. There were 105 comparisons in respiratory specimens and 67 in non-respiratory specimens. In these studies 77 of the tests used were commercially produced (the amplified *Mycobacterium tuberculosis* direct (AMTD) test, the Amplicor, the Ligase Chain Reaction and Ampicis Myco B) and 86 were produced in-house (insertion element IS6110 or other targets).

Methodological issues concern the complexity of pooling data from diagnostic studies in particular due to variation in diagnostic thresholds. Furthermore, studies report pairs of related summary statistics (sensitivity and specificity) rather than a single statistic, requiring alternative statistical methods for pooling results. This review presents diagnostic odds ratios (DOR) in addition to sensitivity and specificity data. This is a single summary of diagnostic performance which although not easy to apply in clinical practice (it describes the ratio of the odds of a positive test result in a patient with disease compared to a patient without disease) is convenient to use when combining studies as it is often fairly constant regardless of diagnostic threshold. The DOR can be calculated from sensitivity and specificity data and where a test provides no diagnostic evidence the DOR is 1. It has been suggested{67} that a DOR of 25 or more in a test may provide convincing diagnostic evidence.

Evidence statements

The health technology appraisal (HTA) on rapid diagnostic tests{66} is not yet published. The GDG considered interim results, reporting the DOR statistic calculated by comparing NAAT *vs*. a reference standard. All evidence is graded at level 2.

From evidence to recommendations

Molecular probes for diagnosis

The HTA of rapid tests showed that their sensitivity was equivalent to culture in microscopy negative pulmonary samples, but there was an increased false negative rate in non-respiratory samples, particularly in pleural fluid and CSF. Significant false negative rates in these settings limit their utility, and could lead to failure to diagnose and treat TB.

Molecular probes for species confirmation

The GDG did not look into the HTA's interim results for molecular probes, but noted their role in rapid confirmation. They were not felt to be more reliable or useful than culture confirmation, and use was therefore limited to occasions when a rapid decision is needed on treatment or infection control measures. A further role was in preventing large scale contact tracing exercises from starting unnecessarily.

Molecular tests are less feasible on poorer samples, and the recommendations given below advise on their use on biopsy material.

Molecular probes for rifampicin resistance

Again, the GDG recognised the advantages of rapid results for drug resistance, but noted that MDR TB risk factors should be used to determine infection control measures at the earliest opportunity.

Molecular typing of M. tuberculosis isolates

Although this has not been subject to formal HTA appraisal, these methods have been considered by the HPA and a unified strategy using a 15 locus VNTR/MIRU system agreed. Such a strategy was recommended in the TB Action Plan.{2}

RECOMMENDATIONS

R21 Rapid diagnostic tests for *M. tuberculosis* complex *(M. tuberculosis, M. bovis, M. africanum)* on primary specimens should be used only if: D(GPP)

- rapid confirmation of a TB diagnosis in a sputum smear-positive person would alter their care, or
- before conducting a large contact-tracing initiative.

R22 Clinicians should still consider a diagnosis of non-respiratory TB if rapid diagnostic tests are negative, for example in pleural fluid, CSF and urine. B(DS)

R23 Clinical signs and other laboratory findings consistent with TB meningitis should lead to treatment (see section 7.1), even if a rapid diagnostic test is negative, because the potential consequences for the patient are severe. D(GPP)

R24 Before conducting a large contact-tracing initiative (for example, in a school or hospital), the species of *Mycobacterium* should be confirmed to be *M. tuberculosis* complex by rapid diagnostic tests on microscopy- or culture-positive material. Clinical judgement should be used if tests are inconclusive or delayed. D(GPP)

R25 If a risk assessment suggests a patient has MDR TB (see section 7.1): D(GPP)

- rapid diagnostic tests should be conducted for rifampicin resistance
- infection control measures and treatment for MDR TB should be started as described in chapter 9, pending the result of the tests.

R26 Rapid diagnostic tests for *M. tuberculosis* complex identification should be conducted on biopsy material only if: D(GPP)

- all the sample has been inappropriately placed in formalin, and
- AFB are visible on microscopy.

Cross-referring:

For details of managing drug-susceptible TB, see chapters 6 and 7.

For details of managing drug-resistant TB, see chapter 9.

Rapid diagnostic tests: automated liquid culture

Clinical introduction

Clinicians have been advised to obtain culture confirmation of tuberculosis whenever possible.{68} This not only confirms the diagnosis, but crucially also obtains material for drug susceptibility testing, which is important because of the current levels of drug resistance in England and Wales. The finding of isoniazid resistance (currently 6% of isolates) requires modification of treatment (see section 9.4), and that of MDR TB (currently about 1% of isolates) different infection control procedures (see section 9.3) and individualised treatment regimens based on the drug susceptibility data.

Until recently, culture for mycobacteria was done mainly on solid media, the Lowenstein-Jensen slope, or in broth media. These methods were slow, with cultures from microscopy positive material taking from 2–4 weeks, and for microscopy negative material 4–8 weeks. More recently rapid culture methods have been developed, with the potential advantages of more rapid growth and hence earlier drug susceptibility data, and also possibly increased sensitivity.

The national TB Action Plan has as one of its aims the use of rapid culture methods for diagnosis of all cases of tuberculosis.{2}

Methodological introduction

The reduced turnaround time of automated liquid culture in comparison with solid media is uncontested. In addition to time to detection of mycobacteria, study outcomes in comparisons between solid and liquid media also report increases recovery rates for mycobacteria.{66} Sensitivity and or specificity cannot be reported in these studies as there is no reference standard.

There were no studies identified which directly addressed the issue of when (ie in what circumstances) automated liquid culture methods for the diagnosis of TB are most useful.

The HTA on rapid diagnostic techniques{66} is not yet published. The GDG considered interim findings on liquid culture techniques.

From evidence to recommendations

Given the evidence base and the self-evident speed of automated liquid culture, the GDG recommended their universal use.

Liquid culture methods require batches of samples to be processed. Their use becomes more costly per test if fewer samples are processed at any one time by a laboratory. The batching of samples sent to regional laboratories may not reflect future service organisation as this technology becomes more widely used over the lifetime of this guideline, but the recommendations allude to the effect of throughput on efficiency, quality control and cost-effectiveness. The NICE guideline, in the absence of clinical evidence, is unable to recommend service configurations to address this, though the GDG considered a 'hub and spoke' arrangement of regional laboratories.

RECOMMENDATIONS

R27 Clinical samples should ideally be sent for culture by automated liquid methods, bearing in mind that laboratories need a certain level of throughput to maintain quality control. D(GPP)

6 Management of respiratory tuberculosis

Drug treatment

Clinical introduction

Respiratory TB is defined as active TB affecting any of the following:

- lungs
- pleural cavity
- mediastinal lymph nodes
- larynx.

1.1.1 Current services

Dedicated TB clinics

In all parts of the country, over half of TB service providers taking part in our review of current services (see section 2.8) had a dedicated TB clinic. The percentage was 64% in London and 53% elsewhere in England and Wales. There may be a trend for these to be sited in services with a higher caseload of active TB (shown by number of notifications), but this is not reflected in caseload of screening (number of people screened). Screening is sometimes reported being carried out in a separate clinic, but it is not possible from our data to conclude whether or not there is consistency (or benefit) in having a combined approach.

This guideline recommends culturally relevant, practical and sensitive advice for patients, involving them in treatment decisions, and having a designated key worker they can contact. Bringing the TB service together in the framework of a dedicated clinic is one way to help the team achieve this. However, it is understandable that it will not be justified in all localities.

Nurse-led follow-up clinics

The review of current services found that outside London, 31% of TB service providers had nurse-led follow-up clinics. The majority of these conducted some follow up at the patient's home. In London, 55% of TB service providers had nurse-led follow-up clinics. None of these followed up patients at home. Variation in the provision of these nurse-led follow-up clinics did not seem to be explained by the caseload (notifications), staffing levels or presence of specialist personnel. It is impossible to conclude from our data whether the variation is appropriate to local epidemiology, geography or service models, but these are all factors that ought to have been considered in the design of the TB service.

Specialist TB+HIV clinics

The review of current services found that, outside London, only 5 of 60 (8%) participating service providers reported a specialist joint TB+HIV clinic, although in three cases this was a service by HIV physicians with TB nurse input. Five other clinics reported access to such specialist clinics elsewhere. In London, 10 of 33 (30%) service providers had a specialist TB+HIV clinic, although five other clinics reported access to these specialist clinics. Outside London, these specialist TB+HIV clinics tended to be sited in areas with higher numbers of notifications.

Specialist paediatric TB clinics

The review of current services revealed a few different models for providing paediatric TB care. Children were seen by respiratory or paediatric doctors with, in some cases, TB nurse input. In one clinic, generalist paediatric doctors ran a service for BCG, and treatment of active and latent TB with TB nurse input.

The number and proportion of service providers running clinics with specialist TB nurse input was 11 (17%) outside London, and 21 (64%) in London. Four other service providers, one outside London and three in London had access to these clinics. In two places outside London, the clinics were community paediatric clinics, and one was a hospital paediatric/BCG clinic. In 22 (34%) outside London, and three (9%) in London, patients were seen in paediatric clinics without TB nurse input. In 27 service providers outside London and six in London, patients were seen either by a respiratory physician, or the responsible healthcare professional was not recorded.

Access to specialist paediatric clinics seemed to predominate in areas of higher caseload outside London, but this distinction was less apparent within London. Variation in the provision of paediatric specialist services did not seem to be explained by staffing levels or the presence of specialist personnel. Given the special considerations required for diagnosing and treating TB in children, as well as providing advice to parents, it is important that adequate specialist expertise is available to the TB service. The above service models represent different ways of approaching this where caseload justifies a specific service model.

Outreach work

The review also looked into outreach in patients' homes and other community settings. This is reported in detail under section 8.3.

Duration of treatment

Six months of daily treatment with rifampicin and isoniazid, supplemented in the initial two months with pyrazinamide and either ethambutol or streptomycin (the six-month four-drug regimen) has been the evidence-based gold standard for TB treatment for at least the last 15 years. No new first-line drugs have been found for over 30 years. Attempts have been made to shorten the total duration of treatment by reducing the duration of the continuation phase of treatment. The comparators for such studies are the results of the six-month, short-course, four-drug regimen, which give a cure and completion rate of >95% and a relapse rate of 0–3% in both clinical trial{69} and routine clinic use.{70},{71} Such controlled studies have been largely conducted in adults not known to be HIV positive, with a few in HIV-positive individuals or in children.

Dosing schedule

Trials have also been conducted on reduced treatment frequency, comparing a daily dosing schedule with higher dosages of drugs given twice or thrice weekly. The aims of these studies were to reduce the total number of doses taken, as both an aid to adherence and treatment monitoring, and to reduce the costs of treatment in resource-poor countries. Intermittent treatment can be given either throughout the initial and continuation phases, or intermittently through the continuation phase after a daily intensive initial phase. Certain drug side effects (for example, 'flu-like syndrome', thrombocytopenia, shock and acute renal failure) are more common when rifampicin is given intermittently rather than daily, and are immunologically mediated. Twice- or thrice-weekly regimens lend themselves more readily to DOT as they require less frequent monitoring of medication, reducing the costs of supervision if done in a healthcare setting.

Methodological introduction

Duration of treatment

A Cochrane systematic review{74} assessed the effects of regimens lasting less than six months, compared to any longer regimens in the treatment of active TB (eg studies could compare two months *vs*. four months or five months *vs*. eight months). Seven trials were included (three trials in India,{75–77} two trials in Hong

Kong,{78},{79} one trial in Singapore{80} and one in Germany{81}) and five of these studies compared regimens of less than six months with regimens of six months or more.

An additional RCT{82} was identified which compared a five-month regimen with a twelvemonth regimen. However, this was excluded due to methodological limitations.

No studies were found comparing treatment regimens of less than six months with longer durations in HIV-infected adults or in children.

A major consideration is that although these studies were very large (4,100 patients included in total), they did not perform intention to treat analyses and thus relapse rates are based only on study participants who complied fully with the treatment protocol (having taken at least 75–90% of scheduled treatment).

Dosing schedule

In terms of HIV-infected populations and children, a US cohort study{89} in an HIV-infected population was identified but excluded on the basis of limitations in the methodology, as was an RCT which compared twice-weekly and daily chemotherapy in children with respiratory TB.{90} No further studies were identified in either of these populations.

Evidence statements

Duration of treatment

A Cochrane systematic review{74} of seven RCTs compared regimens of six months or less with any longer regimens (thus not necessarily six months or longer). For those with active TB, relapse rates were significantly better in the longer groups of the meta-analyses of two months (OR 6.1, 95%CI 2.19 to 17.01), three months (OR 3.67, 95%CI 2.42 to 5.58) and four months (OR 3.64, 95%CI 1.71 to 7.75) of treatment *vs*. longer treatment, but not in the single trial of five *vs*. seven months. Relapse rates after longer (comparison) regimens ranged from 0–7% at one year (or more) and in the shorter treatment arms they ranged from 2–20% (the two highest rates of 18% and 20% being in the three-month regimen). (**1+**)

When only regimens of less than six months were compared with durations of six months or longer, relapse rates were significantly lower in the regimens of six months or more, for three months *vs*. six months (OR 15.61, 95%CI 4.97 to 49.04), three months *vs*. 12 months (OR 5.11, 95%CI 1.37 to 19.08), and four months *vs*. six months (OR 3.64, 95%CI 1.71 to 7.75) but not in the five *vs*. seven months comparison.{74} (**1+**)

There was little or no difference in the rates of adverse reactions or toxicity requiring a change or discontinuation of treatment when comparing regimens of six months or less with longer regimens and few or no deaths were reported in individual trials. Furthermore, the 'sterilising efficacy' (sputum culture negative immediately after the completion of treatment) varied little among treatments, providing no predictive value for relapse rates.{74} (**1+**)

Dosing schedule

From evidence to recommendations

Specialised clinical staff are central to good management of TB, as has been shown in audit results.{97},{98}

The Cochrane review of this area includes trials in adults not known to be HIV positive. Few data are available in either HIV-positive adults or in children, but the Cochrane review's conclusions should be applicable.

The increasing rates of isoniazid resistance seen in the epidemiology of England and Wales (see Appendix G) led the GDG to recommend a standard six-month, four-drug initial treatment regimen. Two studies have looked into the effect of this regimen in clinical settings in the UK and shown it to be effective and safe across susceptible and isoniazid-resistant strains.{99}

RECOMMENDATIONS

R29 A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in:

- adults not known to be HIV positive. A
- adults who are HIV positive. B
- children. B

This regimen is referred to as 'standard recommended regimen' in this guideline.

Infection control

Clinical introduction

It has long been recognised that people who are sputum microscopy positive from spontaneously expectorated sputum are those cases with the highest infectivity, and pose a risk to household and other close contacts such as workplace contacts. For these reasons, traditionally, patients with pulmonary disease in whom tuberculosis is suspected are isolated in a single room. This isolation has been recommended until three separate sputum tests have been analysed. If these sputum tests are negative, the patient is usually deemed to pose a significantly lower infection risk. They may then be moved from the single room to a shared ward, provided there are no HIV-positive or other patients with major immunocompromise on the same ward. If patients are sputum microscopy positive, having so-called 'open' tuberculosis, and need to be admitted to hospital, isolation is required until treatment makes the person non-infectious.{101},{102} Such drug treatment causes an extremely rapid fall in viable organisms in the sputum, even if AFB are still visible on microscopy.

Current clinical practice has been based on the 2000 BTS Joint Tuberculosis Committee guidance, which supported nursing adults with non-pulmonary tuberculosis on a general ward. However, aerosol-generating procedures such as abscess or wound irrigation are carried out in separate facilities.

6.2.2 Methodological introduction

Studies were searched for that focussed on measures directed at patients with infectious TB to prevent transmission to other patients or contacts. It was expected that these measures might include mask wearing by the patient, isolation in a single room, negative pressure rooms, germicidal ultraviolet radiation or air disinfectant at sites of transmission.

There were few studies which considered TB transmission to other patients or contacts rather than healthcare workers when assessing the effectiveness of infection control measures. This is likely to be due to healthcare workers having regular Mantoux tests tests available for analysis, the fact that healthcare workers are easier to follow up than patients and because employers must consider TB as an occupational hazard. Furthermore, studies tended to look at infection control in MDR TB rather than drug-susceptible TB patients. This seems to be because infection control measures were implemented in several hospitals in the USA after MDR TB outbreaks in the late 1980s and early 1990s.

Additional considerations are that the quality of the infection control measures, for example the level of negative pressure in a negative pressure isolation room, may vary over time.

Furthermore, infection control measures are often implemented together, which makes it difficult to assess the contribution of each measure.

One US study{103} without a comparison group that considered hospital transmission of TB among patients after the implementation of infection control measures was identified. This was excluded on the basis of methodological limitations.

No further studies were found that assessed the effects of infection control on patient TB transmission rates in either HIV-positive or negative patients, therefore it was not possible to write evidence statements.

From evidence to recommendations

The GDG felt there was no good evidence to support measures for infection control in patients with smear-positive disease not suspected to have MDR TB, whether or not HIV positive, and endorsed the guidance given in the BTS guideline.{68}

It is important to prevent unnecessary hospitalisation, as this is one of the major cost drivers for TB treatment. Treatment can proceed in the patient's home, considering that the household members will be contacted through contact tracing, and that infectiousness declines rapidly once treatment begins.

When children with TB are admitted to hospital, it is important to consider their visitors as likely close contacts, and to screen them when they visit as part of contact tracing, and also as infection control.

Given the unexpected data on negative pressure facilities from the review of current service (see 9.3.2), and similar findings in other surveys, the recommendations spell out the three categories of infection control, and require simple steps to clarify which rooms meet the agreed standards.

There can be conflicting guidance on whether staff should wear masks. It was agreed that masks are only required for MDR TB or during close contact in cough-inducing procedures, for example bronchoscopy and sputum induction. Patients are reassured by effective infection control measures, but are also often worried unnecessarily by masks or gowns, especially if these steps are not explained to them. The only role for patients wearing masks was within the first two weeks of treatment (when the patient remains infectious) and when they are outside their single room, for example going for an X-ray (as they may come into contact with other, susceptible, patients).

Readers should be aware of relevant guidance available from the Health and Safety Executive.{104}

RECOMMENDATIONS

The recommendations below deal with three levels of isolation for infection control in hospital settings:

- *negative pressure rooms, which have air pressure continuously or automatically measured, as defined by NHS Estates*{105}
- *single rooms that are not negative pressure but are vented to the outside of the building*
- *beds on a ward, for which no particular engineering standards are required.*

R33 All patients with TB should have risk assessments for drug resistance (see section 9.1) and for HIV. If risk factors for MDR TB are present, see section 9.3 for recommendations on infection control. D(GPP)

R34 Unless there is a clear clinical or socioeconomic need, such as homelessness, people with TB at any site of disease should not be admitted to hospital for diagnostic tests or for care. D(GPP)

R35 If admitted to hospital, people with suspected respiratory TB should be given a single room. D(GPP)

R36 Patients with respiratory TB should be separated from immunocompromised patients, either by admission to a single room on a separate ward, or in a negative pressure room on the same ward. D(GPP)

R37 Any visitors to a child with TB in hospital should be screened as part of contact tracing, and kept separate from other patients until they have been excluded as the source of infection. D(GPP)

R38 Smear-positive TB patients without risk factors for MDR TB (see section 9.1) should be cared for in a single room, until: D(GPP)

- they have completed two weeks of the standard treatment regimen (see section 6.1), or
- they are discharged from hospital.

R39 Aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment should be carried out in an appropriately engineered and ventilated area for: D(GPP)

- all patients on an HIV ward, regardless of whether a diagnosis of TB has been considered
- all patients in whom TB is considered a possible diagnosis, in any setting.

R40 Healthcare workers caring for people with TB should not use masks, gowns or barrier nursing techniques unless: D(GPP)

- MDR TB is suspected
- aerosol-generating procedures are being performed.

When such equipment is used, the reason should be explained to the person with TB. The equipment should meet the standards of the Health and Safety Executive. See section 9.3 for further details of MDR TB infection control.

R41 TB patients admitted to a setting where care is provided for people who are immunocompromised, including those who are HIV-positive, should be considered infectious and, if sputum smear-positive at admission, should stay in a negative pressure room until: D(GPP)

1. the patient has had at least two weeks of appropriate multiple drug therapy, *and*
2. if moving to accommodation (inpatient or home) with people who are immunocompromised, including those who are HIV-positive, the patient has

had at least three negative microscopic smears on separate occasions over a 14-day period, *and*

3. the patient is showing tolerance to the prescribed treatment and an ability and agreement to adhere to treatment, *and either*
4. any cough has resolved completely, *or*
5. there is definite clinical improvement on treatment, for example remaining afebrile for a week.

For people who were sputum smear negative at admission (that is, three negative samples were taken on separate days; samples were spontaneously produced sputum if possible, or obtained by bronchoscopy or lavage if sputum samples were not possible): *all* of 1, 2, 3 and 5 above should apply.

R42 Inpatients with smear-positive respiratory TB should be asked (with explanation) to wear a surgical mask whenever they leave their room until they have had two weeks' drug treatment. D(GPP)

Cross-referring:
For details of managing drug-resistant TB, see chapter 9.
For details of contact tracing among hospital inpatients, see section 12.7.

In line with NICE's digitalisation strategy, the algorithms in the full version of the guideline and in the NICE quick reference guide supporting the updated guideline have now been replaced by a NICE pathway. The pathway is an interactive web-based tool for health and social care professionals providing fast access to the NICE guidance and associated products.

7 Management of non-respiratory tuberculosis

Meningeal tuberculosis

Clinical introduction

Tuberculous meningitis occurs when there is blood-borne spread of the TB bacteria to the brain. In the days before treatment was available this usually occurred within 12 months of the original (primary) infection.{106} It is sometimes part of a more widespread blood-borne dissemination, with chest X-ray patterns typical of miliary tuberculosis.{107} It can present with systemic features if due to miliary disease, or more local central nervous system signs if limited to the brain. Unlike acute bacterial meningitis with, for example, the meningococcus, the onset of TB meningitis is insidious over a few weeks. In infants there may be non-specific symptoms such as not feeding or a failure to thrive. There can be headache and vomiting, then increasing drowsiness, and localised neurological signs such as cranial nerve palsies or hemiparesis, progressing to coma.

Clinically, the meningitis is classified according to the following stages:

- stage I: no clouding of consciousness or focal neurological signs
- stage II: clouding of consciousness and/or focal neurological signs
- stage III: coma.{108}

The diagnosis is supported by lumbar puncture suggesting CSF changes: a low glucose, raised protein and a lymphocyte dominant pattern of white blood cells. Diagnosis is confirmed by demonstrating *M. tuberculosis* on microscopy or culture of the CSF, or demonstrating *M. tuberculosis* DNA by PCR testing. TB meningitis may be accompanied by tuberculomas, inflammatory masses in the brain, which can either be present at diagnosis on CT brain scan or develop during treatment.{109} Although only approximately 100 cases of TB meningitis occur in England and Wales each year, this form of TB has a high morbidity and mortality when compared to nearly all other forms of non-respiratory tuberculosis.{110} Disability and death can still occur despite early diagnosis and appropriate treatment.

Methodological introduction: duration of treatment in adults

Studies were included where the majority of patients were adults (16 years of age and over) and where a modern drug treatment regimen was used to treat TB meningitis. Thus, treatment had to include at least isoniazid, rifampicin and pyrazinamide.

Two cohort studies performed in Turkey{111} and Thailand{112} were identified which compared different durations of treatment for TB meningitis. Two case series performed in Thailand{113} and Ecuador{114} and one treatment arm of a study performed in India{115} were also considered. All of the studies were completed more than 15 years ago and were excluded due to methodological limitations.

There is a lack of high-level evidence in this area. There are no RCTs which compare different durations of treatment for TB meningitis and there are no good quality cohort studies. This seems to be due to the relative rarity of the condition (small patient numbers in studies) and the associated high mortality and morbidity. The studies that do exist are plagued by a number of methodological problems including small sample size, a lack of generalisability due to completion in developing countries, patients in variable stages of clinical severity, problems with definitive diagnosis of TB meningitis, concurrent use of glucocorticoid therapy and a lack of inferential statistics. Due to the low quality of the studies in this area, it was not possible to write evidence statements.

Methodological introduction: duration of treatment in children

One systematic review of case series studies{116} was identified. This compared studies of six months treatment duration for TB meningitis with those of more than six months treatment duration. Nine studies were included, four of which were in the six months duration group{113},{114},{117},{118} and five in the more than six months duration group.{111},{119–123} Approximately 75% of the patients included were children. The review had several methodological limitations and due to these issues, the studies included in this review and performed in children were assessed separately. These were two studies performed in India,{120},{122} one in Thailand{117} and another in South Africa;{118} however all of these studies were excluded on the basis of methodological limitations.

Within the area of treatment duration for TB meningitis in children (as with adults) there is a lack of high-level evidence. Studies had similar methodological limitations to those in adult populations. Additionally, the issue of generalisability of results to the UK was even more marked as one study reported high levels of childhood malnutrition.{122} Due to the low quality of the studies in this area, it was not possible to write evidence statements.

Methodological introduction: glucocorticoids as an adjunct to antituberculous drugs

A Cochrane systematic review{124} compared the effects of glucocorticoids in combination with anti-TB treatment with anti-TB treatment alone in patients with TB meningitis. The review consisted of six RCTs{125–130} and was methodologically sound and hence it could technically be given a grading of 1++/1+. However, the methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements. The authors of the review concluded that

'adjunctive steroids might be of benefit in patients with TB meningitis. However, existing studies are small, and poor allocation concealment and publication bias may account for the positive results found in this review'.

In the study steroids were associated with fewer deaths (RR 0.79, 95%CI 0.65 to 0.97) and a reduced incidence of death and severe residual disability (RR 0.58, 95%CI 0.38 to 0.88). Subgroup analysis suggested an effect on mortality in children (RR 0.77, 95%CI 0.62 to 0.96) but the results in a smaller number of adults were inconclusive (RR 0.96, 95%CI 0.50 to 1.84).

Another systematic review{131} was also appraised; however this was excluded due to methodological limitations.

One further RCT was identified.{132} This was a very high-quality study performed in Vietnam in adults and included patients who were HIV positive.

Studies were excluded where glucocorticoids were administered intrathecally as this rarely occurs due to the necessity of a lumbar puncture. This was the approach taken in the Cochrane systematic review.{124}

Due to the methodological issues associated with the studies in the Cochrane review{124} there is no sound evidence available for the use of corticosteroids in children with TB meningitis. There is also no compelling evidence in this area for HIV-positive patients.

Evidence statements

Mortality and severe residual disability

In a RCT performed in Vietnam{132} in TB meningitis patients over 14 years of age, adjunctive treatment with dexamethasone was associated with a reduced risk of death (RR 0.69, 95%CI 0.52 to 0.92, p=0.01). It was not however associated with a significant reduction in the proportion of severely disabled patients or in the proportion of patients who either died or were severely disabled after nine months.{132} (**1++**)

Disease severity and HIV status

The treatment effect of adjunctive dexamethasone was consistent across subgroups that were defined by:

- disease severity grade (stratified RR of death, 0.68, 95%CI 0.52 to 0.91, p=0.007){132}
- HIV status, although the reduction in the risk of death was not significant (the number of HIV-infected patients was too small to confirm or reject confidently a treatment effect).{132} (**1++**)

Adverse effects

Significantly fewer serious adverse events occurred in the dexamethasone group than in the placebo group (26 of 274 patients *vs*. 45 of 271 patients, p=0.02). In particular eight severe cases of hepatitis (one fatal) occurred in the placebo group and none occurred in the dexamethasone group (p=0.004).{132} (**1++**)

From evidence to recommendations

The evidence base in this area is hampered by the difficulty of recruiting patients for participation in studies. Mostly the existing studies included people following a presumptive diagnosis with few positive culture confirmations.

There is no evidence to support treatment durations of less than 12 months, but all the evidence on duration has some methodological limitations. Given the serious risk of disability and mortality, the advice given in the 1998 BTS guidelines{68} remains appropriate.

There is also no evidence to inform the choice of drugs. Caution is required with ethambutol in unconscious patients, streptomycin should be avoided in pregnancy if at all possible (fetal 8th nerve damage) and there is potential teratogenicity with ethionamide and prothionamide.{133}

The important factor in drug choice was penetration into CSF. Ethionamide, isoniazid, prothionamide and pyrazinamide achieve best penetration. Rifampicin is less good in this regard, and ethambutol and streptomycin only penetrate into CSF if the meninges are inflamed.

Given the potential severe effects of neurological damage arising from TB meningitis, and the strong evidence in adults from the Vietnam study{132} supporting additional glucocorticoids, this guideline recommends them. There is no reason to give a high-dose glucocorticoid to most patients, and the GDG reached a consensus on reviewing treatment response after 2–4 weeks with a view to starting to withdraw the glucocorticoid as soon as it is safe to do so.

RECOMMENDATIONS

R43 Patients with active meningeal TB should be offered:

- a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP)
- a glucocorticoid at the normal dose range
  - adults equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg. A
  - children equivalent to prednisolone 1–2 mg/kg, maximum 40 mg. D(GPP)

with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation. D(GPP)

R44 Clinicians prescribing treatment for active meningeal TB should consider as first choice:

- a daily dosing schedule B
- using combination tablets. D

Cross-referring:

For details of standard drug treatment, see section 6.1.

For details of managing drug-resistant TB, see chapter 9.

Peripheral lymph node tuberculosis

Clinical introduction

Lymph node TB is an important form of non-respiratory TB accounting for nearly half of all non-respiratory sites{26},{27} (see epidemiology in Appendix G). Since non-respiratory disease is found less commonly in white UK-born people than in others, who now make up nearly 70% of all cases in the UK, the number of cases of lymph node disease seen is rising.

Trials by the BTS and its predecessors with regimens of 18 months,{134} nine months{134},{135} and six months duration,{135–137} all showed a significant proportion of cases (up to 40%) to have residual nodes at the end of treatment, and up to 10% at 30 month follow-up. Sometimes new nodes and occasionally sinuses develop during treatment and/or during follow-up. Nearly all of these events are thought to be immunologically mediated responses to residual tuberculo-proteins, and not failure to respond to treatment or relapses. When cultured there is seldom evidence of bacteriological activity.

Methodological introduction

A meta-analysis{138} of studies of varying designs compared six-month treatment regimens with nine month regimens in people with peripheral lymph node TB. However, this was excluded due to methodological limitations.

Two RCTs identified in the meta-analysis were assessed seperately.{137} One UK trial comparing six months *vs.* nine months daily treatment was reported in two papers firstly as preliminary results{136} and then follow-up results at 30 months.{137} The other trial performed in Hong Kong{139} compared six months and nine months thrice-weekly treatment, however this was excluded due to limitations in methodology.

There was a lack of high-quality comparative studies in this area, thus only one has been included as evidence.{136},{137}

Evidence statements

A UK RCT{136},{137} of patients with peripheral lymph node TB compared two nine-month drug regimens (2HRE/7HR and 2HRZ/7HR) and one six-month regimen (2HRZ/4HR). Of those patients seen at 30 months (85%), there was no statistically significant difference between the groups in terms of reported residual measurable nodes, relapse, enlargement of existing nodes, development of new glands or sinuses or the need for new operative procedures. Aspiration after commencement of treatment was performed in eight patients: seven on the 2HRE/7HR regimen and the other on 2HRZ/4HR (2HRE/7HR versus all HRZ, p=0.005). (**1+**)

From evidence to recommendations

There was little evidence to guide the GDG in more practical issues, but it was felt that treatment should be stopped at the end of the regimen regardless of the appearance of new nodes, residual nodes or sinuses draining.

One study{136},{137} of six months *vs.* nine-months treatment duration shows equivalence for fully susceptible organisms. However, this trial used a three-drug initial phase (2RHZ), which may be inadequate in view of current drug resistance rates,{140} and the isoniazid resistance rate of 12% in the trial.{136},{137} The standard six-month, four-drug regimen is therefore recommended.

Drug treatment is still required even if a gland has been surgically removed, because of the possibility of residual local and distal TB foci. Surgical excision biopsy for histology and culture is advised if pus cannot be aspirated from a gland. Fine needle aspiration does not give adequate samples for TB culture.

RECOMMENDATIONS

R45 For patients with active peripheral lymph node tuberculosis, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for further details) B
- use a daily dosing schedule B
- include combination tablets. D

R46 Patients with active peripheral lymph node TB who have had an affected gland surgically removed should still be treated with the standard recommended regimen. D(GPP)

R47 Drug treatment of peripheral lymph node TB should normally be stopped after six months, regardless of the appearance of new nodes, residual nodes or sinuses draining during treatment. D(GPP)

Cross-referring:

For details of standard drug treatment, see section 6.1.

For details of managing drug-resistant TB, see chapter 9.

Bone and joint tuberculosis: drug treatment

Clinical introduction

Spinal TB accounts for approximately half of all the sites of bone and joint TB seen in England and Wales.{22},{26},{27} As such it is an important subset of non-respiratory disease, and one which can sometimes have significant morbidity because of spinal cord compression from extradural abscess and/or vertebral collapse. For these reasons, the GDG considered the evidence base on the medical management of spinal TB as a proxy for the management of the many possible joint sites, in which separate drug trials have not been conducted.

Methodological introduction

Three RCTs were identified which compared different durations of treatment in those with TB of the spine.

A Hong Kong study{141} with fourteen years of follow-up compared six, nine and eighteen months of treatment in those who had undergone radical anterior resection with bone grafting. The results of this trial (without the 18 month arm) were also reported at five years in a paper that presented the results of two further trials at five years in Madras and Korea,{142} which both compared six months of treatment with nine months in patients who had not received surgery. The Madras trial was also reported with follow-up at ten years.{143} The Korean trial{142} was excluded due to a number of methodological limitations.

These trials were all originally commenced in the 1960s and 1970s by the British Medical Research Council (MRC) and although they subscribed to the methodological standards of the time, they do not include all patients in the analyses in the groups to which they were originally allocated (ie an intention to treat analysis). In line with NICE guidance in circumstances where an intention to treat analysis has not been used and there is little evidence available, these studies have been evaluated as if they were non-randomised cohort studies.

These studies did not use the standard, four-drug initial treatment regimens currently used in the UK and none of the studies reported blinding methods.

Evidence statements

In a Hong Kong study{142} at five years follow-up, all analysed patients who had received radical anterior resection with bone grafting and a six- or nine-months treatment regimen of isoniazid, rifampicin and streptomycin (except one in each group) had favourable status at five years, and most had achieved favourable status by three years. (Favourable status was defined as full physical activity with radiographically quiescent disease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen). (**2+**)

In the Hong Kong study{141} at 14 years follow-up, clinical outcomes were similar in the six-, nine-and 18-month treatment regimen groups. One patient in the six months group had minor motor deficits whereas one patient in the 18 months group had partial unilateral sensory deficits. No patients had bladder or bowel disturbances at final follow-up and there was no recurrence or reactivation of tuberculosis in either group. Additionally there were no statistically significant differences in the change in mean angle of deformity between the groups and most side effects occurred early in treatment and were not related to duration of treatment. (**2+**)

In a study in Madras{142} of patients who received treatment (isoniazid and rifampicin) without surgery for six or nine months, 91% in the six-month group and 98% in the nine-month group had a favourable status at five years (using the same definition as the Hong Kong study{142}). At ten years{143} there was no significant difference in favourable status, or occurrence of complete bony fusion. The angle of kyphosis increased in both regimens with no significant difference between groups; however, in patients less than 15 years of age with angle of kyphosis >30°, the mean increase by ten years was 30°, compared with 10° in those >15 years (p=0.001). (**2++**)

From evidence to recommendations

A number of trials were conducted in association with the British MRC between the 1960s and 1980s in Korea, India and Hong Kong, designed according to the standards of the time. Whilst they did not use intention to treat analysis, these studies on six, nine and 18 months of treatment, with extensive follow-up of up to 10 years in some cases, show that six months duration of treatment performed just as well as longer regimens. The GDG agreed that these results are likely to be applicable to other forms of bone and joint tuberculosis, and accordingly recommended the standard six-month, four-drug regimen.

The GDG acknowledged the risk of CNS involvement via the spinal cord, and recommended scans to check for any patient with neurological signs or symptoms. The was no evidence to guide a choice of either CT or MR scanning.

RECOMMENDATIONS

R48 The standard recommended regimen (see section 6.1 for details) should be planned and started in people with:

- active spinal TB B
- active TB at other bone and joint sites. C

R49 Clinicians prescribing treatment for active bone and joint tuberculosis should consider as first choice:

- a daily dosing schedule B
- using combination tablets. D

See section 6.1 for details.

R50 CT or MR scan should be performed on patients with active spinal TB who have neurological signs or symptoms. If there is direct spinal cord involvement (for example, a spinal cord tuberculoma), management should be as for meningeal TB (see section 7.1). D(GPP)

Cross-referring:

For details of managing drug-resistant TB, see chapter 9.

Bone and joint tuberculosis: routine therapeutic surgery

Clinical introduction

From before the age of anti-tuberculosis treatment, immobilisation and bed rest were thought to be important for bone and joint tuberculosis. This view continued after the development of anti-tuberculosis drugs and into the time when shorter durations of treatment with newer drugs were available. A series of studies by the MRC, commencing in 1965, showed the respective roles of anti-tuberculosis treatment and other routine management measures in spinal tuberculosis. Studies in Korea found no benefit from routine bed rest,{144},{145} or of a plaster jacket during therapy,{145},{146} and in Rhodesia no benefit from routine initial debridement of lesions.{147} Prior to the introduction of rifampicin, trials of radical anterior fusion showed mixed results.{142},{148–151} The advent of rifampicin led to further trials on the use of anterior spinal fusion in conjunction with short-course treatment regimens.

Methodological introduction

Two RCTs were identified which compared surgery and drug treatment for those with TB of the spine with drug treatment alone.

A study in Rhodesia{149} compared debridement and drug treatment with drug treatment alone but was excluded for methodological issues.

A Madras study, reporting at five{142} and ten years,{143} compared radical resection with bone grafting plus six months' treatment with isoniazid and rifampicin with just six or nine months' treatment with isoniazid and rifampicin.

The Madras trial, whilst in line with the methodological standards at the time it was commenced, did not include all patients in the analysis in the group to which they had been originally allocated (ie an intention to treat analysis). In line with NICE guidance in circumstances where an intention to treat analysis has not been used and there is little evidence available, these studies have been evaluated as if they were non-randomised cohort studies. Furthermore, it should be noted that a two-drug regimen would not now be used in the UK as standard therapy.

Evidence statements

At five years,{142} radical resection with bone grafting in addition to six-months treatment regimen (with isoniazid and rifampicin) showed no benefit in status (favourable status was defined as no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease) compared to six- or nine-months treatment regimen alone. (**2++**)

Whilst at ten years,{143} the surgery and six-months treatment regimen was less effective in terms of favourable status than the nine-month treatment regimen alone (p=0.03), the difference being due to surgical complications. However, patients in the surgery and anti-tuberculosis drug treatment group had a faster resolution of sinuses and/or clinically evident abscesses (p<0.001 at two months) and a lower incidence (p=0.03) than those in the anti-tuberculosis drug treatment only groups.

There was no significant differences found between the groups in terms of occurrence of complete bony fusion or angle of kyphosis. There were four deaths associated with spinal tuberculosis (all within the first six months and all in the surgery and anti-tuberculosis drug treatment group). Three died in the postoperative period and the other had complications of postoperative paraplegia. (**2++**)

From evidence to recommendations

Although the GDG concluded that the evidence showed no additional advantage of routinely carrying out anterior spinal fusion over standard chemotherapy, the recommendations for spinal surgery cannot be extrapolated to bone/joint tuberculosis at other sites.

Aspiration of paraspinal abscesses and/or biopsy from spinal sites may be needed for the diagnosis of TB, which is different from routine anterior fusion. Forms of surgery such as aspiration or arthroscopy of joints may be needed to obtain material for histology and culture by which to make the diagnosis of tuberculosis in bone/joint sites other than the spine.

RECOMMENDATIONS

R51 In patients with spinal TB, anterior spinal fusion should not be performed routinely. B

R52 In patients with spinal TB, anterior spinal fusion should be considered if there is spinal instability or evidence of spinal cord compression. D(GPP)

Pericardial tuberculosis

Clinical introduction

TB of the pericardium accounts for less than 4% of non-respiratory TB in England and Wales,{140} but is potentially important because of the possibilities of cardiac tamponade and constrictive pericarditis, which have a mortality and morbidity higher than most other forms of extrapulmonary TB.

The presence of a pericardial effusion may require aspiration by pericardiocentesis for diagnosis, repeated during treatment. Similarly, considerable pericardial thickening, with or without fluid, may require surgery with pericardectomy or a pericardial window, which is a major invasive intervention. Additional glucocorticoids tailing from the equivalent of prednisolone 60 mg/day have been recommended in the UK,{68} following studies in Transkei, South Africa, where this form of active tuberculosis was particularly common,{152},{153} which appeared to show reduced morbidity and mortality.

Methodological introduction

A Cochrane systematic review{154} attempted to compare six-month anti-tuberculosis drug treatment regimens with regimens of nine months or more in people with tuberculous pericarditis. The Cochrane review search did not identify any RCTs which compared anti-tuberculosis drug regimens of these different durations.

No further studies were identified which compared six months of treatment with longer treatment durations, thus it was not possible to write evidence statements on the duration of treatment for TB pericarditis.

Two systematic reviews, which considered the effectiveness of glucocorticoids in addition to drug treatment in patients with TB pericarditis were identified. A Cochrane systematic review{154} considered this issue in addition to a number of other treatment issues in TB pericarditis (treatment duration, pericardial drainage and pericardectomy) whilst a review by the same authors, published elsewhere, only considered the issue of additional glucocorticoids for TB pericarditis.{155} The same four studies were included in both reviews{152},{153},{156},{157} and the results presented and the publication year were the same.

The two RCTs included in these reviews by Strang{152},{153} have since been reported at ten years.{158} Results from this new report which now includes an intention to treat analysis, along with the two other RCTs identified in the systematic reviews, have thus been considered separately. One of these studies was excluded on methodological grounds.{156} The other study included HIV-positive patients only.{157}

TB pericarditis is relatively rare and so it is difficult to find enough patients to study; furthermore, it is also difficult to diagnose. For example, the study in HIV patients{157} was small (N=58) and the TB diagnosis was confirmed by culture in only 38% of the participants.

Evidence statements

The results of RCTs performed in Transkei, South Africa, comparing prednisolone to placebo in pericardial effusion and pericardial constriction patients with or without drainage are presented in the table below.{158}Table 29 also includes the results of an RCT comparing prednisolone *vs*. placebo in HIV-positive pericardial effusion patients.{157}

7. Table 29 Summary of evidence for pericardial TB

TB pericardial effusion without open drainage	Evidence
	• Prednisolone reduced the need for repeat pericardiocentesis, which was required in 10% of prednisolone patients and 23% of placebo patients (p=0.025).{158}
	• Adverse outcomes of any type were significantly less frequent in the prednisolone than the placebo group, occurring in 19% compared with 40% respectively (p=0.003).{158}
TB pericardial effusion with/without open drainage	**Evidence**
	• Adverse outcomes occurred in 52% with neither open drainage nor prednisolone, *vs*. 14% drainage and prednisolone, 11% drainage and placebo and 19% prednisolone and no drainage (p=0.08 for interaction).{158}
TB pericardial effusion HIV positive	**Evidence**
	• Survival was significantly improved in the prednisolone group compared with the placebo group when patients were followed up for 18 months (p=0.004). However, although steroids were associated with fewer deaths, this was not statistically significant if the timing of the deaths was not taken into account (RR 0.5, 95%CI 0.19 to 1.28).{157}
	• Improvement in physical activity (p=0.02) and resolution of raised jugular venous pressure (p=0.017), hepatomegaly (p=0.007) and ascites (p=0.051) were faster in prednisolone-treated patients than those given placebo.{157}
	• There was no difference in the rate of radiologic and echocardiographic resolution of pericardial effusion, the risk of constrictive pericarditis or the frequency of steroid-related complications between the prednisolone and placebo groups.{157}
TB pericardial constriction	**Evidence**
	• There were no significant differences in adverse outcomes or deaths from pericarditis between prednisolone and placebo groups.{158}
Any pericarditis	**Evidence**
	• In a multivariate survival analysis (stratified by type of pericarditis), prednisolone reduced the overall death rate after adjusting for age and sex (p=0.044) and substantially reduced the risk of death from pericarditis (p=0.004).{158}

From evidence to recommendations

The group were not aware of any further evidence on the treatment regimen and concluded that first-line treatment is with the standard six-month, four-drug regimen.

There are no comparative studies on which to base recommendations on the duration of treatment. Since this is a pauci-bacillary form of extrapulmonary disease by extrapolation from other forms of extrapulmonary disease with more evidence, a six-month duration of treatment is expected to be effective.

The GDG agreed that the RCT evidence{157},{158} strongly supported the use of glucocorticoids in adults with active pericardial tuberculosis and that they were also likely to be beneficial in children.

RECOMMENDATIONS

R53 For patients with active pericardial TB, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

R54 In addition to anti-TB treatment, patients with active pericardial TB should be offered:

- for adults, a glucocorticoid equivalent to prednisolone at 60 mg/day. A
- for children, a glucocorticoid equivalent to prednisolone 1 mg/kg/day (maximum 40 mg/day)

with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation. D(GPP)

Cross-referring:

For details of managing drug-resistant TB, see chapter 9.

Disseminated (including miliary) tuberculosis

Clinical introduction

In the 1997 guidance on notification, it was suggested that those with non-specific symptoms started on TB treatment should be described as having 'cryptic disease' with the term 'cryptic miliary disease' being reserved for those where the organism has been isolated from blood, from bone marrow or from multiple organ systems. In clinical texts there is usually a distinction between 'classical miliary' disease with the diffuse 1–2 mm uniform micronodular chest X-ray from acute haematogenous spread which may also involve other organs, including the CNS, and 'cryptic miliary' where the patient may have fever but few localising signs. The data collection form for enhanced TB surveillance gives possible sites of TB, including miliary and cryptic disseminated. Cryptic disseminated is defined as 'systemic illness without localising features'.

These different labels for forms of what is essentially blood-borne spread of tuberculosis can cause confusion. Essentially, blood-borne spread may or may not be accompanied by chest X-ray or high-resolution CT changes. Such blood-borne spread often also causes significant liver function derangement because of diffuse liver involvement. This is a serious form of TB with a significant morbidity and mortality, so the risks of treating the disease with drugs which have a low incidence of hepatic side effects (3%), are much less than those of leaving the patient inadequately treated. The meninges are also not infrequently involved as part of the blood-borne spread, with up to 30% having clinical or lumbar puncture evidence of such involvement.{140} The detection of CNS disease is important because of the longer duration of treatment required for CNS involvement.

Methodological introduction

One retrospective study{159} where patients with disseminated TB received three different durations of treatment was identified, however this was excluded due to small sample size (N=6).

No other comparative studies were found, hence it was not possible to write evidence statements.

From evidence to recommendations

No data were found to inform recommendations. It is noted that all sites outside the CNS for which data exist show adequate response to a six-month, four-drug initial treatment regimen, but that six-month regimens have not been shown to be adequate for those with CNS involvement (see section 7.1).

Exclusion of CNS disease is important, by CT scan, MRI or lumbar puncture, so that the correct duration of treatment is applied.

Abnormal liver function should not prevent or delay the commencement of TB treatment, which usually causes improvement in liver function abnormalities due to the disease itself.

RECOMMENDATIONS

R55 For patients with disseminated (including miliary) TB, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

R56 Treatment of disseminated (including miliary) TB should be started even if initial liver function tests are abnormal. If the patient's liver function deteriorates significantly on drug treatment, advice on management options should be sought from clinicians with specialist experience of these circumstances. D(GPP)

R57 Patients with disseminated (including miliary) TB should be tested for CNS involvement by:

- brain scan (CT or MRI) and/or lumbar puncture for those with CNS signs or symptoms
- lumbar puncture for those without CNS signs and symptoms.

If evidence of CNS involvement is detected, treatment should be the same as for meningeal TB (see section 7.1). D(GPP)

Cross-referring:

For details of managing drug-resistant TB, see chapter 9.

Other sites of infection

From evidence to recommendations

There is no evidence base available to derive recommendations for other sites of infection. However, as the pathogen and its drug susceptibility is the same, treatment has generally been given with the same regimen as is used for respiratory tuberculosis. The GDG's clinical experience supported this and hence the recommendation below is extrapolated from the evidence base for respiratory tuberculosis, and other non-respiratory sites.

RECOMMENDATION

R58 For patients with:

- active genitourinary TB, or
- active TB of any site other than:

– respiratory system

– CNS (typically meninges)

– peripheral lymph nodes

– bones and joints

– pericardium

– disseminated (including miliary) disease

the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

Cross-referring:

For details of managing drug-resistant TB, see chapter 9.

8 Monitoring, adherence and treatment completion

Improving adherence: directly observed therapy

Clinical introduction

People with TB can either be given treatment to take without supervision (self-administered therapy) or under direct observation by a health professional or other person such as a family member, where the swallowing of the medication is observed. The latter is known as directly observed therapy. Intermittent (less often than daily) dosing regimens lend themselves to DOT because of the lower frequency of dosing to supervise. The monitoring of DOT is however only one part of the WHO DOT strategy,{166} which has five elements.

1. Supervised medication taking.
2. Drug availability including reserve drugs.
3. Sputum testing facilities with quality control.
4. Patient tracking systems.
5. Political commitment at Governmental level.

The WHO advocates universal DOT as part of their overall strategy, the aim being to increase treatment completion rates to over 85%, which particularly for smear-positive pulmonary disease, is the level above which modelling shows that case numbers then begin to decrease. Treatment completion rates of over 90% however have been reported from both the USA and UK using mainly self-administered therapy and only selective – not universal – DOT.{160},{167}

Sceptics who have labelled DOT as 'supervised pill swallowing'{168} say that the success of DOT programmes is derived from the substantial technical and financial investment in tuberculosis programmes that the DOT strategy represents and not the DOT element itself.{169}

DOT is commonly used in the UK, as the 1998 BTS guidelines{68} recommended, for patients who are unlikely to comply, those with serious mental illness, patients with multiple drug resistances, and for those with a history of non-adherence with anti-tuberculosis medications, either in the past or documented during treatment monitoring. For those without multiple drug resistances, a three-times weekly regimen was recommended.

Current practice

Of the TB service providers participating in the review of current services, 79% in London and 80% elsewhere used DOT. Some of the other respondents stated that it was not needed. There was no obvious variation in the provision of DOT by notifications, personnel or specialist personnel, nor was there any correlation between the number of patients given DOT and the number of notifications, personnel or specialist personnel. It would seem that the variation in practice is due to different clinical habits. Given the cost of DOT, it would seem timely to promote a consistent and evidence-based approach to its provision.

Methodological introduction

Three systematic reviews{170–172} and four additional RCTs{173–176} were identified comparing DOT with self-administered treatment. Two systematic reviews{171},{177} and one RCT{175} were excluded due to methodological limitations. The included studies were a Cochrane systematic review of six RCTs (four studies of patients being treated for active TB conducted in Thailand,{178} Pakistan{179} and South Africa{180},{181} and two US studies of individuals receiving preventive therapy for latent TB{182},{183}) plus a US study of homeless patients{176} and a study of illegal immigrants in Italy{174} both with latent TB on prophylaxis, and a study of active TB patients in Australia.{173}

Numerous elements of a DOT programme may affect cure and treatment completion rates and therefore it is difficult to isolate the contribution of observing the patient taking their TB medication. For example, the relationship a patient has with their observer or the distance of the clinic from a patient's home are integral parts of a DOT programme which may influence outcomes. This also means that due to the number of elements which may differ within a DOT programme and cultural differences between populations, it is difficult to generalise from one setting to another. The way it is possible to offer DOT services will be dependent on the way healthcare systems are configured and the resources available. DOT services may differ in terms of:

- hospital or clinic versus home-based DOT

- observers may be lay persons (community or family members who may or may not have received training or advice on DOT) or healthcare professionals (doctors, nurses or health visitors)
- DOT may be given throughout treatment or for only part of it
- DOT may be introduced with other (less explicit) elements which may affect outcomes, for example new enthusiastic staff, education, incentives (food, drink, travel vouchers etc), counselling or psychosocial support.

None of the studies identified were performed in the UK.

In terms of who should observe DOT, six RCTs comparing different types of DOT observers were identified. The studies were performed in Tanzania,{184},{185} Pakistan,{179} the USA,{176} Swaziland{186} and South Africa.{181}

A number of different types of observers are used in the studies and may not necessarily be comparable across studies. These were:

- a volunteering community member selected by a village leader who was interviewed and trained by a health worker, compared with observation by a health worker in the nearest health centre{185}
- a trained guardian (family member) or former TB patient compared to a health worker in a health facility{184}
- a health worker at a health facility where a patient met access criteria to the facility, compared with supervision by a family member who was orientated in the role{179}
- a lay health worker in the lay health worker's home compared with observation by a nurse at a clinic{181}
- a trained family member compared with a community health worker{186}
- a research assistant observing homeless patients at a study site with a $5 incentive compared with observation by a trained, paid, homeless peer health advisor.{176}

In the US study,{176} the monetary incentive in the research assistant observer arm meant that the contribution of the observer to this result was unclear.

Additional factors for consideration include the duration of supervision (this was only for the first two months in the studies in Tanzania{184},{185}), variable motivation and training of observers and the convenience of the site of the observation. None of the studies were UK based.

With regard to terminology in this area, in recent years use of the term compliance has been discouraged due to its connotations of patient subservience. The term adherence has instead been used to describe the patient's choice as to whether to complete treatment. More recently the term concordance has been recommended to reflect 'the active exchange of information, negotiation, and spirit of cooperation'.{187}

Evidence statements

Efficacy of DOT

A Cochrane systematic review{172} found that patients allocated to DOT compared to self-administered treatment had similar outcomes in relation to cure and cure plus treatment completion based on a meta-analysis of four RCTs of patients with tuberculous disease.{178–181} In terms of population groups where DOT may be effective, only one of these RCTs (in sputum positive TB patients over 15 years of age with no previous treatment history for TB{178}) significantly favoured DOT (in terms of both cure (RR 1.13, 95%CI 1.04 to 1.24) and cure plus treatment completion (RR 1.11, 95%CI 1.03 to 1.18) compared with self-administered treatment. However, this study allowed participants to choose their supervisor and involved home visits by health workers every two weeks. (**1++**)

In an RCT of homeless patients in the USA{176} on prophylaxis for latent TB, no significant difference was found in treatment completion between a peer health advisor performing DOT and usual care (self-administered treatment). Treatment completion in a monetary incentive arm however (where DOT was provided by a trained research assistant and patients were given a monetary incentive at each visit), was significantly better than in the usual care arm (p=0.04). Residence in a hotel or other stable housing at entry into the study *vs.* residence on the street or in a shelter at entry was an independent predictor of treatment completion (OR 2.33, 95%CI 1.00 to 5.47). (**1++**)

In illegal immigrants on prophylaxis for latent TB{174} in Italy, those on supervised (directly observed clinic-based) treatment were significantly less likely to complete treatment than did those on an unsupervised regimen (p=0.006, log rank test).

Treatment completion rates were 7.3% in the supervised group and 26% in the unsupervised group. (**1++**)

In an Australian RCT,{173} when comparing a family based programme of DOT for active TB patients with standard supervised but non-observed therapy no significant difference was found in relation to treatment completion or non-adherence. (**1+**)

Observers for DOT

None of three strategies tested in patients with active TB in Pakistan{179} (self-supervision, health worker DOT and family member DOTS) was superior to the others in terms of cure rate or cure rate and treatment completion combined. (**1++**)

In homeless patients in the US{176} on prophylaxis for latent TB, completion in the research assistant observer with monetary incentive arm was significantly better than in the peer health advisor arm (44% *vs*. 19%, p=0.01). (**1++**)

In patients treated for active TB in Tanzania,{185} no significant difference in biological conversion rate at two months or cure at seven months was found between institutional-based directly observed treatment and community-based directly observed treatment. (**1+**)

The cure rate and the treatment success rate (cure and treatment completion) for smear-positive patients in Tanzania{184} was not significantly different under community DOT (by a family member or former TB patient) compared with health facility-based DOT. (**1+**)

In new smear-positive patients in Swaziland,{186} there was no significant difference in cure rate or cure and completion rate between community health workers' and family members' DOT. (**1+**)

Treatment outcomes (cure combined with treatment completion) in South African{181} patients with active TB were not significantly different in the lay health worker supervision group compared to clinic DOT. (**1+**)

From evidence to recommendations

The generalised application of DOT is shown to be effective in only one study,{178} which allowed participants to choose their supervisor and also involved home visits by health workers every two weeks. One study in homeless men (street- or shelter-dwelling) in the USA indicated that, for street homeless men, financial incentives with personal support and/or more secure accommodation is associated with higher completion rates of treatment of latent TB infection when given as DOT. Studies in Australia and Italy did not show improved outcomes for those in the DOT arms. There is no high-level UK evidence in this area.

The interventions involved in DOT are not just supervised taking of medicines, but include increased contact and support. Given the resources required for DOT, and the attendant opportunity costs, the GDG decided not to recommend DOT for the general TB population. Improved adherence in both DOT and routine care may be achieved through more frequent contact with healthcare professionals.

Contamination between treatment arms in any DOT trial may have caused underestimated efficacy. In order to provide DOT, the infrastructure and culture of TB services changes (in particular, the emphasis given to ensuring treatment is completed). These changes may also have affected the control arms of studies. No trials have yet been conducted using designs to eliminate this effect.

There are also concerns about the outcomes which are necessarily used in these trials. Treatment completion and/or microscopy conversion are the outcomes used in trials to date, but the outcomes DOT aims to prevent are development of drug resistance and relapse of disease. Existing trials have neither the necessary long-term follow-up, nor are powered to look directly at these outcomes.

The model of DOT administered is also not optimum in most RCTs, for example if patients are sometimes expected to travel large distances for their treatment rather than DOT being available at the most convenient location. The only trial that allowed patients to have an input into where DOT was administered did find a beneficial effect. This is an issue of applicability for trials conducted in developing countries.

The GDG could not reach unanimity on making a recommendation to limit the use of DOT, but agreed that it is not useful in the UK as a universal mode of TB treatment, and consequently set out to recommend groups in whom DOT may be useful, and for whom it should be considered on an individual basis.

The GDG felt that evidence was sufficient to require a recommendation on DOT for street- or shelter-dwelling homeless people. The GDG did not feel able to make a recommendation to use DOT routinely for people with histories of alcoholism, drug abuse or mental illness.

One of the studies considered{176} indicates some effect of stable housing on adherence. Considering this and the multifaceted support contained within DOT programmes, the GDG regarded it as crucial to DOT's success that environmental and psychosocial factors, and the pragmatic patient-centred delivery of DOT, be considered at the start of the patient's treatment.

RECOMMENDATIONS

R62 Use of DOT is not usually necessary in the management of most cases of active TB. A All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

- street- or shelter-dwelling homeless people with active TB B
- patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)

R63 Clinicians who are planning to offer a course of DOT should consider ways to mitigate the environmental, financial and psychosocial factors that may reduce adherence, including stability of accommodation, prescription charges and transport. The setting, observer and frequency of treatment should be arranged to be most practicable for the person with TB. The person with TB and his or her assigned key worker should be involved in deciding these arrangements. DOT should also be supported by frequent contact with the key worker (see 8.3). D(GPP)

9 Improving adherence: non-pharmacological strategies

Clinical introduction

With regard to terminology in this area, in recent years use of the term compliance has been discouraged due to its connotations of patient subservience. The term adherence has instead been used to describe the patient's choice as to whether to complete treatment. More recently the term concordance has been recommended to reflect 'the active exchange of information, negotiation, and spirit of cooperation'.{187}

Concordance on TB treatment has been recognised as an issue for many years.{188} Problems can arise with both physicians' adherence with recommended regimens and with patients' adherence with the agreed treatment.{189},{190} Adherence is the single most important determinant of treatment outcome, with poor adherence being strongly associated with treatment failure and relapse.{72} Strategies to improve adherence with treatment are therefore very important in those patients taking self-administered treatment. Any measure which increases adherence is therefore likely to improve outcome, by increasing the cure and completion rate, and reducing the failure rate of treatment and the relapse rate after treatment completion.

Current practice

Improving adherence

Participants in the review of current services were asked about incentives and measures to improve adherence to therapy, including free prescriptions.

94% of clinics in London, and 73% of participants outside London, reported using some measures to improve adherence. Most clinics reported using urine assays, examining urine colour, using tablet counts, and controlled dosage systems. Other respondents (outside London) also asked patients to sign care plans with regular support or gave the patients tablet diaries. Five responders outside London cited the use of home visits as a measure of improving adherence. There was no apparent variation by notifications, personnel or specialist personnel which might account for some clinics providing these while a few do not. As these simple measures appear to be almost universally used, and given the potential benefits, it seems appropriate that all clinics have some such measure available, unless their work is only in screening, vaccination or contact tracing.

61% of clinics in London, and 19% of participants outside London, used incentives to increase clinic attendance. Respondents mainly reported refunding travel costs, but others stated were food and prizes for children. Three clinics (all in London) offered cash. There was no obvious variation by notification rates in the clinics using incentives outside London, although there may be a trend in London toward high-notification clinics using incentives. This may explain the contrast in use between London and the rest of England and Wales. There was no obvious variation by personnel or specialist personnel.

Only 16% of participants outside London had free prescriptions. Within London, this figure was 67%. The contrast between London and elsewhere may be because within London, the use of free prescriptions appeared to be related to the clinics that had more nursing staff.

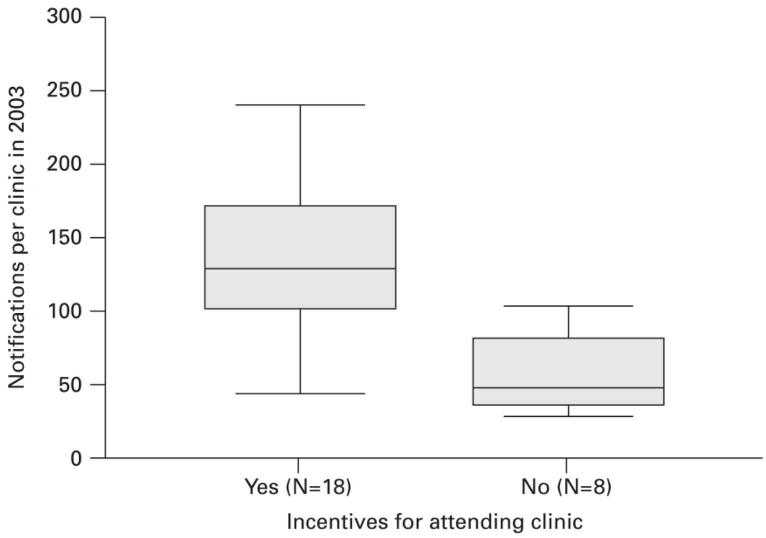


Figure 5 Box plot of notifications of TB per clinic in London, by use of incentives

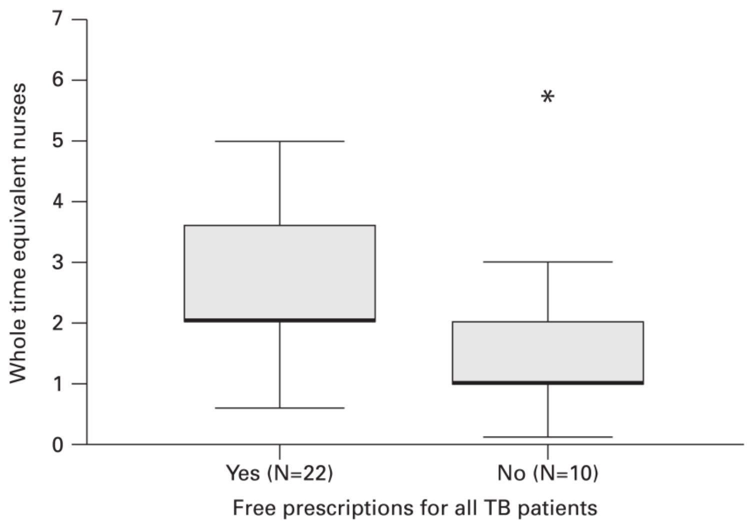


Figure 6 Box plot of notifications of TB per clinic in London, by use of free prescriptions

Outreach work

Some form of outreach was carried out by 67% of clinics outside London. Within London, this was 82%. Most outreach was to patients' homes. Some respondents reported outreach in care homes, detox shelters and other drug treatment venues, homeless shelters, clubs and other community centres and places of work. Variation in the provision of outreach work was not obviously explained by caseload (notifications), staffing levels or availability of specialist personnel.

Methodological introduction: adherence among patients on treatment for active TB

A systematic review{191} examined the evidence from five randomised trials of the effectiveness of various strategies to promote adherence. The review included two trials of patients with active TB,{192},{193} two trials of those on prophylactic drug treatment for latent TB{194},{195} and one trial which included both groups.{196} As the review included trials of both patient groups and did not attempt statistically to combine the results, it was thought that it would be more informative to evaluate the trials on an individual basis.

In terms of strategies to promote adherence in those with active TB, a trial performed in India{193} compared outcomes in those defaulters who failed to collect their drugs and then did or did not receive reminder letters. Two studies included in the systematic review,{191} performed in Korea{192} and the USA{196} were excluded due to methodological limitations.

Three further RCTs were found. Another Indian study compared two policies of default management{197} while a trial performed in Pakistan{198} studied the impact of intensive counselling on treatment outcomes. A third RCT{199} was excluded due to methodological issues.

Two cohort studies and a case control study were also identified. A cohort study performed in South Africa{200} assessed whether the combined strategy of a patient-centred interview plus the issuing of a patient education booklet would increase adherence to treatment. The other cohort study{201} was excluded due to methodological limitations as was the case control study.{202}

Strategies to promote adherence may be specific to their setting, population or treatment (in terms of drug, dose and duration) and thus not generalisable. No studies were identified which had been performed in UK populations.

Methodological introduction: adherence among patients on prophylactic drug treatment for latent TB

With regard to strategies to promote adherence in those with latent TB, the systematic review{191} on adherence strategies for TB treatment included two trials of those on prophylactic drug treatment for latent TB.{194},{195}

One of these studies in a homeless population{194} was excluded on the basis that the only outcome measure was adherence to first referral. The other study{195} however was excluded on the basis of methodological limitations.

Five further studies were found that were not included in the systematic review.{191} One of these was excluded due to methodological limitations.{203}

Of the four remaining studies, all were American trials. Two studies{204},{205} were in adolescents (mainly of Latino origin). One{204} looked at the effects of adherence coaching, self-esteem counselling and usual care on treatment completion. In the other study{205} peer counselling, parent participant contingency contracts, both of these interventions combined and usual care interventions were assessed. Another study{206} was in prisoners released whilst on TB prophylaxis who received either education or the promise of an incentive (a food or travel voucher) when attending the TB clinic. The final study was in a community-based population of homeless adults who received either a cash or non-cash incentive of equivalent value when attending their TB clinic appointments.{207}

Few high-quality trials have been completed, and where there are studies, these are in very specific non-UK population groups raising generalisability concerns. Furthermore, in these studies it is often difficult to assess the contribution of increased attention and motivation from healthcare professionals or other individuals, rather than an intervention itself, which may have been responsible for improved outcomes.

Evidence statements

Active disease

In a study conducted in India{193} a significantly higher treatment completion rate (88%) was achieved among a group of patients who received reminder letters when they defaulted (failed to collect their TB medication) in comparison to patients in a group where no action was taken for default (73%) (p<0.001). (**1+**)

The default rate of the intervention group in a Pakistani study{198} who received monthly health education counselling was 46.6% which was significantly lower compared to 53.6% in the control group (RR 0.87, 95%CI 0.77 to 0.98, p=0.03). (**1+**)

Two policies of default management were compared in an Indian study.{197} Under routine policy, failure to collect TB drugs within three days resulted in a reminder letter and then a home visit on the 11th day and then no further action, whilst under the intensive policy, home visits were made on the same day and followed by further visits at one and two months. No statistically significant difference was found. (**1+**)

In a study conducted in South Africa,{200} the relative risk of being non-adherent to treatment at the control clinic (standard clinic treatment) compared to the intervention clinic (where patients received a patient-centred interview and a health education booklet in addition to standard clinic treatment) was 4.3 (95%CI 1.3 to 14.5, p=0.014). (**2+**)

Latent infection

In teenage people of Latino origin in the USA on treatment for latent TB,{204} the coaching condition (where bilingual Latino college students were trained to provide education concerning latent TB and treatment) had the highest cumulative mean number of pills consumed over six months (129.27), and members of the coaching group took significantly ($p<0.05$) more pills than members of the usual care (113.09) and self-esteem groups (112.02) (in the latter bilingual Latino college students served as self-esteem counsellors). Treatment completion however, was not significantly different between the three groups. (**1+**)

In a study performed in the USA of adolescents on treatment for latent TB,{205} treatment completion rates did not vary significantly across study groups. Treatment was completed by 84.8% of participants in the combined intervention group (peer counselling and incentives), 80.3% in the peer counselling group (adolescents who had completed therapy for latent TB were recruited and trained as peer counsellors), 77.8% receiving usual care (treatment and educational services customarily provided by the clinic) and 76.4% in the incentive group (parents and adolescents negotiated an incentive provided by the parent to be received if the adolescent adhered to the prescribed TB treatment). (**1+**)

In US prisoners released whilst on treatment for latent TB,{208} rates of completion of therapy were 23% in the education group (where patients were seen every two weeks for the duration of their stay, to reinforce initial information), 12% in the incentive group (patients were able to choose food or transport vouchers of equivalent cash value if they went to the TB clinic within one month of release) and 12% in the control group (where there was no further contact with study personnel). Those in the education group were more than twice as likely as those in the control group to complete treatment (adjusted OR 2.2, 95%CI 1.04 to 4.72, $p=0.04$), whereas treatment completion in the incentive group did not significantly differ from the controls. (**1+**)

In a community-based population of homeless adults in the USA on TB prophylaxis,{207} no statistically significant difference in completion was found between those in a cash arm (89%) who received a monetary incentive for keeping each twice-weekly medication appointment and those in the non-cash incentive arm (81%), who could choose fast-food or grocery store coupons, telephone cards or bus tokens with an equivalent face value. (**1++**)

From evidence to recommendations

It is important to involve the patient in treatment decisions, and emphasise the importance of adherence through education in an appropriate language.

In the GDG's experience, useful adherence strategies include:

- reminder letters in appropriate languages
- supervision and support from healthcare workers
- home visits
- patient diaries
- urine tests and other monitoring (for example, pill counts) during visits by a nurse or health visitor
- an appropriately trained and experienced named key worker
- assisting or advising patients regarding links to social security benefits and housing/social services.

Involvement of primary care professionals throughout a course of anti-tuberculosis drugs may also promote adherence.

Prescriptions for people with TB are not free in all parts of England and Wales. This clearly complicates the work of clinicians trying to improve adherence to therapy. The Chief Medical Officer's TB Action Plan{2} sets as one of its essential actions to improve TB services 'explore ways of reducing the cost of TB drugs to patients, and of facilitating their dispensing'. The GDG considered this issue but it is not the role of NICE guidelines to address charges for NHS services at the point of delivery, and no recommendation has been made.

It is important to ensure the availability of liquid drug preparations, to assist treatment of children or people who have swallowing difficulties. However, it should be noted that pharmacies may need up to a week to access these medicines in liquid form and therefore there is a need to ensure prescriptions are written in advance of the patient's current supply running out. If a community pharmacist is involved in the supply of these drugs then discharge summaries/clinic letters and prescriptions will need to be provided to the community pharmacist at the earliest opportunity to ensure a continuous supply.

The GDG considered the difference demonstrated in default rate in one of the studies,{198} while statistically significant, to be small and clinically insignificant. Another study{208} had shown a significant difference in completion rates but both groups had rates that would be very poor in a UK context.

Recommendations are also given here to assist adherence through patient and public information (see chapter 4 for further details). Patient and public information is available in many languages.

RECOMMENDATIONS

R64 To promote adherence, patients should be involved in treatment decisions at the outset of treatment for active or latent TB. The importance of adherence should be emphasised during discussion with the patient when agreeing the regimen. D(GPP)

R65 The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)

R66 TB services should consider the following interventions to improve adherence to treatment for active or latent TB if a patient defaults:

- reminder letters in appropriate languages B
- health education counselling B
- patient-centred interview and health education booklet B
- home visits D(GPP)
- patient diary D(GPP)
- random urine tests and other monitoring (for example, pill counts) D(GPP)
- information about help with paying for prescriptions D(GPP)
- help or advice about where and how to get social security benefits, housing and social services. D(GPP)

R67 Pharmacies should make liquid preparations of anti-TB drugs readily available to TB patients who may need them – for example children and people with swallowing difficulties. D(GPP)

R68 TB services should assess local language and other communication needs and, if there is a demonstrated need, provide patient information accordingly.[5] D(GPP)

[5] Patient information should be drawn from national high-quality resources if available; for examples, see www.hpa.org.uk or www.nks.nhs.uk

10 Risk assessment and infection control in drug-resistant TB

Risk factors

Clinical introduction

Drug resistance is an important issue in the management of TB, as it may prolong the period during which patients are infectious to others as well as compromising the effectiveness of treatment. Resistance to particular single drugs develops in individual bacteria by natural mutations in between one in 10^5 and one in 10^7 organisms, depending upon the drug in question. Multiple drug combinations overcome this problem provided enough drugs are given and taken correctly, but modification of the treatment may be required. Resistance to TB drugs is defined as a level of resistance to four times or greater the concentration of drug required to inhibit a fully susceptible organism.

Resistance can be acquired, in a patient with a fully susceptible organism, by inadequate drug treatment being prescribed (physician error) and/or inadequate adherence with treatment (patient error). Resistance can be also be primary, with a patient being infected with an already drug-resistant organism, thus having drug resistance without a prior treatment history. Resistance can be to a single drug, for example mono-resistance to isoniazid, or to multiple drugs, for example to both isoniazid and streptomycin. MDR TB is defined as high-level resistance to both rifampicin and isoniazid with or without additional drug resistances.

Controlled clinical trials for respiratory tuberculosis show that 100% of cases positive on microscopy and culture pre-treatment have become negative on culture after four months of standard treatment.{209} Positive cultures after four months treatment, ie in month five or later, therefore by definition represent treatment failure.{210} Cases of treatment failure have a high chance of having developed acquired drug resistance, which can be rapidly assessed with molecular probes for rifampicin resistance and a repeat drug susceptibility profile.

MDR TB is important because there is loss of both the main bactericidal drug (isoniazid) and the main sterilising drug (rifampicin). The consequences of this situation are considerable. Such patients who are sputum smear positive remain infectious for much longer than those with susceptible organisms, have a higher death rate from, and a lower cure rate for, their tuberculosis, require individualised complex regimens using multiple reserve drugs of higher toxicity, and cost at least £50,000–70,000 each to treat.{211}

Drug resistance in TB is found in nearly all settings in the world, but some countries or areas have higher levels of drug resistance and MDR TB than others. Drug resistance in England, Northern Ireland and Wales has been monitored continuously by MycobNet, based at the Centre for Infections, Colindale (see chapter 14 for details). This information is available at www.hpa.org.uk

International monitoring of drug resistance is undertaken by the WHO and IUATLD.{212} Russia and the Baltic states recently joining the European Union (Estonia, Latvia and Lithuania) have had high levels of MDR TB (>5% of all cases) reported, as have Argentina, Côte D'Ivoire, Dominican Republic, Iran, and some parts of China and India.

Methodological introduction

Studies were sought that examined risk factors for any type of drug resistance or MDR TB. However, if the study population was dissimilar to the UK the studies were excluded. Thus studies from most developing countries were excluded except those in sub-Saharan Africa and India or Pakistan, as these represent significant ethnic minority groups in the UK. Other studies from Japan, Taiwan, or localised areas of the USA and European countries were excluded as these were felt not to be representative of the ethnic mix of the UK population. National studies undertaken in European countries were included.

Thirteen studies were identified which met the above criteria. Four of these studies were analyses of drug resistant TB in the UK,{213–216} four studies were performed in sub-Saharan Africa,{215},{217–220} and additionally there were studies undertaken in the USA,{221} France,{222} The Netherlands,{223} Switzerland{224} and India.{225} Two studies (one in sub-Saharan Africa and one in India) were excluded due to methodological limitations.{217},{225}

Most studies reported national surveillance data and were graded as level 2 as they involved significant comparative analysis even if they did not fall strictly into a case control study design type. It should be noted that the UK studies which cover notified TB cases over the same time period will include the same cases in their analyses.

The retrospective nature of these studies often means data about some risk factors is not recorded in detail or at all, so there may be incomplete risk factor data. This is especially true of HIV status, which for many patients is often unknown.

To aid comparison, the number of participants included in each study is indicated.

Evidence statements

All evidence statements are graded level 2+.

8. *Table 30: Risk factors*

• Study	• Association
Age as a risk factor	
UK national surveillance study{213} (N=25,217)	A slightly higher proportion of isoniazid resistance (7.6%) was observed in those aged 15–44 years than in other age groups. This was significantly higher than in those aged >44 years for isoniazid resistance only and significantly higher than in those aged >65 years for MDR TB.
UK study based in one London hospital{214} (N=121)	Patients with drug-resistant TB were younger than those with drug-sensitive TB (OR 1.03, 95%CI 1.02 to 1.05, p<0.001). The mean age of those with resistance to more than one first-line drug was 40 years, resistance to only one first-line drug was 32 years and drug-sensitive TB was 47.4 years.
National US study{221} (N=67,340)	Those who were younger than 65 years were at increased risk of drug resistance to at least isoniazid with adjusted OR 1.7 (95%CI 1.4 to 2.2) for those aged 0–14 years, 2.0 (95%CI 1.8 to 2.2) for those aged 15–24 years, 1.8 (95%CI 1.6 to 1.9) for ages 25–44 years and 1.4 (95%CI 1.3 to 1.6) for those aged 45 to 64 years.
National surveillance study in Switzerland{224} (N=1,056)	An increased risk of resistance to any first-line drug was associated with being <65 years of age (adjusted OR 1.5, 95%CI 1.0 to 2.3).
National surveillance study in the Netherlands{223} (N=1,836), a surveillance study in Kenya{218} (N=491) and two South African studies{219},{220} (N=7,266 and N=275 respectively)	No significant association was found between age and drug resistance.
Prior treatment history as a risk factor	
UK national surveillance study{213} (N=25,217)	Those reported to have had a previous episode of TB, exhibited a significantly higher proportion of resistance to at least isoniazid (15.5%) and MDR (9.4%) than either those patients who had never had TB (5.7% and 0.8% respectively), or those whose history regarding previous TB was not available (4.9% and 0.7%, respectively; p<0.001 (isoniazid resistance); p<0.001 (MDR)).

UK study of TB patients in England and Wales reported during two time periods (1993 to 1994 and 1998 to 2000){216} (N=9,541)	There was a strong association between previous treatment and MDR TB (OR 9.1, 95%CI 6.3 to 13.2). This overall relationship was weaker for isoniazid resistance (OR 1.6, 95%CI 1.2 to 2.1).
UK study based in one London hospital{214} (N=121)	The highest risk for resistance to any drug was associated with previous treatment for TB (OR 22.85, 95%CI 5.1 to 102.5; p<0.001).
UK study in Leicestershire{215} (N=104)	Previous history of TB (OR 3.7, 95%CI 1.2 to 11.8, p=0.022) was significantly associated with resistance to at least one first line drug.
National US study{221} (N=67,340)	For resistance to any drugs and the combination of isoniazid and rifampin (MDR TB), the rate of resistance was higher among patients with prior TB compared with those without prior TB (p<0.05). Those with prior TB were at increased risk of resistance to at least isoniazid with an adjusted OR of 2.6 (95%CI 2.4 to 2.9).
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 2.7, 95%CI 2.0 to 3.8) and MDR TB (OR 10.2, 95%CI 4.1 to 25.3) was associated with previous history of treatment. Similarly, unknown treatment history was associated with an increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.5) and MDR TB (OR 3.4, 95%CI 1.1 to 11.2).
National surveillance study in the Netherlands{223} (N=1,836)	Rates of acquired resistance (those who had been previously treated for TB) to isoniazid alone (11.4%) and isoniazid and rifampicin (MDR TB, 5.7%) were higher than rates of primary resistance (those who had never been diagnosed with TB before) to these drugs (5.2% and 0.7% respectively, p<0.05)
National surveillance study in Switzerland{224} (N=1,056)	An increased risk of resistance to any first-line drug was associated with previous history of treatment (adjusted OR 7.3, 95%CI 3.9 to 13.6).
Surveillance study of 26 districts in Kenya{218} (N=491)	Of 90.6% of patients with no history of previous treatment, 6.3% had a resistant strain while of 9.4% with a previous history of anti-tuberculosis drug treatment, 37% had a resistant strain (p<0.005).
South African study analysing rates of drug resistance in the West Cape region{219} (N=7,266)	Patients with a history of TB treatment were found to be at an increased risk of developing drug resistance (RR 2.6).
South African study based in one hospital{220} (N=275)	No significant association was found between previous treatment history and drug resistance.
Previous TB status in addition to other risk factors	
In a UK study of TB patients reported during two time periods (1993 to 1994 and 1998 to 2000){216} (N=9,541)	In those with previous TB, significant risk factors for isoniazid resistance were smear positive status (OR 3.2, 95%CI 1.1 to 9.2) and being of non-UK origin but arriving in the UK in the past 10 years (OR 3.2, 95%CI 1.4 to 7.0). This was similar for MDR TB where the most significant risk factors were smear positive disease (OR 5.9, 95%CI 1.8 to 19.0) and non-UK origin – particularly those who had arrived in the last five years in whom the risk compared with UK-born

	was approximately sixfold (OR=0.58, 95%CI 1.8 to 18.5). In those without previous TB, significant risk factors for isoniazid resistance were London residence (OR 1.4, 95%CI 1.1 to 1.7), being HIV positive (OR 2.4, 95%CI 1.1 to 5.2) although this was only significant in 1993 to 1994 (OR 2.4, 95%CI 1.1 to 5.2), and ethnicity. Compared with the white ethnic group, adjusted odds ratios were similar in people of Indian (subcontinent) origin (OR 1.6, 95%CI 1.2 to 2.1), people of black African origin (OR 1.7, 95%CI 1.2 to 2.4) and other ethnic groups combined (OR 1.9, 95%CI 1.3 to 2.8). For MDR TB the most significant risk factors were being HIV positive (OR 2.5, 95%CI 1.2 to 5.2) and London residence (OR 2.0, 95%CI 1.2 to 3.3). Birth outside the UK was also important, with the risk of MDR TB higher for those arriving in the last five years (OR 3.2, 95%CI 1.4 to 7.3).
Ethnicity as a risk factor	
UK national surveillance study{213} (N=25,217)	Among the three ethnic groups from whom substantial numbers of isolates were received, the highest proportion of resistance to at least isoniazid and MDR TB was reported in isolates from people of black African origin (10.1% and 2.0% respectively) with 7.2% and 1.4% in those originating from the Indian subcontinent, and 4.1% and 1.4% in those of white ethnic origin. Resistance to at least isoniazid was significantly different between all three ethnic groups (p<0.001).
UK study based in one London hospital{214} (N=7,266), Kenyan study{218} (N=491), South African study{219} (N=7,266)	No significant association was found between Caucasian and non-Caucasian ethnicity and drug resistance{214} and in the other two studies similarly no association was found between drug resistance and ethnic group.
Gender as a risk factor	
UK national surveillance study{213} (N=25,217)	The proportion of those resistant to at least isoniazid was higher in men (5.9%) than in women (5.4%), although the difference was not significant. However, men were significantly more likely to have MDR TB (1.4% *vs*. 0.9%, p<0.001).
National surveillance study in Switzerland{224} (N=1,056)	Increased risk of resistance to any first-line drug was associated with male sex (adjusted OR 1.4, 95%CI 1.1 to 2.0).
UK study based in one London hospital{214} (N=121), national surveillance study in the Netherlands{223} (N=1,836), Kenyan study{218} (N=419), two South African studies{219},{220} (N=7,266 and N=275 respectively)	No association was found between drug resistance and gender.
Place of birth as a risk factor	
UK national surveillance study{213} (N=25,217)	People born outside the UK were significantly more likely to have resistance to at least isoniazid than those born in the UK (9.1% *vs*.

	4.2%, OR 2.27, p<0.001). Similarly, 2.0% of people born outside the UK had an MDR isolate compared with 1.0% of those born in the UK (OR 1.97, p<0.001).
National US study{221} (N=67,340)	Foreign-born cases had significantly higher rates of resistance to isoniazid (12.4% *vs*. 6.4%, p<0.05) and streptomycin (10.0% *vs*. 4.3%, p<0.05) than US-born case patients but similar rates of rifampin resistance (3.1% *vs*. 2.9%) and MDR TB (2.4% *vs*. 2.0%). Those who were foreign born were at increased risk of resistance to at least isoniazid with an adjusted OR 1.5, 95%CI 1.4 to 1.6.
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.3 to 2.2) and MDR TB (OR 2.7, 95%CI 1.1 to 6.2) was associated with foreign birth.
National surveillance study in the Netherlands{223} (N=1,836)	Drug resistance was reported in 9% of patients born in the Netherlands and in 18% of foreign-born TB patients (p<0.001).
National surveillance study in Switzerland{224} (N=1,056)	Foreign-born patients showed a slightly but not significantly elevated risk of resistance (adjusted OR 1.5, 95%CI 0.8 to 2.8).
Two UK studies, (N=121){214} (N=104){215} and a Kenyan study {218} (N=491)	Drug resistance was not associated with foreign birth.
Place of diagnosis as a risk factor	
UK national surveillance study{213} (N=25,217)	Compared with other English NHS regions and Scotland, Northern Ireland and Wales, patients diagnosed in London were more likely to have isolates resistant to at least isoniazid (7.6% *vs*. 4.6%, p<0.001). Similarly, patients from London were more likely to have MDR isolates (1.7% *vs*. 0.9%, p<0.0001).
HIV status as a risk factor	
UK national surveillance study{213} (N=25,217)	Those known to be co-infected with HIV were more likely to be either resistant to at least isoniazid (11.6% *vs*. 5.5%) or be MDR (4.6% *vs*. 1.1%) than those from people of unknown or negative HIV infection status (p<0.001 (isoniazid resistance); p=<0.001 (MDR)).
National US study{221} (N=67,340)	For all drugs, resistance was significantly higher (p<0.05) in HIV-positive *vs.* HIV-negative patients and HIV-positive *vs*. those with unknown status, except for patients with isolates resistant to ethambutol. Those who were HIV positive were at increased risk of resistance to at least isoniazid with an adjusted OR 1.6 (95%CI 1.4 to 1.8).
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.4) was associated with HIV positive status however an association was not found for MDR TB.
National surveillance study in the Netherlands{223} (N=1,836)	HIV positivity was more frequently reported in the drug-resistant group than in the drug-susceptible group (7.7% *vs*. 4.9%) but this difference was not significant.

South African study based in one hospital{220} (N=275)	No significant association was found between HIV status and drug resistance.
History of poor treatment adherence as a risk factor	
UK study in Leicestershire{215} (N=104)	Poor adherence (OR 4.8, 95%CI 1.4 to 14.4, p=0.005) was significantly associated with resistance to at least one first-line drug.
Other risk factors	
UK study based in one London hospital{214} (N=121)	Bilateral disease at presentation was associated with drug resistance (OR 8.5, 95%CI 2.1 to 35.0, p<0.005) but not with recent entry to the UK for foreign-born patients, alcoholism, psychological disturbances, homelessness, living in care homes or poor understanding of the English language (although for many of these risk factors patient numbers identified were very small).
UK study in Leicestershire{215} (N=104)	No significant associations were found between site of TB, foreign travel or recent immigration and resistance to at least one first-line drug (although it should be noted that only a small number of participants had these risk factors).
In a national surveillance study in the Netherlands{223} (N=1,836)	Asylum seekers diagnosed on arrival in the Netherlands showed an increased risk of resistance to any drug with 4.8% of cases in the drug-susceptible group and 10.4% in the drug-resistant group (p<0.001). With regard to site of disease and other clinical features (diabetes, malignancy and pregnancy) and a number of other risk groups (sailors, travellers, illegal immigrants, the homeless, alcohol users, drug users, prisoners and healthcare workers), no differences were observed between the groups.

From evidence to recommendations

The GDG noted that the evidence base came from studies conducted in different parts of the world. The most significant risk factors depend on the population within which a drug-resistant strain is transmitted. Even factors found to be valid for London should not be extrapolated to the whole of England and Wales.

One of the UK studies{215} was noted to be a sub-population of the larger population-wide study.{213}

The data clearly show that there are a number of risk factors for drug resistance, which listed in order of importance for relative risk are as follows.

1. A history of prior TB drug treatment.
2. Birth in a foreign country, particularly sub-Saharan Africa and the Indian subcontinent.
3. HIV infection.

4. Residence in London.

5. Age profile, with highest rates between the ages of 25 and 44 years.

6. Male gender.

The GDG also regarded contact with a known case of TB, and treatment failure as risk factors.

It is still not known whether risk factors for MDR TB are the same as those for lesser forms of drug resistance.

Based on the conclusions of section 5.3, rifampicin-resistance molecular probes were recommended for those patients with risk factors.

The absence of risk factors is not enough in itself to remove clinical suspicion of drug-resistant TB.

The GDG agreed that intensive contact tracing should be carried out in all cases of MDR TB.

The GDG recognised the dangers associated with failure of drug treatment, and sought to advise readers that it needs to be recognised early.

RECOMMENDATIONS

R69 A risk assessment for drug resistance should be made for each patient with TB, based on the risk factors listed below: C

- History of prior TB drug treatment; prior TB treatment failure.
- Contact with a known case of drug-resistant TB.
- Birth in a foreign country, particularly high-incidence countries as defined by the HPA on its website.[6]
- HIV infection.
- Residence in London.
- Age profile, with highest rates between ages 25 and 44.
- Male gender.

[6] Countries with more than 40 cases per 100,000 per year, as listed by the Health Protection Agency go to www.hpa.org.uk and search for 'WHO country data TB'.

R70 The TB service should consider the risk assessment for drug resistance and, if the risk is regarded as significant, urgent molecular tests for rifampicin resistance should be performed on smear-positive material or on positive cultures when they become available (see section 5.2). D(GPP)

R71 Response to treatment should be closely monitored in patients at increased risk of drug resistance. If there is no clinical improvement, or if cultures remain positive after the fourth month of treatment ('treatment failure'), drug resistance should be suspected and treatment reviewed with a clinician experienced in the treatment of MDR TB. D(GPP)

(See section 6.1 for details of the standard recommended regimen.)

11 Infection control

Clinical introduction

Patients with sputum microscopy-positive MDR TB are no more infectious than similar patients with fully susceptible TB, ie they should not infect a higher proportion of contacts, because the organism is no more virulent. The consequences of acquiring MDR TB infection and then disease, however, are much more serious than for fully susceptible TB, because MDR TB needs prolonged treatment (often with more toxic second-line drugs) and the outcome in terms of death and proportions cured are worse. Because of the loss of the most effective killing drug (isoniazid), and the most effective sterilising drug (rifampicin), such patients take much longer to become non-infectious than if organisms are fully susceptible (covered in section 6.5). In these cases there is not the rapid fall in numbers of viable organisms in the sputum seen in drug-susceptible cases, so they have a much prolonged infective potential after starting treatment.

Because of these differences it has been advised that patients with suspected or proven MDR TB should be isolated in a negative pressure room (as defined in recommendations below), and staff should wear FFP3 masks meeting the standards of the Health and Safety Executive{104} during patient contact whilst the patient is considered infectious.

The two major nosocomial outbreaks of MDR TB in the UK occurred because of failures in infection control procedures, either by carrying out risky procedures such as sputum induction in a communal HIV setting, or by isolating patients with active disease in a setting which had positive rather than negative pressure to the main ward.{232}

In 2005, the Chief Medical Officer's TB Action Plan{2} identified this as an essential area for improvement if trends for increasing incidence are to be reversed and better care provided for people with tuberculosis: 'Identify, facilitate access to, and ensure staff are aware of the appropriate isolation facilities and infection control precautions to be taken for patients with infectious, or potentially infectious TB, or who have drug resistant TB'. The recommendations provide the guidance the NHS needs to achieve this goal and prevent nosocomial infection.

Current practice

The review of current services collected the number of negative pressure units in service providers and aggregated these within HPU areas. There appears to be a positive relationship between the number of negative pressure units and number of notifications (see Figure 7).

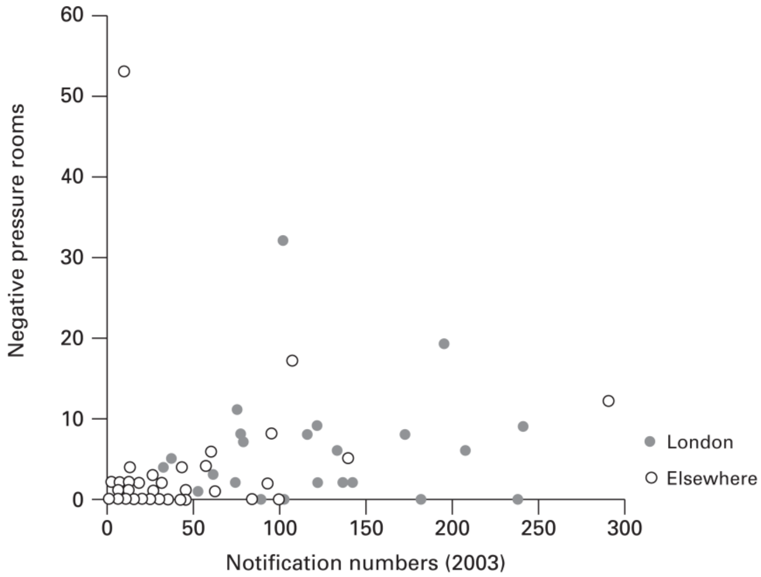


Figure 7 Negative pressure rooms vs. notified cases of TB per service provider

However, there seem to be errors in the reporting of the number of negative pressures units, which are much higher than expected, despite contacting the respondents to check. This discrepancy is too large to be accounted for by facilities being shared across HPU areas and counted twice, and so it seems that there is confusion among TB staff as to separate isolation rooms and negative pressure facilities. Given their use in cases of MDR TB, and the risk to other inpatients (with medicolegal implications), it would seem vital that staff working with TB are aware of the existing regulatory standards{105} regarding these facilities, and that it is made clear which isolation units meet these standards.

Methodological introduction

Studies were searched for which examined measures directed at patients with infectious suspected MDR TB to prevent transmission to other patients or contacts. (Measures to prevent transmission of TB to healthcare workers are addressed in chapter 13.)

Three retrospective cohort studies{233–235} were identified, all of which were performed in US hospitals after MDR TB outbreaks in wards of HIV-positive or AIDS patients. All hospitals introduced a range of infection control measures following the outbreaks.

There are a number of methodological considerations with regard to all three studies. Firstly, as multifaceted infection control programmes were implemented over time, it is difficult to assess the contribution to outcome of each individual infection control measure. Secondly, the implementation of control measures was associated with a decrease in the number of case patients; the effectiveness of these control measures in the presence of a high concentration of infectious patients with MDR TB over a long time period could not be fully evaluated. Finally, each study involved only small numbers of MDR TB patients in one hospital and was completely reliant on the accuracy of patients' medical and laboratory records.

Evidence statements

Although approximately equal numbers of AIDS patients had same-ward exposures with MDR TB patients before and after the implementation of infection control measures (which were in accordance with Centers for Disease Control and Prevention recommendations), the MDR TB attack rate was significantly lower in the period after implementation (8.8% *vs.* 2.6%, p=0.01).{234} (**2+**)

The proportion of patients with MDR TB decreased in a period when infection control measures were introduced compared with the period before (14% compared with 32% of patients; RR 0.5, 95%CI 0.2 to 0.9, p=0.02). Patients diagnosed during the intervention period were less likely than those diagnosed during the pre-intervention period to have had an identified nosocomial exposure to another case patient during a previous hospitalisation (10% compared with 67% patients; RR 0.2, p=0.003).{233} (**2+**)

Exposure before implementation of improved infection control measures to an infectious MDR TB patient on the HIV ward was recorded in 80% of MDR TB patients and 45% of MDR TB patients post-implementation. After implementation of control measures, no episodes of MDR TB could be traced to contact with infectious MDR TB patients on the HIV ward.{235} (**2+**)

From evidence to recommendations

The evidence for infection control measures in patients with smear-positive TB suspected to be MDR is limited. This applies to both HIV-negative and HIV-positive cases. One limitation of the studies analysed was that they often introduced several measures at once, so the effect of a single action was not determinable. Secondly, measures were compared before and after an outbreak, when there may have been better application of the pre-existing infection control measures after such an outbreak, as well as the introduction of new measures.

Although MDR TB is no more infectious than fully drug-susceptible TB, the consequences of acquiring MDR TB are much more serious because of the greater difficulty and costs of treating it, with prolonged infectivity and the risk of much poorer outcomes. Immunosuppressed patients (particularly those HIV infected) are much more likely to acquire TB infection, and to progress to clinical disease.

The recommendations reinforce the essential role of negative pressure facilities in providing MDR TB care, based on a continuation of the practices previously recommended by the BTS.{6}

RECOMMENDATIONS

R73 Patients with suspected or known infectious MDR TB who are admitted to hospital should be admitted to a negative-pressure room. If none is available locally, the patient should be transferred to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases. Care should be carried out in the negative-pressure room until the patient is found to be non-infectious or non-resistant, and ideally until cultures are negative. D(GPP)

R74 Staff and visitors should wear FFP3 masks,[7] during contact with a patient with suspected or known MDR TB while the patient is considered infectious. D(GPP)

R75 Before the decision is made to discharge a patient with suspected or known MDR TB from hospital, secure arrangements for the supervision and administration of all anti-TB therapy should have been agreed with the patient and carers. D(GPP)

R76 The decision to discharge a patient with suspected or known MDR TB should be discussed with the infection control team, the local microbiologist, the local TB service, and the consultant in communicable disease control. D(GPP)

[7] European standard EN149:2001; masks should meet the standards in ‘Respiratory protective equipment at work: a practical guide HSG53’ published by the Health and Safety Executive (2005). Available from www.hse.gov.uk

R77 Negative pressure rooms used for infection control in MDR TB should meet the standards of the Interdepartmental Working Group on Tuberculosis,{386} and should be clearly identified for staff, for example by a standard sign. Such labelling should be kept up to date. D(GPP)

Cross-referring:

For details of contact tracing in hospital in-patients, see section 12.7.

12 Treatment of non-MDR TB resistance

Clinical introduction

This guideline concentrated on the evidence base for MDR TB through a systematic literature search and critical appraisal, but for completeness this subsection addresses the other forms of drug resistance. The GDG, having examined the evidence base for MDR TB, were in agreement that the guideline should reflect the guidance given by the BTS in 1998.{68} Treatment of patients with drug-resistant tuberculosis is carried out only by specialist physicians with appropriate experience in managing such cases.

Isolated streptomycin resistance

The recommended standard regimen for fully susceptible TB (see chapters 6 and 7) is unaffected.

Isolated isoniazid resistance

If this resistance is known before treatment commences, a regimen of rifampicin, pyrazinamide, ethambutol and streptomycin for two months followed by rifampicin and ethambutol for a further seven months gives good results by DOT.

If this resistance is found after treatment has been started, isoniazid may be stopped. Ethambutol, pyrazinamide and rifampicin should be given for two months followed by ethambutol and rifampicin for a further 10 months.

Isolated pyrazinamide resistance

Pyrazinamide resistance is usually due to infection by *M. bovis*. Ethambutol, isoniazid and rifampicin should be given for two months followed by isoniazid and rifampicin for a further seven months. Isolated pyrazinamide resistance in *M. tuberculosis* infection should be treated with the same regimen.

Isolated ethambutol resistance

Isolated ethambutol resistance is uncommon. Isoniazid, pyrazinamide and rifampicin should be given for two months followed by isoniazid and rifampicin for a further four months.

Isolated rifampicin resistance

If rifampicin resistance is detected by either genetic probe or drug susceptibility testing, the patient should be isolated (see Fig 10) and treated as MDR TB until a full drug susceptibility profile of first-line drugs is available. Isolated rifampicin resistance is very uncommon but does occur and requires modification and extension of treatment to a period of 18 months, that is ethambutol, isoniazid and pyrazinamide for two months followed by isoniazid and ethambutol for a further 16 months. In approximately 90% of cases however, rifampicin resistance is not isolated and is a genetic marker for MDR TB.

Combined streptomycin and isoniazid resistance

This is the commonest dual resistance. This should be treated with the regimen for isolated isoniazid resistance found during treatment (see above).

Other non-MDR TB combinations

These are uncommon. Treatment would need to be individualised depending on the combination involved, and is best determined after discussion with a highly experienced clinician and the HPA Mycobacterium Reference Units.

RECOMMENDATION

R78 Patients with drug-resistant TB, other than MDR, should be under the care of a specialist physician with appropriate experience in managing such cases. First-choice drug treatment is set out in Table 31.

Table 31 Recommended drug regimens for non-MDR drug-resistant TB

• Drug resistance	• Initial phase	• Continuation phase
S	2RHZE	4RH
H known before to treatment	2RZSE	7RE
H found after starting treatment	2RZE	10RE
Z	2RHE	7RH
E	2RHZ	4RH
R (only if confirmed isolated resistance)	2HZE	16HE
S+H	2RZE	10RE
Other	Individualised	
See Appendix D for details of the system of drug regimen abbreviations		

13 Management of latent tuberculosis

Treatment regimens for latent tuberculosis infection

Clinical introduction

Latent TB is defined in this guideline as infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. In people with latent TB, the rationale for treating those identified as infected by either Mantoux or IGTs is to kill any residual dormant bacilli in order to reduce or prevent later reactivation of tuberculosis disease. Single-agent isoniazid has been used in this role for at least 35 years, with considerable data on its efficacy in regimens of between six and 12 months.

In 2005, the Chief Medical Officer's TB Action Plan{2} set a goal of advising 'on the management of patients requiring preventive chemoprophylaxis according to national (currently British Thoracic Society) guidelines'. These guidelines should provide such advice, with an updated review of evidence in this field for clinicians in England and Wales.

Current practice

The review of current services found that the number of cases receiving treatment for latent TB infection correlated with neither the number of contacts nor new entrants screened. These data were aggregated across HPU localities to account for the different functions performed by different service providers. It would seem that different practices in contact tracing and new entrant screening have different yields in detecting or treating latent TB.

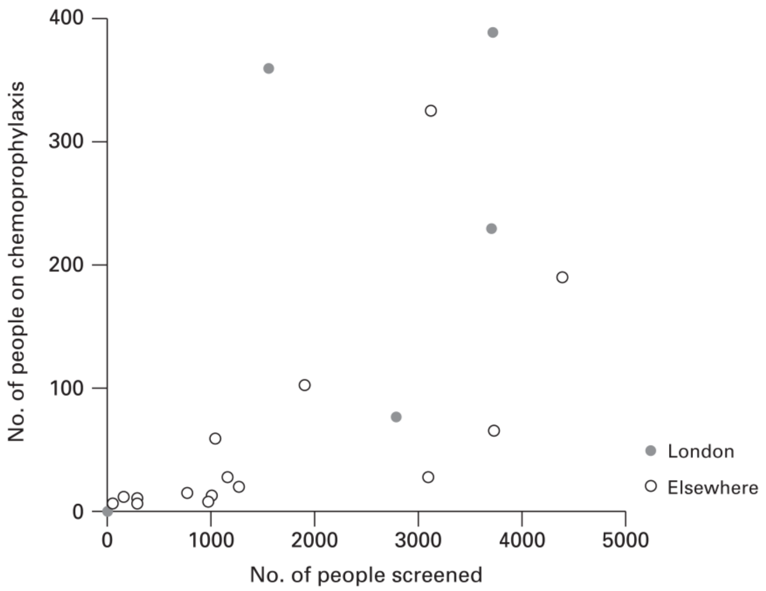


Figure 8Correlation of people screened against people given treatment for latent TB infection (chemoprophylaxis)

Methodological introduction

A detailed Cochrane review{236} looked at randomised trials of isoniazid of at least six months duration which were placebo controlled with at least two years follow-up, but excluded patients with known HIV infection. This review (11 trials totalling 73,375 patients) showed that durations of isoniazid of longer than six months had no additional benefit over that of six months (RR of 0.44, 95% CI 0.27 to 0.73 for six month, and 0.38, 95% CI 0.28 to 0.50 for 12 months). The toxicity of isoniazid was 0.26% of people on six months treatment and 0.52% of people treated for 12 months. Consideration of regimens for treatment of latent TB infection in this guideline was limited to those of six months' duration or shorter.

Two RCTs in adults with latent TB compared regimens of six months of prophylactic drug treatment with regimens of lesser duration in the prevention of the development of active TB. One study{237} compared rifampin given for three months, isoniazid and rifampin given for three months, isoniazid given for six months and placebo, in Chinese men with silicosis and Mantoux test results of greater than or equal to 10 mm of induration. The other study{238} compared isoniazid given for either three months or six months with placebo in tuberculin-positive participants with fibrotic lesions in seven European countries.

Several other studies compared regimens of six months of prophylactic treatment with isoniazid with two months of treatment with pyrazinamide and rifampin.{239–241} However, these studies were excluded as outcomes reported were adverse events and treatment completion rates and not the number of active TB cases which developed during follow-up.

Two studies in children were found. One RCT compared groups of tuberculin positive 5–15-year-olds in India who either did not receive prophylaxis, or received isoniazid for three months, rifampicin and isoniazid for one month, rifampicin and isoniazid for three months or isoniazid, rifampicin and pyrazinamide for one month.{242} This study however, was excluded due to methodological limitations. The only other study found in children was an observational study which described the use of various durations of isoniazid and rifampicin over a 15-year period in a UK health district and looked at active TB notification rates during this period.{243}

Three systematic reviews examined prophylaxis for TB in individuals with HIV infection.{244–246} The most recent of these reviews was a Cochrane review{246} which looked at preventive treatment for TB in comparison with placebo and additionally included studies which compared different regimens of preventive treatment (ie no placebo comparison). It included eleven trials with a total of 8,130 participants. This review replaced a previous Cochrane review.{247} The authors of the previous Cochrane review additionally published a systematic review of preventive treatment in HIV-infected individuals which included only studies which compared preventive treatment with placebo.{245} This study has been excluded as the four trials it included, plus several more, are all included in the updated Cochrane review {246} and in another systematic review published in 1999.{244} The 1999 systematic review{244} of isoniazid prophylaxis treatment compared with placebo has also been excluded to avoid double counting of trials as all of the studies it included (except two which have only been published as abstracts) are in the Cochrane review.{246}

The case definition of TB used varies across studies as does the proportion of cases with culture verification.

Evidence statements

Efficacy

In a European study{238} of tuberculin-positive participants with fibrotic lesions in seven European countries, the risk of active TB was reduced by 21% by 12 weeks of isoniazid and 65% by 24 weeks when compared with placebo. The difference between the 12-week regimen and placebo was not statistically significant but the difference between the 12-week and the 24-week regimen was ($p<0.05$). (**1++**)

In a study in Hong Kong{237} of Chinese men with silicosis, the cumulative percentage of patients with active pulmonary TB over five years was compared in the patients who had received their prophylactic treatment without interruption. This percentage was higher in the placebo series than in the three treatment of latent TB infection groups combined ($p<0.01$) but there was no evidence of significant differences between the three treatment of latent TB infection regimens (placebo=27%, isoniazid and rifampin for three months=16%, isoniazid for six months=14% and rifampin for three months=10%). When the patients with extrapulmonary TB and those whose regimen was interrupted were included, the estimated rates at five years were 27% in the placebo series and 17% in the three treatment of latent TB infection series combined ($p<0.05$). (**1+**)

Treatment completion

In the European study{238} in the 12-week treatment groups, 87% completed isoniazid treatment and 91% placebo. These percentages were 78% and 82% respectively for the 24-week groups. (**1++**)

In the Hong Kong study,{237} 86% of participants in the three-month rifampin group, 76% in the isoniazid and rifampin three-month group, 74% in the six-month isoniazid group and 84% in the placebo group completed their allocated regimen without known interruption. (**1+**)

Adverse events

In the European study{238} the excess risk of hepatitis per 1,000 persons of isoniazid over placebo was 2.5 in the first 12 weeks and 1.1 in weeks 13–24. The number of hepatitis cases which could be avoided by shortening the duration of isoniazid from 24 weeks to 12 weeks would be 1.1 per 1,000 persons. (**1++**)

In the Hong Kong study{237} adverse effects were reported with a similar frequency in all four groups in the first 12 weeks. During this time, hepatic toxicity was reported in eight (1%) patients (three in the three-month isoniazid and rifampin group, three in the six-month isoniazid group and two in the placebo group) with only one (in the six-month isoniazid group) having symptomatic hepatitis. Only 4% of patients had their regimen stopped because of reactions. The serum alanine aminotransferase concentrations were higher in the three month isoniazid and rifampin and six month isoniazid series than in the three-month rifampin series ($p<0.001$) but there was no significant difference between the three-month rifampin series and placebo. (**1+**)

Children

In a study conducted in one health district in the UK{243} of children on treatment for latent TB infection, no child notified with TB in the period 1987–1996 (when shorter four month and three month regimens were introduced) had received treatment for latent TB infection previously. Furthermore, no child on treatment for latent TB infection required their three or four month regimen of isoniazid and rifampicin treatment to be stopped for possible side effects during the nine year period since the introduction of these regimens. (**3**)

People with HIV: development of active TB

A Cochrane systematic review{246} found that preventive therapy (any anti-TB drug) *vs.* placebo was associated with a lower incidence of active TB (RR 0.64, 95%CI 0.51 to 0.81). All drug regimens regardless of type, frequency or duration of treatment, reduced the incidence of active TB compared with placebo and no differences were found between active regimens in terms of effectiveness. (**1++**)

The review{246} found that among individuals who were tuberculin skin test positive, preventive therapy reduced the risk of active TB by 62% (RR 0.38, 95%CI 0.25 to 0.57). Although a similar trend was found for individuals with a negative tuberculin test these results were not statistically significant. (**1++**)

People with HIV: all-cause mortality

The review{246} found no evidence that preventive therapy versus placebo reduced all-cause mortality. (**1++**)

People with HIV: incidence of adverse drug reactions

Compared to placebo, preventive therapy led to more adverse events resulting in stopping treatment (RR 2.49, 95%CI 1.64 to 3.77). The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for isoniazid monotherapy compared with placebo (eg for isoniazid *vs*. placebo: RR 1.66, 95%CI 1.09 to 2.51 whilst for isoniazid and rifampicin *vs*. placebo: RR 16.72, 95%CI 3.29 to 84.9).{246} (**1++**)

From evidence to recommendations

A European study{238} found six months isoniazid to be more effective than three months whilst a Hong Kong study{237} found no difference in effectiveness between isoniazid and rifampin for three months (3RH) and isoniazid for six months (6H) in those who were not HIV positive. Therefore, either 6H or 3RH could be used.

The Hong Kong study also demonstrated no difference between these two regimens and three months of rifampicin. In the UK, six months of rifampicin has been demonstrated to be effective, and the GDG recommended a six-month course to avoid any risk of rifampicin-resistant strains developing.

In 2000 a regimen of rifampicin and pyrazinamide for two months (2RZ) was recommended for treatment for latent TB infection in the USA.{248} In the UK, although this 2RZ regimen was felt to have equivalent efficacy to a regimen of three months rifampicin and isoniazid (3RH), because it was predicted to have significantly higher toxicity, the 2RZ regimen was not recommended for use in the UK.{68} Subsequent experience in clinical practice in the USA confirmed significant hepatotoxicity, including deaths, in clinical practice,{249–251} which led in 2003 to the American Thoracic Society and the Centers for Disease Control advising that this regimen no longer be routinely used for treatment for latent TB infection.{250}

There was no high-level evidence in neonates or children, so recommendations are based on clinical experience. The recommendations shown below were drawn up to reflect the group consensus.

A Cochrane review{246} in HIV-positive people found in those who were tuberculin positive, preventive therapy reduced the risk of active TB. A similar but non-significant trend was found for individuals with a negative Mantoux test. The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for isoniazid monotherapy, therefore the latter has been recommended in this population.

People should be selected for treatment for latent TB infection by the risk factors set out in section 10.1. Risk of hepatotoxicity from these drugs increases with age. Although there was no evidence to recommend an age threshold, it has been common practice in the UK not to advise treatment for latent TB infection for otherwise eligible people who are over the age of 35, as the risk may start to outweigh the potential benefit.

All the recommendations identify people on the basis of the two-step testing process for latent TB which is recommended in section 5.1. Obvious exceptions will occur when, for example, the patient is immunocompromised and Mantoux test is not reliable, and clinical judgement will be required.

The recommendations state that treatment for latent TB infection with 3RH or 6H regimens would be ineffective in contacts of people with MDR TB. In these and other cases where treatment for latent TB infection is not recommended, 'inform and advise' information is needed. Follow-up is also recommended for contacts of a person with MDR TB.

RECOMMENDATIONS

R79 Treatment of latent TB infection should be considered for people in the following groups, once active TB has been excluded by chest X-ray and examination: D(GPP)

- people identified through screening who are:
  – 35 years or younger (because of increasing risk of hepatotoxicity with age[8])
  – any age with HIV
  – any age and a healthcare worker

and are either:

  – Mantoux positive (6 mm or greater), and without prior BCG vaccination, *or*
  – strongly Mantoux positive (15 mm or greater), interferon-gamma positive, and with prior BCG vaccination

- children aged 1–15 years identified through opportunistic screening, to be:
  – strongly Mantoux positive (15 mm or greater), *and*
  – interferon-gamma positive (if this test has been performed), *and*
  – without prior BCG vaccination
- people with evidence of TB scars on chest X-ray, and without a history of adequate treatment.
-

R80 People with HIV who are in close contact[9] with people with sputum smear-positive respiratory TB should have active disease excluded and then be given treatment for latent TB infection (see R10-13).

R81 Treatment for latent TB infection should not be started in close contacts of people with sputum smear-positive MDR TB who are strongly Mantoux positive (15 mm or greater), as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease. Long-term monitoring should be undertaken for active disease. D(GPP)

R82 People who have agreed to receive treatment for latent TB infection should be started on one of the following regimens: C

[8] For people aged 36 or older, consider risks and benefits for the individual before offering treatment.
[9] Close contacts may include a boyfriend or girlfriend and frequent visitors to the home of the index case, in addition to household contacts.

- either six months of isoniazid (6H) or three months of rifampicin and isoniazid (3RH) for people aged 16–35 not known to have HIV A
- either six months of isoniazid (6H) or three months of rifampicin and isoniazid (3RH) for people older than 35 in whom treatment for latent TB infection is recommended (see R62) and who are not known to have HIV D(GPP)
- six months of isoniazid (6H) for people of any age who have HIV A
- six months of rifampicin (6R) for contacts, aged 35 or younger, of people with isoniazid-resistant TB. D(GPP)

People eligible for treatment of latent TB infection, but who decline to take this treatment, should be given 'inform and advise' information about TB and have chest X-rays three and 12 months later. D(GPP)

R83 Neonates who have been in close contact with people with sputum smear-positive TB who have not received at least two weeks' anti-tuberculosis drug treatment should be treated as follows. D(GPP)

- The baby should be started on isoniazid (refer to the current ‘British national formulary for children’) for three months and then a Mantoux test performed after three months' treatment.

- If the Mantoux test is positive (6 mm or greater) the baby should be assessed for active TB (see section 5.2). If this assessment is negative, then isoniazid should be continued for a total of six months.

- If the Mantoux test is negative (less than 6 mm), it should be repeated together with an interferon-gamma test. If both are negative then isoniazid should be stopped and a BCG vaccination be performed (see chapter 11).

R84 Children older than four weeks but younger than two years who have not had BCG vaccination and are in close contact with people with sputum smear-positive TB should be treated as follows. D(GPP)

- The child should be started on isoniazid (refer to the current ‘British national formulary for children’) and a Mantoux test performed.

- If the Mantoux test is positive (6 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is ruled out, full treatment for latent TB infection should be given (see R86).

- If the Mantoux test is negative (less than 6 mm), then isoniazid should be continued for six weeks, and then a repeat Mantoux test together with an IGT test should be carried out.

- If the repeat tests are negative, isoniazid may be stopped and BCG vaccination performed (see chapter 11).

- If either repeat test is positive (6 mm or greater), then the child should be assessed for active TB (see section 5.2.) and consider treating for latent TB. Contact tracing for children younger than two years when the index case is sputum-smear-positive is summarised in an algorithm (section 12.2).

R85 BCG-vaccinated children aged older than four weeks but younger than two years, in close contact with people with sputum-smear-positive respiratory TB, should be treated as follows. D(GPP)

- The child should have a Mantoux test. If this is positive (15 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is excluded, then treatment for latent TB infection should be given (see R86).

- If the result of the test is as expected for prior BCG (less than 15 mm), it should be repeated after six weeks together with an interferon-gamma test.

- If the repeat Mantoux test is also less than 15 mm, and the interferon-gamma test is also negative, no further action is needed.

- If the repeat Mantoux test becomes more strongly positive (15 mm or greater and an increase of 5 mm or more over the previous test), or the interferon-gamma test is positive the child should be assessed for active TB (see section 5.2). If active TB is excluded, treatment for latent TB infection should be given.

R86 For children requiring treatment for latent TB infection, a regimen of either three months of rifampicin and isoniazid (3RH) or six months of isoniazid (6H) should be planned and started, unless the child is known to be HIV positive, when 6H should be given (see R82). D(GPP)

R87 Healthcare workers should be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: D(GPP)

- are HIV positive
- are injecting drug users
- have had solid organ transplantation
- have a haematological malignancy
- have had a jejunoileal bypass
- have chronic renal failure or receive haemodialysis
- have had a gastrectomy
- are receiving anti-tumour necrosis factor (TNF)-alpha treatment
- have silicosis.

Patients in these groups should be advised of the risks and symptoms of TB, on the basis of an individual risk assessment basis, usually in a standard letter of the type referred to as 'inform and advise' information.

Cross-referring:

For details of excluding active TB, see section 5.2.

For details of DOT, see section 8.2.

For details of approaches to improving adherence, see section 8.3.

For details of active case finding, including contact tracing, see chapter 12.

For examples of 'inform and advise' information, see Appendix H.

Risk factors for tuberculosis infection: selecting people for treatment for latent tuberculosis infection

Clinical introduction

The risk of developing clinical TB depends on both the risk of becoming infected, and the risk that after acquiring infection this will progress to disease. This section addresses the latter risk.

Further considerations are the age at which initial infection occurs and time since initial infection. Infection earlier in life, particularly under age five, may be associated with increased risks of progression and dissemination of disease. The greatest chance of progressing to disease is within the first two years after infection, with half of all cases of disease occurring within five years of the original infection.{252} There however remains a lifelong risk of progression to disease for all those with 'dormant' organisms. Such people are a minority of infected patients. International data shows,{253} that whilst some 32% of the world's population (1.9 billion) was estimated infected as judged by a positive Mantoux test, only some 8–11 million persons per year are estimated to develop clinical disease.

Many more studies exist which examine the risk factors for active tuberculosis in groups irrespective of tuberculin skin test status. These studies do not show whether such groups are more likely to develop latent infection, or if infected progress to clinical disease, or whether both mechanisms apply.

Treatment for latent TB infection can be either secondary, after latent infection has occurred (see section 10.1), or primary to try to prevent the acquisition of infection after exposure. Most studies concentrate on secondary treatment for latent TB infection, but there are circumstances where primary treatment for latent TB infection may be appropriate, for example exposure of neonates to sputum smear-positive parents, or of people with HIV to people with sputum smear-positive TB.

Current practice

The Health Protection Agency's systems of notification and enhanced surveillance (see chapter 14 for details) do not collect data on cases of latent tuberculosis, or on people screened and found to be uninfected.

The review of current services followed-up respondents reporting more than five people screened for latent tuberculosis in 2003, and sought a breakdown between those who were new entrants and those who were contacts of people with infectious TB. Although all the clinics that were followed-up were able to provide some response, in the majority they reported that they could not derive such detail from the data that they had collected locally. Many reported ongoing work to improve their local collection of data on screening.

Methodological introduction

The evidence was examined to consider which TB-infected population groups are the most likely to progress from infection to active TB. This information identifies those who would benefit most from treatment for latent TB infection.

Few studies considered the risk of developing active TB in those known to have (or highly likely to have) latent infection, probably because these groups are likely to receive treatment for latent TB infection (except in older studies). Furthermore, these studies do not in general have a tuberculin-positive control group without the risk factor, so it is not possible to calculate relative risks, only incidence rates. Additionally, the consideration of HIV infection as a risk factor for active TB in those with latent infection is problematic. This is due to the difficulties of diagnosing latent tuberculosis in this population using conventional skin test methods.

Many more studies exist which examine the risk factors for active TB in groups irrespective of Mantoux test status. It is unclear, however, whether these groups are more likely to develop latent tuberculosis or once they had infection, are at a higher risk of progressing to active TB, both of which could be explanations for these groups having a high rate of active TB compared to control groups.

From evidence to recommendations

The GDG discussed the issues and agreed that, rather than attempting to synthesise all the evidence in this area, it would be more useful to provide tables of risk factor data. These tables, modified from the American Thoracic Society official statement of 'targeted tuberculin testing and treatment of latent infection'{248} are shown below. Table 32 ranks a range of active TB incidence rates in tuberculin-positive persons with certain risk factors/medical conditions. Table 33 (overleaf) ranks a range of relative risks of active tuberculosis, in populations with certain risk/factors/medical conditions, independent of Mantoux test status.

While people who are underweight and/or have diabetes are at increased relative risk of TB, the GDG did not feel that it would be appropriate to alert them all to the symptoms and signs of TB as their absolute risks of TB are very low.

RECOMMENDATIONS

The evidence supporting this section informed the recommendations given in section 10.1.

9. Table 32: Incidence of active TB in persons with a positive tuberculin test by selected risk factors

• **Risk factor**	•	• **TB cases/1,000 person-years**
HIV infection{254}		35.0–162
Injecting drug use{255}	HIV seropositive	76.0
	HIV seronegative or unknown	10.0
Silicosis{237}		68.0

Recent latent tuberculosis{256}	Infection <1 year past	12.9
	Infection 1–7 years past	1.6
Radiographic findings consistent with prior TB{257–259}		2.0–13.6
Weight deviation from standard{260}	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

10. Table 33: Relative risk for developing active TB by selected clinical conditions

• **Clinical condition**	•	• **Relative risk**
Solid organ transplantation	Renal{261}	37
	Cardiac{262},{263 }	20–74
Jejuno-ileal bypass{264},{265}		27–63
Silicosis{266}		30
Chronic renal failure/haemodialysis{267–269}		10–25.3
Gastrectomy{270–272}		2.5
Diabetes mellitus{273–275}		2.0–41
Anti-TNF-alfa treatment{276},{277}		4–8
Contact smear-positive TB{278}		5–10

14 The Guideline: Prevention and Control

Case finding

New entrants screening (people recently arriving in or returning to the UK)

Clinical introduction

The five-yearly national notification surveys have consistently shown the highest rates of clinical tuberculosis disease in recent arrivals, particularly within the first few years after initial entry. This trend has been shown from 1978/9{355} through to 1998,{26} and in continuous enhanced surveillance from 1999–2002,{140} with 63% of all cases in 2001 being non-UK born. From 1978/9 to 1988 the great majority of people other than of white ethnicity with TB were of Indian subcontinent origin, but from 1988 onwards there has been a significant increase in the proportion of cases of black African origin, from 1.7% in 1988 to 13% in 1998, and most recently 21% in 2002.

Deficiencies in the official port of arrival system were recognised in these documents, with advice that local systems and information be used to augment new entrant identification. Screening for new entrants from settings of high incidence (defined as those with an incidence rate of at least 40/100,000) was advised. In practice this applied to all new entrants apart from those from the then European Union countries, Australia, New Zealand, Canada and the USA.{6}

Following identification of appropriate new entrants, the tools available for screening were the same as those for household contacts of cases of tuberculosis: enquiry about symptoms of (and any prior history of) tuberculosis, BCG history corroborated by documentation or scar, tuberculin skin testing and chest X-ray.{6} Interferon-gamma immunological tests were not available in the UK in the 1990s.

Current practice

The review of current services found that, where new entrants services were provided, it could be via a dedicated new entrants service, often a primary care-based, holistic new entrants programme. Otherwise, new entrants may be seen in general TB clinics. Some clinics did not appear to have any provision for new entrant screening. The review did not cover the newer arrangements in fast-track induction centres for refugees, which are organised by the Home Office.

Outside London, 44% of service providers had a dedicated new entrant clinic and 35% saw new entrants in a general clinic, usually the BCG clinic. For two local services (3%), new entrants were seen at home. Other respondents had no specific new entrant screening programme. Within London, 55% had a dedicated clinic.

Methodological introduction

Studies that compared different service models of TB screening for new immigrants in order to evaluate which was most effective were targeted.

Two cohort studies from the UK{297},{356} and one cohort from the Netherlands{357} were found. None of the studies reported whether blinding of the investigators to the different service models being evaluated had taken place. Two studies, one from the UK{296} and one conducted in Italy,{358} were excluded due to additional methodological limitations listed in Appendix I.

In addition, there was a search for studies that compared different screening methods for latent and active tuberculosis in new immigrants and ethnic minority residents returning from settings with a high incidence of TB to evaluate which was most effective.

Three non-analytic studies were identified. One study{359} focused on symptom questionnaire and chest X-ray screening methods applied to a group of East Timor refugees screened on entry into Australia. A second study{360} examined the sensitivity of Mantoux test and chest X-ray for a subsequent diagnosis of active TB in Tibetan refugees entering the USA. A third study conducted in the USA{361} was excluded due to methodological limitations presented in Appendix I.

Evidence statements: service models

Proportions of new immigrants identified by different service models

Two studies{297},{356} compared the proportions of new immigrants screened for TB by different service models within the same area. Service models included:

- port of arrival identification
- primary care (GP or family practitioner) identification
- targeted screening of the homeless.

The evidence for the proportions of new entrants identified by the different models is presented in Table 52.

Table 52: Summary of evidence: models of new entrant screening

POA model, N (%) screened	Primary care model, N (%) screened	Homeless screening model, N (%) screened	Statistical significance	Ref and NICE grade
199 (48)	45 (11) – GPs	172 (41) – targeted screening	Not reported	{297},{356} 2+
905 (53)	787 (47) – family practitioner committee model	Not done	Not reported	{297},{356} 2+
4/103 (3.8) homeless new immigrants arriving in UK in previous two years	N/A	103/172 arrived in the UK in the previous two years	Not reported	{297},{356} 2+

Proportions of new immigrants identified with latent tuberculosis

In one study{356} the POA service model identified more new immigrants with weak tuberculin-positive reactions, but fewer with strongly positive Mantoux test reactions in comparison to targeted screening of homeless new immigrants and new immigrants screened in GP settings. The evidence is presented in Table 53.

Table 53: Detection of latent TB in contact tracing among new entrants

POA mo	Primary c	Homeless scre	Statistical signif	NICE g

del, N (%) Heaf tested, Heaf grade	are model, N (%) Heaf tested, Heaf grade	ening model, N (%) Heaf tested, Heaf grade	icance	rade
100/181 (55) grade 2	14/39 (35) grade 2	84/172 (49) grade 2	Not reported	2+
9/181 (5) grade 3 or 4	8/39 (21) grade 3 or 4	13/172 (8) grade 3 or 4	Not reported	2+

Proportions of new immigrants identified with active tuberculosis

Two studies{356},{297} focused on comparing the proportions of new immigrants with active TB disease identified by different service models within the same area. Service models were:

- port of arrival identification
- primary care (GP or family practitioner) identification
- targeted screening of the homeless
- passive case finding.

The evidence is presented in Tables 54 and 55 below.

Table 54: Detection of latent TB in contact tracing among new entrants

Port of arrival model, N (%)	Primary care model, N (%)	Homeless screening model, N (%)	Statistical significance	Ref and NICE grade
3/181 (2)	0/39	0/172	Not reported	{297} 2+

Table 55: Detection of active TB disease in new entrants detected within the same five-year time period, N (%)

Port of arrival and primary care models combined	Primary case finding model	Statistical significance	Ref and NICE grade
11/57 (19)	27/57 (47.3)	Not reported	{356} 2+

Comparing hospital admissions and duration of symptoms in TB disease cases identified by new immigrant screening and passive case finding

One study{357} found that active TB cases detected by new immigrant screening had on average shorter duration of symptoms and fewer hospital admissions compared to TB patients detected by passive case finding. The evidence is presented Table 56.

Table 56: Symptoms and hospital admissions in new entrants identified with active TB

Outcome	New immigrant screening	Passive case finding	Association/statistical significance	NICE grade
Mean (median) duration of symptoms, all TB cases	4.2 (0) weeks	10.5 (7.5) weeks	p<0.001	2+
Mean (median) duration of symptoms, smear-positive cases only	4.2 (0) weeks	11.4 (6) weeks	p<0.001	2+
Mean (median) duration of symptoms, TB cases resident six plus months	4.6 (0) weeks	10.5 (8) weeks	p<0.001	2+
Hospital admissions, N (%)	91/446 (20) admitted	215/361 (60) admitted	OR 0.2 (95% CI 0.1 to 0.2)	2+

Evidence statements: screening methods

Effectiveness of symptom questionnaire in comparison to chest X-ray for predicting a diagnosis of active tuberculosis

One study from Australia{359} found that a symptom questionnaire was less accurate in predicting cases of active tuberculosis in East Timor refugees compared to chest X-ray.

Chest X-ray suggestive of TB was the only statistically significant predictor of a diagnosis of TB, with 95.8% of those diagnosed with TB having an abnormal chest X-ray (OR 2.76, 95%CI 1.25 to 6.07, p= 0.01). (**3+**)

Effectiveness of Mantoux tests in comparison to chest X-ray for predicting a diagnosis of active tuberculosis

One study from the USA{360} found that chest X-ray was significantly associated with cases of active TB in Tibetan refugees whereas the size of Mantoux test induration in the sample was not.

Chest X-ray abnormalities were associated with an increased risk of subsequent diagnosis of active TB (RR 6.78, p=0.005). (**3+**)

Health economic modelling

A decision analytic model was used to estimate the cost-effectiveness of alternative screening algorithms for new entrants from high-risk countries. The economic model was based on an initial algorithm which included initial screening for active disease using a symptom checklist with clinic follow-up for suspected cases, and skin testing for detecting latent infection in new entrants aged 35 or younger. It was assumed that prophylaxis would be offered to those with positive skin tests, and no active disease, and that BCG vaccination would be offered to people with a negative skin test and no evidence of prior BCG. The model included assumptions about the attendance and treatment concordance rates. We then estimated the cost-effectiveness of variations to the screening algorithm, and the overall cost-effectiveness of the algorithm as a function of the prevalence of active and latent TB in the cohort, and the future incidence for people with/without latent infection at the time of screening.

The model used a simple decision tree approach, assuming a fixed number of secondary cases per primary case, rather than modelling the dynamics of transmission within the population. The results should thus be treated with caution. Caution is also required because of considerable uncertainty over various data inputs and assumptions, and also because of likely variation in programme effectiveness and costs in different areas. As far as possible, the model was based on best available empirical evidence. However, no data were available for some key parameters, so judgement from GDG members was used to estimate likely ranges of values.

It is important to recognise that the model does not take account of other potential benefits of screening – for example, community-based screening may act to introduce new entrants to local health services, and as a screen for other possible health problems. The model also does not take account of other ways in which screening and treatments could be better targeted. For example, the decision to offer prophylaxis could be informed by individuals' likely exposure to TB, risk factors for developing active TB, and/or evidence of latent infection from X-ray.

Cost-effectiveness of prophylaxis for suspected latent infection

The economic model suggests that prophylaxis is not cost-effective in the context of new entrant screening. Using the base case assumptions, the estimated incremental cost per QALY gained for including prophylaxis in the new entrant screening algorithm was nearly £400,000. This result was robust to variation in the model parameters.

Cost-effectiveness of BCG for Mantoux test -negative new entrants

The model predicts that BCG vaccination is cost-saving for the NHS in the context of new entrant screening. Removing vaccination for Mantoux test -negative new entrants from the new entrant screening algorithm would lead to a cost increase of £20,000 and a QALY loss of 1.8 per 100,000 screened, under the base case assumptions.

Symptom checklist vs. chest X-ray for detecting active disease

The cost-effectiveness of initial screening for active disease with a symptom checklist compared with chest X-ray depends on their relative costs and accuracies. Under the base case assumptions, the model suggests that although X-ray screening is more expensive, it leads to an overall saving in NHS expenditure due the lower number of false positive results that is predicted.

Interferon-gamma test vs. tuberculin skin test for latent infection

The model suggests that, despite its higher initial cost, interferon-gamma testing might be a cost-effective alternative to skin testing if it is demonstrated to give a lower number of false positive results. Under the base case assumptions, the model predicted that IGTs would be cost-saving in comparison with skin tests.

Cost-effectiveness of new entrant screening

At low levels of prevalent TB in the cohort tested, none of the screening algorithms was cost-effective. The algorithm without prophylaxis achieves an ICER of £30,000 per QALY at a TB prevalence of about 3%, and an ICER of £20,000 per QALY at about 4% prevalence. This is relatively high compared with rates of disease found in many new entrant screening programmes.

From evidence to recommendations

Current political policy aims for increasing use of chest X-ray screening for active TB prior to entry to the UK. This excludes children under 11 and women who might be pregnant. This NICE guideline addresses activities in the NHS, ie after arrival, and does not address services provided at the port of arrival or in induction centres for asylum seekers. However, the first consideration in screening is whether or not this pre-entry X-ray has been carried out and results are available. Readers are advised to check for new developments in these policies when interpreting the recommendations below.

The GDG were mindful of the legal restrictions on access to NHS services for overseas visitors, and the difficulty this introduces for screening. The data on comparisons of methods of screening is weak and does not show a clear best method. The GDG is aware of the rapidly developing field of interferon-gamma testing for latent TB. Insufficient data is currently available on its utility in this setting to recommend its routine use at this stage.

National surveys up to 1998 and continuous enhanced surveillance since 1999 show the highest rates of TB in new arrivals. Some cases are found by X-ray screening at port of arrival, and some by new-entrant screening soon after arrival, but most cases arise at least one year after initial entry to the UK (see Appendix G for details).

The purpose of screening high-risk groups, such as arrivals from high-incidence settings (defined as an incidence of 40 cases/100,000 per annum), and all asylum seekers, is threefold.

1. To detect cases with active disease, particularly respiratory, to enable treatment to be given, and prevent secondary cases.

2. To detect those with tuberculosis infection, particularly children, for whom treatment for latent TB infection is appropriate.

3. To identify those with no evidence of tuberculosis infection who, if previously unvaccinated, may benefit from BCG vaccination.

The health economics in this area clearly indicate that targeting screening activities on the new entrants at highest risk of developing active TB is crucial if the screening is to be cost-effective to the NHS. However, the data are very limited and further economic research is needed to support policy in this area. The epidemiology shows that most cases of active TB in new entrants develop some time after arrival in the UK. There are also policy changes under way in terms of pre-entry screening for active TB. The GDG drafted the algorithm shown below to reflect their consensus on screening new entrants.

In order to identify a subgroup of new entrants in whom risk of developing active TB is especially high (and therefore testing for latent TB, and giving treatment for latent TB infection may become cost-effective), the following criteria are given in the recommendation and algorithm:

- people aged under 16 (because they are at highest absolute risk over their whole lifetime, and screening under-16s is current practice)
- people between ages 16 and 35 (inclusive), if they have come from sub-Saharan Africa (because of very high rates of both TB and HIV, meaning the greatest possible gains from treatment for latent TB infection or vaccination)
- people between ages 16 and 35 (inclusive), if their country of origin is outside sub-Saharan Africa but has incidence >500/100,000.

The threshold of 500/100,000 was chosen because the health economic model shows cost effectiveness when risk over the 15 years after entry to the UK exceeds 12%, which equates to 800/100,000. This estimate has some uncertainty (as detailed above), pre-entry rates will not equate to post-entry, and the whole population may not reflect the health of migrants, therefore the threshold is set somewhat lower.

The process of identifying new entrants for screening through port of arrival notification to the local CCDC has limitations, and the recommendations therefore advise on different sources which can be used. This is relevant to conditions other than TB, but is not currently practised uniformly around the country, and therefore is specified here.

RECOMMENDATIONS

R123 Healthcare professionals, including primary care staff, responsible for screening new entrants[10] should maintain a coordinated programme to:

- detect active TB and start treatment B
- detect latent TB and start treatment B
- provide BCG vaccination to those in high-risk groups who are not infected and who are previously unvaccinated D(GPP)
- provide relevant information to all new entrants. D(GPP)

R124 New entrant screening for tuberculosis should be incorporated within larger health screening programmes for new entrants, linked to local services. D(GPP)

R125 Assessment for, and management of TB in new entrants should consist of the following. D(GPP). See also R5 for assessment of latent TB

- Risk assessment for HIV, including HIV prevalence rates in the country of origin, which is then taken into account for Mantoux testing and BCG vaccination.

- Assessment for active TB if interferon-gamma test is positive, which would include a chest X-ray.

- Treatment for latent TB infection for people aged 35 or younger in whom active TB has been excluded, with a positive Mantoux test inconsistent with their BCG history, and a positive interferon-gamma test.

- Consideration of BCG for unvaccinated people who are Mantoux negative (see section 11.4).

- 'Inform and advise' information for people who do not have active TB and are not being offered BCG or treatment for latent TB infection.

R126 New entrants should be identified for TB screening from the following information:

[10] In this guideline, new entrants are defined as people who have recently arrived in or returned to the UK from high-incidence countries, as defined by the HPA; go to **www.hpa.org.uk** and search for 'WHO country data TB'.

- port of arrival reports D(GPP)
- new registrations with primary care B
- entry to education (including universities) D(GPP)
- links with statutory and voluntary groups working with new entrants. D(GPP)

R127 Any healthcare professional working with new entrants should encourage them to register with a GP. D(GPP)

Cross-referring:

For details of diagnosing latent TB, see section 5.1.

For details of diagnosing active TB, see section 5.2.

For details of BCG vaccination, see section 11.4

For examples of 'inform and advise' information, see Appendix H.

In line with NICE's digitalisation strategy, the algorithms in the full version of the guideline and in the NICE quick reference guide supporting the updated guideline have now been replaced by a NICE pathway. The pathway is an interactive web-based tool for health and social care professionals providing fast access to the NICE guidance and associated products.

Notification and enhanced surveillance

This chapter sets out the facts of national systems of data collection for TB, as co-ordinated and reported by the HPA's Centre for Infections. Recommendations are not made in this section; readers are reminded that notification is a statutory requirement.

Tuberculosis surveillance

TB surveillance aims to provide information that can be acted on to prevent and control tuberculosis. High-quality surveillance, as defined in the national TB Action Plan aims to provide the information required at local, national and international levels to:

- identify outbreaks (and other related incidents) and guide immediate action
- monitor trends and measure the occurrence of disease and anti-TB drug resistance
- inform policy
- inform development of services, and
- monitor the success of the TB programme.

Surveillance should also aim to identify population characteristics that predispose to a higher risk of infection and disease in order to appropriately target public health action and health services.

Monitoring the prevalence of infections should be part of surveillance of TB. However, in countries with low disease incidence, high immigration and generalised use of BCG, prevalence surveys on TB infection are very difficult to perform and interpret. Therefore tuberculosis surveillance is mainly based on morbidity associated with disease. It does however also include mortality information (derived from cause of death certification) as annual notifications of infectious diseases (NOIDs) deaths in residents of England and Wales (Office for National Statistics).

Information for TB case reports is currently mainly based on statutory notifications (NOIDs) implemented in 1913 and Enhanced Tuberculosis

Surveillance (ETS) implemented in 1999. Treatment outcome monitoring was implemented as part of ETS in 2002. Information on tuberculosis isolates is based on MycobNet (Mycobacterial Surveillance Network) developed in 1994, which collates information on all isolates of *M. tuberculosis* complex confirmed at reference centres for mycobacteriology, including species and drug susceptibility results. On a yearly basis, data on TB cases reports from ETS are linked at national level with information from MycobNet on initial isolates in order to improve the completeness of laboratory information (including drug susceptibility results) among TB incident cases.

The case definition used to identify incident cases to be included in the reporting system (NOIDs and ETS) is shown overleaf.

Tuberculosis surveillance is constantly evolving to reflect information needs at local and national levels, and availability of new microbiological and information technology. Some new systems are currently under development, including a national microbiological strain typing database and a national TB incidents and outbreaks database (TBIOS), both of which are held at the HPA's Centre for Infections.

All new tuberculosis cases (culture-confirmed cases and other than culture confirmed cases) should be reported.
A **culture-confirmed case** is defined as culture confirmed disease due to *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis* or *M. africanum*).
A **case other than culture confirmed** is defined as a case, that in absence of culture confirmation, meets the following criteria:

1. clinician's judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis,
2. *and*
3. clinician's decision to treat the patient with a full course of anti-tuberculosis treatment.

Persons receiving preventive chemoprophylaxis are not to be reported to NOIDs or ETS (but may be reported by letter if this information is required locally for service audit or other purposes).

Statutory notifications of infectious diseases

It is a statutory requirement in England, Wales and Northern Ireland for the diagnosing clinician to notify all cases of clinically diagnosed tuberculosis, whether or not microbiologically confirmed. This statutory requirement for the notification of certain infectious diseases came into being in 1891 and included TB from 1913. Notification must be made to the local ‘proper officer’, usually the CCDC. Regular returns are made by the proper officer to the Centre for Infections where NOIDs data are collated.

The prime purpose of the NOIDs system is speed in detecting possible outbreaks and epidemics, rather than accuracy of diagnosis. Since 1968 clinical suspicion of a notifiable infection is all that is required, but if a clinical diagnosis of TB later proves incorrect it should be denotified to the local proper officer. The data from this system is the most timely information about TB cases available but is not the most comprehensive or reliable. The dataset is very limited and errors are introduced through problems with removing duplicate entries and excluding, through denotification, cases wrongly diagnosed as TB.

Enhanced Tuberculosis Surveillance in England, Wales and Northern Ireland

ETS commenced on 1 January 1999 in England and Wales, and the following year in Northern Ireland. Its aims are to continuously provide detailed and comparable information on the epidemiology of tuberculosis, and to enable more precise estimates to be made of trends in tuberculosis incidence in subgroups of the population. ETS is less timely than NOIDs but in this system checking and de-duplication of cases is possible, providing a more accurate number of cases reported as well as more detailed information on each case. The minimum dataset on each case currently includes notification details and demographic, clinical and microbiological information. Cases are reported by clinicians to local coordinators in HPU, then via HPA regional units to the HPA Centre for Infections, Colindale. In most of the regions/countries ETS data are collected through a paper form, entered at local level or at regional level, to then be imported into a national database. The exact process varies according to the HPU or region. For example, in London these data are collected through a internet-based register. ETS provides an annual corrected analysis of reports by age, sex, ethnic group, country of birth, site of disease and region.

Treatment outcome monitoring in England, Wales and Northern Ireland

Outcome surveillance is an essential tool to determine the effectiveness of the national effort to control TB by providing a valuable insight into the proportion of patients who either complete treatment, die, experience complications resulting in changed or prolonged drug therapy, or who are lost to follow-up prior to finishing treatment.

Tuberculosis treatment outcome surveillance is the last component of the ETS system and began, following pilot work, in January 2002 on TB cases reported in 2001. Information on outcome of treatment is collected on all TB cases reported at twelve months after starting treatment, or after notification where the treatment starting date is not available.

MycobNet (UK)

The UK's Mycobacterial Surveillance Network (MycobNet) was developed in 1994 in response to the need for effective information on the antibiotic susceptibility profile of TB cases. A specimen taken from the patient is tested at the local hospital laboratory and if found, or suspected, to be mycobacteria is forwarded to one of seven regional reference centres for mycobacteriology for further investigation.

Information gathered on isolates identified as *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis* or *M. africanum*) is collated through MycobNet at the HPA Centre for Infections, and includes species, drug sensitivity results, and some demographic and clinical data. This information is used to monitor trends in drug resistance in TB, and is also the basis of surveillance of *M. bovis* disease in humans.

15 Priorities for future research

11. Research recommendation 1

A diagnostic and qualitative study, assessing whether interferon-gamma tests are acceptable to patients and more effective than tuberculin skin tests for: • predicting subsequent development of active TB, *or* • diagnosing or ruling out current active TB • new entrants from high TB prevalence countries • healthcare workers • children in high-risk areas who missed neonatal BCG • contacts of sputum smear-positive TB • HIV-positive patients.	
Population	• New immigrants from high TB prevalence countries. • Healthcare workers. • Children in high-risk areas who missed neonatal BCG. • Contacts of sputum-positive TB. • HIV-positive patients.
Intervention	Interferon-gamma tests.
Comparison	Tuberculin skin tests.
Outcome	Subsequent development of active TB. Qualitative patient acceptability outcome.

12. Research recommendation 2

A cluster RCT of DOT compared with self-administered treatment for latent and/or active TB should be conducted in a UK population. This should be targeted at homeless people, and those with a history of non-adherence, alcoholism, drug abuse or mental illness.	
Population	Homeless people, those with a history of non-adherence, alcoholism, drug abuse, or mental illness.
Intervention	DOT.
Comparison	Self-administered treatment.
Outcome	Treatment completion, cure and relapse rates.

13. Research recommendation 3

A study is needed of people found by new entrant screening (as set out above in 12.7) to be Mantoux positive and interferon-gamma positive, to establish better estimates of the cost-effectiveness of screening and treatment for latent TB infection in this population. This could identify factors predisposing people to developing active TB so that more effective targeted treatment programmes can be developed for latent TB infection..	
Population	New entrants with latent TB infection.
Intervention	Screening and treatment for latent TB infection.
Comparison	Not applicable.

Outcome	Risk factors for the development of active TB and the cost-effectiveness of screening and treatment for latent TB infection (£/QALY).

14. Research recommendation 4

A case control study, comparing people who developed active or latent TB with those who did not, and comparing the proportions of people in each group who had been vaccinated and the time since vaccination. The aim will be to derive improved estimates of protective efficacy and duration of protection of the BCG vaccine.	
Population	Patients eligible to receive BCG vaccine (this could be neonates, contacts, healthcare workers, new immigrants, schoolchildren).
Intervention	BCG.
Comparison	No BCG.
Outcome	Development of active TB. Possibly the development of latent TB infection as assessed by interferon gamma test (to avoid BCG effects on Mantoux test).

15. Research recommendation 5

A study to ascertain quality-of-life score estimates from those with TB (both active disease and latent infection) including adverse treatment effects, using an appropriate, quality-of-life instrument. This will improve economic decision-making throughout TBcare.	
Population	Those with TB disease or latent infection.
Intervention	Quality of life instrument.
Comparison	None.
Outcome	Quality of life score (single score estimate of health status).

16. Research recommendation 6

Research is needed to determine whether contact tracing is more effective (in terms of identifying cases of latent infection and active disease) among household contacts than among street homeless contacts of patients with confirmed TB disease (including those using direct-access hostels for the homeless).	
Population	• pulmonary smear-positive TB • pulmonary smear-negative TB • non-pulmonary TB.
Intervention	Contact screening of household contacts.
Comparison	Contact screening of homeless contacts.
Outcome	Case yields for latent TB infection and active TB disease among screened contacts.

17. Research recommendation 7

Research is needed to determine whether Port of Arrival scheme referrals with incentives for attending screening identify more cases of latent TB infection and active TB disease in new entrants than Port of Arrival scheme referrals with no incentives.	
Population	New immigrants from high TB prevalence (40+/100,000) countries.
Intervention	Port of arrival referrals with screening attendance incentives.
Comparison	Port of arrival referrals with no screening attendance incentives.
Outcome	Case yields for TB infection and active TB disease in intervention and comparison groups.

18. Research recommendation 8

Research is needed to determine whether incentives for attending chest X-ray screening achieve better coverage in the homeless population, or identify more cases of latent TB infection and active TB disease, than no incentives.

Population	Individuals in temporary accommodation, hostels, and street homeless.
Intervention	Invitation with incentives to attend chest X-ray screening.
Comparison	Invitation without incentives to attend chest X-ray screening.
Outcome	Case yields for TB infection and active TB disease in intervention and comparison groups.

Other potential research recommendations

These are other topics where evidence is lacking, and where new research could improve future guidelines. They are not developed to the extent of the eight priorities above.

- A multicentre RCT in patients with bacteriologically confirmed tuberculous meningitis, comparing six to 11 months of chemotherapy with 12 months of treatment to ascertain if different treatment duration affects mortality and residual disability.
- Effectiveness of skills training for TB key workers, eg in motivational interviewing methods.
- An RCT of prisoners being treated for TB disease or latent infection who are discharged early, to assess whether contingency plans are cost-effective and improve treatment completion, cure and relapse rates.
- Is contact tracing using one method (eg home screening and follow-up of contacts) more effective than another (eg clinic-based screening and follow-up of contacts) in identifying cases of latent infection and active TB disease among adult and child household contacts of patients with confirmed TB disease?
- What is the impact of screening casual (low exposure) *vs.* close (high exposure) contacts of patients with confirmed TB on the yield of latent tuberculosis infection and active TB disease cases?
- Does screening of patient contacts in the same hospital bay as a pulmonary smear-positive index case of TB yield more cases of latent

TB infection and active disease compared to other patient contacts on the same hospital ward?

A number of studies were suggested in areas not addressed by guideline questions, therefore the current evidence base for these areas is not known. These were:

- a study investigating risk factors for adverse outcomes from tuberculosis (deaths, acquired resistance and loss to follow-up)
- studies on patient and healthcare delay, to identify how to shorten the period of infectivity of active cases
- a diagnostic study of the efficacy of interferon-gamma testing in confirming active non-respiratory tuberculosis if other tests have remained inconclusive
- a study on whether interferon-gamma tests are more effective than chest X-ray screening for identifying cases of active TB disease in new immigrants undergoing TB screening.

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Appendices

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Appendix C: Glossary and Abbreviations

Abbreviations

AFB
Acid Fast Bacilli

BAL
Bronchoalveolar Lavage

BCG
Bacille Calmette-Guerin

BTS
British Thoracic Society

CCDC
Consultant in Communicable Disease Control

CFP-10
Culture Filtrate Protein 10

CI
Confidence Interval

CNS
Central Nervous System

CSF
Cerebrospinal Fluid

CT
Computed Tomography

DNA
Deoxyribonucleic Acid

DOR
Diagnostic Odds Ratio

DOT
Directly Observed Therapy

DOTS
Directly Observed Therapy Short Course

DS
Diagnostic Study

ELISA
Enzyme-Linked Immunosorbent Assay

ELISPOT
Enzyme-Linked Immunospot

ESAT-6
Early Secretion Antigen Target 6

FM
Fluorescence Microscopy staining

GDG
Guideline Development Group

GRADE
Grading of Recommendations, Assessment, Development and Evaluation

GPP
Good Practice Point

HCW
Health Care Workers

HIV
Human Immunodeficiency Virus

HPA
Health Protection Agency

HPU
Health Protection Unit

HTA
Health Technology Assessment

IFN Gamma
Interferon Gamma

JCVI
Joint Committee on Vaccination and Immunisation

LJ Slope
Lowenstein-Jensen Slope solid-media

LTBI
Latent Tuberculous Infection

MDR-TB
Multi-Drug Resistant Tuberculosis

MR
Magnetic Resonance

NAAT
Nucleic Acid Amplification Technologies

NCC-CC
National Collaborating Centre for Chronic Conditions

NHS
National Health Service

NICE
National Institute for Health and Clinical Excellence

NNT
Number Needed to Treat

OR
Odds Ratio

PA
Posterior-Anterior (chest X-ray)

PCR
Polymerase Chain Reaction

PHLS
Public Health Laboratory Service

PPD
Purified Protein Derivative

QALY
Quality Adjusted Life Year

RCT
Randomised Controlled Trial

ROR
Ratio of Odds Ratios

RR
Relative Risk

TB
Tuberculosis

TST
Tuberculin Skin Test

WHO
World Health Organization

ZN
Ziehl-Neelsen microscopy staining

System for Drug Regimen Abbreviations

Drug regimens for anti-tuberculosis treatment are often abbreviated according to the following system: a number indicating the length of a phase of treatment in months, followed by letters for the drugs administered in that phase. Consecutive phases are separated by an oblique.

H = isoniazid

R = rifampicin

Z = pyrazinamide

E = ethambutol

Examples:

2HRZE/4HR is the standard "six month, four drug regimen": 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin.

2HRE/7HR is 2 months of isoniazid, rifampicin and ethambutol followed by 7 months of isoniazid and rifampicin

2HRZ/7HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 7 months of isoniazid and rifampicin

2HRZ/4HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 4 months of isoniazid and rifampicin

Glossary

Acid fast bacilli

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

Action Plan

See "TB action plan"

Active tuberculosis

Infection with mycobacteria of the *M. tuberculosis* complex, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent TB, where mycobacteria are present, and may be dormant, but are not causing disease. The symptoms of disease include weakness, weight loss, fever, no appetite, chills and sweating at night. Other symptoms of TB disease depend on where in the body the bacteria are growing. If TB is in the lungs (pulmonary TB), the symptoms may include a cough, pain in the chest, and coughing up blood. (Source: www.hpa.org.uk)

Adherence

The term adherence refers to the patient's ability or choice to adhere to a treatment regimen. Also see "Concordance")

Algorithm (in guidelines)

A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked by arrows.

Atypical mycobacteria

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

Audit

See "Clinical audit"

Automated liquid culture system

Automated systems allow continuous monitoring of cultures grown using a liquid medium (see "Liquid culture"). Time to detection is more rapid than traditional methods.

Bacille Calmette-Guerin vaccine

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

Bacteriological conversion rate

The proportion of people tested for latent TB infection who convert from a negative to a positive test.

Case-control study

Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Case series

Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

Chemoprophylaxis

Treatment for latent TB infection. The administration of anti-tuberculosis drug(s) to prevent the acquisition or progression of tuberculosis infection. The former may be referred to as *primary chemoprophylaxis* or *preventive therapy*, the latter as *secondary chemoprophylaxis*. (Source: www.hpa.org.uk)

Class of recommendation

See "Grade of recommendation".

Clinical audit

A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

Clinician

In this guideline, the term clinician means any health care professional.

Chemotherapy

The multi-drug antibiotic treatment regimens used to treat active TB.

Cochrane Review

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

Cohort study

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

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

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

Concordance (as used in section 5.1)
The percentage of agreement between two tests

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

Contact (domestic, close, casual, workplace)
A person who has spent time with a person with infectious TB. (Source: www.hpa.org.uk)

Contact tracing
The identification of contacts (See "Contact") to find associated cases, to detect people with latent TB infection and to identify those not infected but for whom BCG vaccination might be appropriate.

Conversion rate
See "Bacteriological conversion rate".

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

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-utility analysis

A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYS).

Culture

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

Cure and completion rate

The proportion of people receiving treatment for active TB who either have negative culture results during the continuation phase of treatment, or who complete treatment without documented culture status.

Decision analytic model/techniques

A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.

Descriptive study

Observational studies or surveys designed to quantify current service provision or clinical conditions. Such studies are not designed to test hypotheses about the data.

Diagnostic odds ratio

This is a single summary of diagnostic performance (it describes the ratio of the odds of a positive test result in a patient with disease compared to a patient without disease). The DOR can be calculated from sensitivity and specificity data and where a test provides no diagnostic evidence the DOR is 1.

Directly observed therapy

A way of helping patients take their medicine for TB. A person receiving DOT, will meet with a health care worker every day or several times a week. They will meet at an agreed place. This can be the TB clinic, the patient's home or work, or any other convenient location. They will take their medicine at this place. Sometimes someone in their family or a close friend will be able to help in a similar way to the health care worker. (Source: www.hpa.org.uk)

Directly observed therapy short-course

The World Health Organization has developed a control strategy known as Directly Observed Therapy, Short-course, which requires microscopy based diagnosis, standardised treatment under direct supervision, a secure supply of quality drugs and equipment, careful monitoring and supervision, and political commitment to support these activities. (Source: www.hpa.org.uk)

Discordance
The percentage of disagreement between two tests

Disseminated (including miliary) tuberculosis
Blood borne spread of TB which may or may not be accompanied by chest X-ray or high resolution CT changes.

Dual Strategy
A dual strategy uses Mantoux as the initial test. If the Mantoux test is positive this is followed by an interferon-gamma test.

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

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

Gastric washings (Gastric lavage)
Some patients (particularly children) with suspected TB are unable to cough up any sputum. As an alternative, in a gastric lavage, saline solution is introduced into the stomach through a tube, the contents are pumped out and are examined for *M. tuberculosis* complex bacteria.

Gold standard
See "Reference standard"

Good practice point
Recommended good practice based on the clinical experience of the guideline development group (GDG) in the absence of robust, published clinical evidence.

Grade (Class)of recommendation
All recommendations are assigned a grade (A,B,C,D or D(GPP)) according to the level of evidence the recommendation is based on (See "Level of evidence").

Guideline development group
The guideline development group (GDG) agrees the clinical questions for the guideline, considers the evidence and develops the recommendations. The GDG membership is multidisciplinary comprising clinicians, patients and/or carers and technical experts.

Heaf test
A type of tuberculin skin test in which tuberculin is injected intradermally with a multiple puncture apparatus. The injection site is examined for signs of an immune response within 7 days. (Also see "Tuberculin skin test" and "Mantoux test").

Hard to reach population
Children, young people and adults whose social circumstances or lifestyle, or those of their parents or carers, make it difficult to:

- recognise the clinical onset of tuberculosis
- access diagnostic and treatment services
- self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer)
- attend regular appointments for clinical follow-up.

Health Technology Assessment
These consider the effectiveness, appropriateness and cost of technologies and are funded by the NHS Research and Development Division.

High-incidence country
Following the widely used threshold, any country with an incidence equal to or greater than 40 cases per 100,000 population per year. A similar definition can be made for parts of the UK, for instance for neonatal BCG vaccination. This guideline categorises, in Table 27, Section 10.2, the countries which are the most common origins of people successfully applying for residence in the UK according to this threshold. Up-to-date and comprehensive information is held by the Health Protection Agency and is available online.

Histology
Microscopic examination of cells and clinical samples.

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

Incremental cost-effectiveness ratio

A measure of the additional cost of a health care activity per unit of benefit (usually a QALY, see below).

Index case

The initial person found to have TB, whose contacts are screened. Consequently, the source of their infection may be found, but the initial presenting patient is regarded as the index case.

Infectious TB

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

Inform & Advise information

Information provided to patients so that they are able to recognise the symptoms of TB and be aware of the action they should take should these symptoms arise. Examples are given in Appendix F.

Intention-to-treat analysis (ITT analysis)

An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Interferon-gamma test

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

Kappa Value

A measure of agreement of accuracy beyond chance

Latent tuberculosis

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

Level of evidence

A code (e.g. 1++, 1+,2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.

Liquid culture

Culture grown using a liquid medium where mycobacteria grow faster (compared to solid media). (Also see "Automated liquid culture systems").

Mantoux test
A type of tuberculin skin test in which tuberculin is injected intracutaneously. The injection site is examined for signs of an immune response after 2–3 days. (Also see "Tuberculin skin test" and "Heaf test").

Meta-analysis
A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

Methodological limitations
Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Molecular probe
A process used to detect the presence of a particular genetic sequence in the cells of interest, using suitably labelled complementary sequences. In the case of TB, particular genetic sequences can confirm the mycobacterial species or the presence of certain drug resistance mutations.

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

Mycobacterium tuberculosiscomplex (M. TB Complex)
The related mycobacterial species *M. tuberculosis*, *M. bovis* and *M. africanum* which can cause tuberculosis in humans.

Non-respiratory TB
Active TB affecting any part of the body other than the lungs, bronchi, pleura or thoracic lymph nodes (for example, the meninges or cervical lymph nodes).

Nucleic Acid Amplification Test
A test to detect fragments of nucleic acid, allowing rapid and specific diagnosis of *M. tuberculosis* directly from a range of clinical samples.

National Health Service
This guideline is written for the NHS in England and Wales.

National Collaborating Centre for Chronic Conditions
A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the Patient Involvement Unit at NICE, the Royal College of General Practitioners,

the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient and Carers Liaison Committee, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2000 to undertake commissions from NICE to develop clinical guidelines for the NHS.

National Clinical Guideline Centre (NCGC)
Develops clinical guidelines on behalf of NICE to describe care for long term conditions delivered across primary and secondary care. NCGC was formed in April 2009 by the merger of four national collaborating centres. It is hosted by the Royal College of Physicians (RCP) and replaces four former NCCs - Acute Conditions, Chronic Conditions, Nursing and Supportive Care and Primary Care.

National Institute for Health and Clinical Excellence
NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

Needs assessment
An assessment of the potential benefit from health care activities at a population-wide level. A needs assessment takes into account epidemiology, current service provision, and evidence of clinical effectiveness and cost-effectiveness.

Negative predictive value
The proportion of individuals with a negative test result who do not have the disease.

Negative pressure room
Used for the isolation of certain patients known or suspected to have infectious TB. A negative pressure room is one where the air from the room is sucked out into dedicated ducting through a filter and into the outside air, at a distance from all other air intakes. The level of pressure should be 10 Pascals below the ambient pressure.

New entrant
Anyone coming to work or settle in the UK. This will include immigrants, refugees, asylum seekers, students and people on work permits. This group is intended to include UK-born people, or UK citizens, re-entering the country after a prolonged stay in a high-incidence country.

Non-analytic study
Any study with a level of evidence grading of 3 in the NICE levels of evidence hierarchy.

Number needed to treat
The number of patients who must be treated to prevent a single occurrence of the outcome of interest, based on an average calculated from the available data.

Non-respiratory TB
See "Extra pulmonary TB"

Odds ratio
A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The "odds" is the ratio of non-events to events.

Outbreak
There is no robust, widely accepted threshold for an outbreak of a disease, but in practical terms, an outbreak is the occurrence of an unusually high number of cases in associated individuals, in a small geographical area, and/or in a relatively short period of time.

Positive predictive value
The proportion of individuals with a positive test result who actually have the disease.

Post-primary tuberculosis
The stage following primary tuberculosis, when infection with the bacteria has advanced to disease, possibly symptomatic, with bacterial growth demonstrable by culture.

Primary tuberculosis
The initial stage of infection with TB bacteria, which is often asymptomatic, but can be detected by tuberculin conversion or interferon-gamma testing.

Quality-adjusted life- year
An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis.

Randomised controlled trial
A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

Ratio of odds ratios (ROR)
A measure of effect which reflects test performance and provides an approach to evaluating tests in the absence of a reference test. In this guideline ROR is mathematically defined as (odds of positive IGT in a high risk area divided by the odds of a positive test in a low risk area) divided by (odds of a positive TST test in a high risk area divided by a positive TST test in a low risk area)

Reactivation
The advancement of old latent TB (whether previously detected or not) into active TB

Reference standard
An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Relative risk
The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A, divided by the risk of the event in group B).

Schools vaccination programme
BCG vaccination programme performed in schools in children aged 10–14 years.

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

Short-course treatment
Modern 6 month treatment regimens for active TB (previously treatment had been for at least 12 months).

Six month, four drug regimen
These guidelines recommend a drug treatment regimen using four different drugs over a duration of 6 months. This is not applicable in all cases.

Skin test
See "Tuberculin skin test"

Smear-positive
See "Sputum smear-positive"

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

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

Sputum smear-positive ("Smear positive")
Respiratory tuberculosis in which mycobacteria ('acid-fast bacilli', AFB) have been seen in a stained smear of sputum examined under a microscope. Confirmation of the diagnosis requires

culture to differentiate the organisms from atypical mycobacteria (those which are not in the *M. Tuberculosis* complex). (Source: www.hpa.org.uk)

Systematic review
Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

TB action plan
"Stopping Tuberculosis in England: An Action Plan from the Chief Medical Officer" (October 2004) is a Department of Health publication which sets out actions regarded as essential to keep TB under control.

Treatment failure
Failure of the prescribed drug regimen to eliminate the TB bacteria from the body. Demonstrated by a lack of clinical improvement, or by positive culture after the end of the fourth month of treatment.

Tuberculin conversion
A change from a negative to a positive test for latent TB. Tuberculin conversion is defined as the second of two tuberculin skin tests increasing by 2 Heaf grades, or >10mm Mantoux, over the first test. This does not apply if vaccination takes place in the meantime.

Tuberculin skin test
Any one of a range of simple tests which inject tuberculin (purified protein derivative, PPD) into the skin. Immune reaction can be assessed after a few days according to the size of induration at the site of injection. They can demonstrate acquired immunity to TB, lack of immunity, or possible current infection (a strong response), but are confounded by immuno-compromise, serial TST, and prior exposure to atypical mycobacteria. The results are generally referred to as "positive" or "negative". (Also see "Heaf test" and "Mantoux test" (Source: www.hpa.org.uk)

Tuberculosis
Active TB; disease due to infection with *M. tuberculosis* complex.

Appendix D: Unlicensed medicines

This guideline does not contain any recommendations for medicines outside their licensed indications. Tuberculin purified protein derivative for Mantoux testing has no marketing authorisation in the United Kingdom at the time of writing but is administered on a named patient directive.

Appendix H: Examples of Inform & Advise information - 2006

These are typically provided as standard letters to individual patients, but can take other form such as leaflets. Readers should be aware of the guideline recommendations about translation and non-verbal communication.

Example letter for a contact of a person with sputum smear-positive TB, with negative TST/interferon-gamma test

Dear... You have been screened as a close contact of someone who has tuberculosis (TB). Not all forms of TB are infectious. The test you had shows no evidence of TB infection. It is very unlikely that you will have any problem from TB in the future and no further check-ups are needed. However, if in the future you develop weight loss, cough up blood, have a persistent cough or fever or swollen glands in the neck, which lasts for over four weeks, you should contact your family doctor. Yours etc.

Example letter for a new entrant to the UK with positive TST/interferon-gamma test, but negative chest X-ray

Dear... You have been screened for tuberculosis (TB) as you recently arrived in the United Kingdom from abroad. The test you had was stronger than we would normally expect, but the X-ray you had was clear, so no follow-up arrangements are needed. However, if in the future you develop weight loss, cough up blood, have a persistent cough or fever or swollen glands in the neck, which lasts for over four weeks, you should contact your family doctor. Yours etc.

CG117, 2011

B: Clinical questions and search strategies - 2011

J: Details of excluded studies – 2011

L: Health economic model – 2011

P: Data for meta-analysis for children

Q: Data for meta-analysis for contacts

- ***Appendix J Excluded Papers – 2011***

- **Excluded Studies for the Use of IGRA testing in people from high prevalence countries and reasons for exclusion**

Kariminia, A., Sharifnia, Z., Aghakhani, A., Banifazl, M., Eslamifar, A., Hazrati, M., & Ramezani, A. 2009. Comparison of QuantiFERON TB-G-test to TST for detecting latent tuberculosis infection in a high-incidence area containing BCG-vaccinated population. *Journal of Evaluation in Clinical Practice*, 15, (1) 148-151
Ref ID: 91

EXC: Study done in high incidence area

Baker, C.A., Thomas, W., Stauffer, W.M., Peterson, P.K., & Tsukayama, D.T. 2009. Serial testing of refugees for latent tuberculosis using the QuantiFERON-gold in-tube: effects of an antecedent tuberculin skin test. *American Journal of Tropical Medicine & Hygiene*, 80, (4) 628-633
Ref ID: 200

EXC: Serial testing using IGRA

Higuchi, K., Kawabe, Y., Mitarai, S., Yoshiyama, T., Harada, N., & Mori, T. 2009. Comparison of performance in two diagnostic methods for tuberculosis infection. *Medical Microbiology & Immunology*, 198, (1) 33-37
Ref ID: 211

EXC: Comparison of IGRA tests active

Hargreaves, S., Carballo, M., & Friedland, J.S. 2009. Screening migrants for tuberculosis: where next? *The Lancet Infectious Diseases*, 9, (3) 139-140
Ref ID: 216

EXC: Summary

Ribeiro, S., Dooley, K., Hackman, J., Loredo, C., Efron, A., Chaisson, R.E., Conde, M.B., Boechat, N., & Dorman, S.E. 2009. T-SPOT.TB responses during treatment of pulmonary tuberculosis. *BMC Infectious Diseases*, 9, 23
Ref ID: 240

EXC: Treatment

Pai, M., Joshi, R., Dogra, S., Zwerling, A.A., Gajalakshmi, D., Goswami, K., Reddy, M.V., Kalantri, A., Hill, P.C., Menzies, D., & Hopewell, P.C. 2009. T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. *International Journal of Tuberculosis & Lung Disease*, 13, (1) 84-92
Ref ID: 250

EXC: To be assessed for question 2

Muller, L.L., Bennet, R., Gaines, H., Zedenius, I., & Berggren, I. 2008. Complexity in estimating recent tuberculosis transmission among predominantly immigrant school children in Stockholm, Sweden 2006. *Scandinavian Journal of Infectious Diseases*, 40, (9) 709-714
Ref ID: 307

EXC: Paper included children

Lewinsohn, D.A., Zalwango, S., Stein, C.M., Mayanja-Kizza, H., Okwera, A., Boom, W.H., Mugerwa, R.D., & Whalen, C.C. 2008. Whole blood interferon-gamma responses to mycobacterium tuberculosis antigens in young household contacts of persons with tuberculosis in Uganda. *PLoS ONE [Electronic Resource]*, 3, (10) e3407
Ref ID: 324

EXC: Foreign based study and looking at children

Eum, S.Y., Lee, Y.J., Kwak, H.K., Min, J.H., Hwang, S.H., Via, L.E., Barry, C.E., III, & Cho, S.N. 2008. Evaluation of the diagnostic utility of a whole-blood interferon-gamma assay for determining the risk of exposure to Mycobacterium tuberculosis in Bacille Calmette-Guerin (BCG)-vaccinated individuals. *Diagnostic Microbiology & Infectious Disease*, 61, (2) 181-186
Ref ID: 444

EXC: To be assessed for Question 2

Haley, C.A., Cain, K.P., Yu, C., Garman, K.F., Wells, C.D., & Laserson, K.F. 2008. Risk-based screening for latent tuberculosis infection. *Southern Medical Journal*, 101, (2) 142-149
Ref ID: 491

EXC: IGRA not included

Dosanjh, D.P., Hinks, T.S., Innes, J.A., Deeks, J.J., Pasvol, G., Hackforth, S., Varia, H., Millington, K.A., Gunatheesan, R., Guyot-Revol, V., & Lalvani, A. 2008. Improved diagnostic evaluation of suspected tuberculosis.[see comment][erratum appears in Ann Intern Med.2008 Apr 15;148(8):635]. *Annals of Internal Medicine*, 148, (5) 325-336
Ref ID: 515

EXC: Focus not on LTBI

Adetifa, I.M., Lugos, M.D., Hammond, A., Jeffries, D., Donkor, S., Adegbola, R.A., & Hill, P.C. 2007. Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia. *BMC Infectious Diseases*, 7, 122
Ref ID: 577

EXC: To be assessed for question 2

Bua, A., Molicotti, P., Delogu, G., Pirina, P., Mura, M.S., Madeddu, G., Franca, S.F., Maida, I., Sechi, L.A., & Zanetti, S. 2007. QuantiFERON TB Gold: a new method for latent tuberculosis infection. *New Microbiologica*, 30, (4) 477-480
Ref ID: 584

EXC: To be assessed for question 2

Ozekinci, T., Ozbek, E., & Celik, Y. 2007. Comparison of tuberculin skin test and a specific T-cell-based test, T-Spot.TB, for the diagnosis of latent tuberculosis infection. *Journal of International Medical Research*, 35, (5) 696-703
Ref ID: 636

EXC: To be assessed for question 2

Drobniewski, F., Balabanova, Y., Zakamova, E., Nikolayevskyy, V., & Fedorin, I. 2007. Rates of latent tuberculosis in health care staff in Russia. *PLoS Medicine / Public Library of Science*, 4, (2) e55
Ref ID: 690

EXC: To be assessed for question 2

Tuuminen, T., Sorva, S., Liippo, K., Vasankari, T., Soini, H., Eriksen-Neuman, B., Miettinen, A., & Seppala, I.J. 2007. Feasibility of commercial interferon-gamma-based methods for the diagnosis of latent Mycobacterium tuberculosis infection in Finland, a country of low incidence and high bacille Calmette-Guerin vaccination coverage. *Clinical Microbiology & Infection*, 13, (8) 836-838
Ref ID: 716

EXC: Research Note

Friedman, L.N., Nash, E.R., Bryant, J., Henry, S., Shi, J., D'Amato, J., Khaled, G.H., Russi, M.B., O'Connor, P.G., Edberg, S.C., Pisani, M.A., Cain, H.C., Tanoue, L., & Weissman, D.N. 2006. High rate of negative results of tuberculin and QuantiFERON tests among individuals with a history of positive skin test results. *Infection Control & Hospital Epidemiology*, 27, (5) 436-441
Ref ID: 1010

EXC: PPD based IGRA

Shams, H., Weis, S.E., Klucar, P., Lalvani, A., Moonan, P.K., Pogoda, J.M., Ewer, K., & Barnes, P.F. 2005. Enzyme-linked immunospot and tuberculin skin testing to detect latent tuberculosis infection. *American Journal of Respiratory & Critical Care*

Medicine, 172, (9) 1161-1168
Ref ID: 1121

EXC: To be assessed for question 2

Meier, T., Eulenbruch, H.P., Wrighton-Smith, P., Enders, G., & Regnath, T. 2005. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. *European Journal of Clinical Microbiology & Infectious Diseases*, 24, (8) 529-536
Ref ID: 1138

EXC: Not focused on LTBI

Nguyen, M., Perry, S., & Parsonnet, J. 2005. QuantiFERON-TB predicts tuberculin skin test boosting in U.S. foreign-born. *International Journal of Tuberculosis & Lung Disease*, 9, (9) 985-991
Ref ID: 1147

EXC: QFT IGRA is PPD based

Hill, P.C., Brookes, R.H., Fox, A., Fielding, K., Jeffries, D.J., Jackson-Sillah, D., Lugos, M.D., Owiafe, P.K., Donkor, S.A., Hammond, A.S., Otu, J.K., Corrah, T., Adegbola, R.A., & McAdam, K.P. 2004. Large-scale evaluation of enzyme-linked immunospot assay and skin test for diagnosis of Mycobacterium tuberculosis infection against a gradient of exposure in The Gambia. *Clinical Infectious Diseases*, 38, (7) 966-973
Ref ID: 1470

EXC: Not focused on LTBI

Mandalakas, A.M. & Starke, J.R. 2004. Tuberculosis screening in immigrant children. [Review] [15 refs]. *Pediatric Infectious Disease Journal*, 23, (1) 71-72
Ref ID: 1491

EXC: Concise Review not a study

Bellete, B., Coberly, J., Barnes, G.L., Ko, C., Chaisson, R.E., Comstock, G.W., & Bishai, W.R. 2002. Evaluation of a whole-blood interferon-gamma release assay for the detection of Mycobacterium tuberculosis infection in 2 study populations.[see comment]. *Clinical Infectious Diseases*, 34, (11) 1449-1456
Ref ID: 1734

EXC: PPD based IGRA

Vekemans, J., Lienhardt, C., Sillah, J.S., Wheeler, J.G., Lahai, G.P., Doherty, M.T., Corrah, T., Andersen, P., McAdam, K.P., & Marchant, A. 2001. Tuberculosis contacts but not patients have higher gamma interferon responses to ESAT-6 than do community controls in The Gambia. *Infection & Immunity*, 69, (10) 6554-6557
Ref ID: 1828

EXC: To be assessed for question 2

Bakhshi, S. 2001. Tuberculosis screening of new entrants; how can it be made more effective?[comment]. *Journal of Public Health Medicine*, 23, (1) 82-83
Ref ID: 1880

EXC: Correspondence

Lalvani, A., Nagvenkar, P., Udwadia, Z., Pathan, A.A., Wilkinson, K.A., Shastri, J.S., Ewer, K., Hill, A.V., Mehta, A., & Rodrigues, C. 2001. Enumeration of T cells specific for RD1-encoded antigens suggests a high prevalence of latent Mycobacterium tuberculosis infection in healthy urban Indians.[see comment]. *Journal of Infectious Diseases*, 183, (3) 469-477
Ref ID: 1911

EXC: Not addressing question 1

2000. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society.[see comment]. [Review] [101 refs]. *Thorax*, 55, (11) 887-901
Ref ID: 1954

EXC: Guideline

Bothamley, G.H., Griffiths, C., Beeks, M., MacDonald, M., & Beasley, E. 2000. Detecting tuberculosis in new arrivals to UK. Failure to register with a general practice compounds the problem.[comment]. *BMJ*, 321, (7260) 570
Ref ID: 1970

EXC: BMJ Comment

Bakhshi, S. 2000. Detecting tuberculosis in new arrivals to UK. Screening is of doubtful value.[comment]. *BMJ*, 321, (7260) 569-570
Ref ID: 1971

EXC: BMJ Comment

Lamden, K., Cheesbrough, J., & Madi, S. 2000. Detecting tuberculosis in new arrivals to UK. Occupational health screening of doctors must be improved.[comment]. *BMJ*, 321, (7260) 569
Ref ID: 1972

EXC: BMJ Comment

Hargreaves, S., Holmes, A., & Friedland, J.S. 2000. Refugees, asylum seekers, and general practice: room for improvement?[see comment]. *British Journal of General Practice*, 50, (456) 531-532
Ref ID: 1975

EXC: Editorial

Van den Bosch, C.A. & Roberts, J.A. 2000. Tuberculosis screening of new entrants; how can it be made more effective?[see comment]. *Journal of Public Health Medicine*, 22, (2) 220-223
Ref ID: 1984

EXC: Not focused on LTBI- general TB screening

Pottumarthy, S., Morris, A.J., Harrison, A.C., & Wells, V.C. 1999. Evaluation of the tuberculin gamma interferon assay: potential to replace the Mantoux skin test. *Journal of Clinical Microbiology*, 37, (10) 3229-3232
Ref ID: 2069

EXC: PPD based IGRA

Weber, G.S. 1996. Unresolved issues in controlling the tuberculosis epidemic among the foreign-born in the United States. [Review] [353 refs]. *American Journal of Law & Medicine*, 22, (4) 503-536
Ref ID: 2393

EXC: Does not address diagnosis

Daftary, V.G., Banker, D.D., & Daftary, G.V. 1994. ELISA test for tuberculosis. *Indian Journal of Medical Sciences*, 48, (2) 39-42
Ref ID: 2652

EXC: Not focused on LTBI

1992. Guidelines for the investigation of individuals who were placed under surveillance for tuberculosis post-landing in Canada. Immigration and Overseas Health Services and the Bureau of Communicable Disease Epidemiology. *Canada Communicable Disease Report*, 18, (20) 153-155
Ref ID: 2769

EXC: Guideline

Davidow, A.L. 2009. Interferon-gamma release assay test characteristics depend upon the prevalence of active tuberculosis. *International Journal of Tuberculosis & Lung Disease*, 13, (11) 1411-1415
Ref ID: 3414

EXC: Study looking at methods regarding specificity

Hansted, E., Andriuskeviciene, A., Sakalauskas, R., Kevalas, R., & Sitkauskiene, B. 2009. T-cell-based diagnosis of tuberculosis infection in children in Lithuania: a country of high incidence despite a high coverage with bacille Calmette-Guerin vaccination. *BMC Pulmonary Medicine*, 9, 41
Ref ID: 3427

EXC: Foreign based paper which includes children

Pai, M., Joshi, R., Dogra, S., Mendiratta, D.K., Narang, P., Dheda, K., & Kalantri, S. 2006. Persistently elevated T cell interferon-gamma responses after treatment for latent tuberculosis infection among health care workers in India: a preliminary report. *Journal of Occupational Medicine & Toxicology*, 1, 7
Ref ID: 3447

EXC: To be assessed for question 2

Daley, P. & Chordia, P. 2008. What is the clinical utility of interferon-gamma release assays for the diagnosis of TB in high-TB-burden countries? *Therapy*, 5, (3) 367-375
Ref ID: 3908

EXC: Not focused on LTBI

Kuzniar, T.J., Kasibowska-Kuzniar, K., & Sporn, P.H.S. 2005. Tuberculin skin test in diagnosis of latent tuberculosis infection. *Advances in Clinical and Experimental Medicine*, 14, (4) 799-806
Ref ID: 4620

EXC: Not a study on IGRA

Comstock, G.W., Bellete, B., Ko, C., Coberly, J., Chaisson, R.E., & Bishai, W.R. 2003. Whole-blood interferon-gamma release assay versus the TST: Newer not better [6]. *Clinical Infectious Diseases*, 36, (9) 1209-1210
Ref ID: 5031

EXC: Editorial

Wyss, L.L. & Alderman, M.K. 2007. Using theory to interpret beliefs in migrants diagnosed with latent TB. *Online Journal of Issues in Nursing*, 12, (1) -19p available from:
http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009526633&site=ehost-live;Publisher URL:
www.cinahl.com/cgi-bin/refsvc?jid=1331&accno=2009526633
Ref ID: 6370

EXC: Paper focused on education and environmental factors rather than diagnostic tools

Excluded Studies for Clinical Question 2 (children) and reason for exclusion

1) Petrucci, R., Abu, A.N., Gurgel, R.Q., Sherchand, J.B., Doria, L., Lama, C., Ravn, P., Ruhwald, M., Yassin, M., Harper, G., & Cuevas, L.E. 2008. Interferon gamma, interferon-gamma-induced-protein 10, and tuberculin responses of children at high risk of tuberculosis infection. *Pediatric Infectious Disease Journal*, 27, (12) 1073-1077
Ref ID: 9

EXC-Focus on specific biomarker (IP-10)

2) Haustein, T., Ridout, D.A., Hartley, J.C., Thaker, U., Shingadia, D., Klein, N.J., Novelli, V., & Dixon, G.L. 2009. The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of Mycobacterium tuberculosis infection in children correlates with age and immune status.[see comment]. *Pediatric Infectious Disease Journal*, 28, (8) 669-673
Ref ID: 55

EXC-To be addressed in CQ4

3) Kampmann, B., Whittaker, E., Williams, A., Walters, S., Gordon, A., Martinez-Alier, N., Williams, B., Crook, A.M., Hutton, A.M., & Anderson, S.T. 2009. Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test.[see comment]. *European Respiratory Journal*, 33, (6) 1374-1382
Ref ID: 63

EXC-Comparison of active and latent TB

4) Bianchi, L., Galli, L., Moriondo, M., Veneruso, G., Becciolini, L., Azzari, C., Chiappini, E., & de, M.M. 2009. Interferon-gamma release assay improves the diagnosis of tuberculosis in children.[see comment]. *Pediatric Infectious Disease Journal*, 28, (6) 510-514
Ref ID: 73

EXC-No grading of exposure to TB

5) Lighter, J., Rigaud, M., Huie, M., Peng, C.H., & Pollack, H. 2009. Chemokine IP-10: an adjunct marker for latent tuberculosis infection in children. *International Journal of Tuberculosis & Lung Disease*, 13, (6) 731-736
Ref ID: 118

EXC-Focus on specific biomarker (IP-10)

6) Herrmann, J.L., Belloy, M., Porcher, R., Simonney, N., Aboutaam, R., Lebourgeois, M., Gaudelus, J., De, L.L., Chadelat, K., Scheinmann, P., Beydon, N., Fauroux, B., Bingen, M., Terki, M., Barraud, D., Cruaud, P., Offredo, C., Ferroni, A., Berche, P., Moissenet, D., Vuthien, H., Doit, C., Bingen, E., & Lagrange, P.H. 2009. Temporal dynamics of interferon gamma responses in children evaluated for tuberculosis. *PLoS ONE [Electronic Resource]*, 4, (1) e4130
Ref ID: 283

EXC-Focus on effect of treatment

7) Bakir, M., Dosanjh, D.P., Deeks, J.J., Soysal, A., Millington, K.A., Efe, S., Aslan, Y., Polat, D., Kodalli, N., Yagci, A., Barlan, I., Bahceciler, N., Demiralp, E.E., & Lalvani, A. 2009. Use of T cell-based diagnosis of tuberculosis infection to optimize interpretation of tuberculin skin testing for child tuberculosis contacts. *Clinical Infectious Diseases*, 48, (3) 302-312
Ref ID: 290

EXC-Use ELISPOT as gold standard

8) Whittaker, E., Gordon, A., & Kampmann, B. 2008. Is IP-10 a better biomarker for active and latent tuberculosis in children than IFNgamma? *PLoS ONE [Electronic Resource]*, 3, (12) e3901
Ref ID: 295

EXC-Focus on specific biomarker (IP-10)

9) Van-Lume, D.S., Souza, J.R., Melo, W.G., Melo, V.L., Cabral, M.M., Rego, J.C., Schindler, H.C., Abath, F.G., & Montenegro, S.M. 2008. Preliminary results in the immunodiagnosis of tuberculosis in children based on T cell responses to ESAT-6 and PPD antigens. *Memorias do Instituto Oswaldo Cruz*, 103, (4) 401-404
Ref ID: 317

EXC-Focus on PPD based IGRA

10) Lewinsohn, D.A., Zalwango, S., Stein, C.M., Mayanja-Kizza, H., Okwera, A., Boom, W.H., Mugerwa, R.D., & Whalen, C.C. 2008. Whole blood interferon-gamma responses to mycobacterium tuberculosis antigens in young household contacts of persons with tuberculosis in Uganda. *PLoS ONE [Electronic Resource]*, 3, (10) e3407
Ref ID: 324

EXC-Non-commercial IGRA with unknown antigens

11) Ruhwald, M., Petersen, J., Kofoed, K., Nakaoka, H., Cuevas, L.E., Lawson, L., Squire, S.B., Eugen-Olsen, J., & Ravn, P. 2008. Improving T-cell assays for the diagnosis of latent TB infection: potential of a diagnostic test based on IP-10. *PLoS ONE [Electronic Resource]*, 3, (8) e2858
Ref ID: 327

EXC-Focus on specific biomarker (IP-10)

12) Rehman, A. & Irfanullah 2008. Interferon gamma assays for tuberculosis in children. [Review] [36 refs]. *JPMA - Journal of the Pakistan Medical Association*, 58, (9) 508-511
Ref ID: 351

EXC-Review article

13) Rothel, J. & Veeser, P.I. Response to "Tuberculosis Screening on a Health Science Campus: Use of QuantiFERON-TB Gold Test for Students and Employees".[comment]. *Journal of American College Health*, 57, (1) 121-124
Ref ID: 376

EXC-Letter

14) Richeldi, L., Bergamini, B.M., & Vaienti, F. 2008. Prior tuberculin skin testing does not boost QuantiFERON-TB results in paediatric contacts.[comment]. *European Respiratory Journal*, 32, (2) 524-525
Ref ID: 384

EXC-Focus on boosting of IGRA

15) Etuwewe, O.M. & Riordan, A. 2008. IGRA for children in the UK: patchy availability, problems with funding, lack of clarity about its role.[comment]. *Archives of Disease in Childhood*, 93, (8) 714
Ref ID: 390

EXC-Letter

16) Soysal, A., Turel, O., Toprak, D., & Bakir, M. 2008. Comparison of positive tuberculin skin test with an interferon-gamma-based assay in unexposed children. *Japanese Journal of Infectious Diseases*, 61, (3) 192-195
Ref ID: 441

EXC-Used T-SPOT as a gold standard

17) Mandalakas, A.M., Hesseling, A.C., Chegou, N.N., Kirchner, H.L., Zhu, X., Marais, B.J., Black, G.F., Beyers, N., & Walzl, G. 2008. High level of discordant IGRA results in HIV-infected adults and children. *International Journal of Tuberculosis & Lung Disease*, 12, (4) 417-423
Ref ID: 486

EXC-To be addressed in CQ4

18) Shingadia, D. & Novelli, V. 2008. The tuberculin skin test: a hundred, not out?[comment]. *Archives of Disease in Childhood*, 93, (3) 189-190
Ref ID: 512

EXC-Review

19) Tuuminen, T., Sorva, S., Liippo, K., Vasankari, T., Soini, H., Eriksen-Neuman, B., Miettinen, A., & Seppala, I.J. 2007. Feasibility of commercial interferon-gamma-based methods for the diagnosis of latent Mycobacterium tuberculosis infection in Finland, a country of low incidence and high bacille Calmette-Guerin vaccination coverage. *Clinical Microbiology & Infection*, 13, (8) 836-838
Ref ID: 716

EXC-Insufficient data for analysis

20) Lalvani, A. & Millington, K.A. 2007. T cell-based diagnosis of childhood tuberculosis infection. [Review] [52 refs]. *Current Opinion in Infectious Diseases*, 20, (3) 264-271
Ref ID: 776

EXC-Review article

21) Ranganathan, S., Connell, T., & Curtis, N. Interferon-gamma release assays in children--no better than tuberculin skin testing?[comment]. *Journal of Infection*, 54, (4) 412-413
Ref ID: 800

EXC-Letter to editor

22) Dogra, S., Narang, P., Mendiratta, D.K., Chaturvedi, P., Reingold, A.L., Colford, J.M., Jr., Riley, L.W., & Pai, M. 2007. Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India.[see comment]. *Journal of Infection*, 54, (3) 267-276
Ref ID: 824

EXC-Focus on active TB

23) Richeldi, L., Ewer, K., Losi, M., Bergamini, B.M., Millington, K., Fabbri, L.M., & Lalvani, A. 2007. T-cell-based diagnosis of neonatal multidrug-resistant latent tuberculosis infection. *Pediatrics*, 119, (1) e1-e5
Ref ID: 850

EXC-Case study

24) Starke, J.R. 2006. Interferon-gamma release assays for diagnosis of tuberculosis infection in children. [Review] [15 refs]. *Pediatric Infectious Disease Journal*, 25, (10) 941-942
Ref ID: 913

EXC-Review article

25) Joos, T.J., Miller, W.C., & Murdoch, D.M. 2006. Tuberculin reactivity in bacille Calmette-Guerin vaccinated populations: a compilation of international data. [Review] [70 refs]. *International Journal of Tuberculosis & Lung Disease*, 10, (8) 883-891
Ref ID: 942

EXC-Review

26) Kampmann, B., Tena-Coki, G., & Anderson, S. 2006. Blood tests for diagnosis of tuberculosis.[comment]. *Lancet*, 368, (9532) 282-283
Ref ID: 959

EXC-Review

27) Wagstaff, A.J. & Zellweger, J.P. 1964. T-SPOT.TB: an in vitro diagnostic assay measuring T-cell reaction to Mycobacterium tuberculosis-specific antigens. *Molecular Diagnosis & Therapy*, 10, (1) 57-63
Ref ID: 1014

EXC-Focus on active TB

28) Jeffries, D.J., Hill, P.C., Fox, A., Lugos, M., Jackson-Sillah, D.J., Adegbola, R.A., & Brookes, R.H. 2006. Identifying ELISPOT and skin test cut-offs for diagnosis of Mycobacterium tuberculosis infection in The Gambia. *International Journal of Tuberculosis & Lung Disease*, 10, (2) 192-198
Ref ID: 1049

EXC-PPD based IGRA

29) Scholvinck, E., Wilkinson, K.A., Whelan, A.O., Martineau, A.R., Levin, M., & Wilkinson, R.J. 2004. Gamma interferon-based immunodiagnosis of tuberculosis: comparison between whole-blood and enzyme-linked immunospot methods. *Journal of Clinical Microbiology*, 42, (2) 829-831
Ref ID: 1485

EXC-Adult study

30) Mandalakas, A.M. & Starke, J.R. 2004. Tuberculosis screening in immigrant children. [Review] [15 refs]. *Pediatric Infectious Disease Journal*, 23, (1) 71-72
Ref ID: 1491

EXC-Review

31) Vekemans, J., Ota, M.O., Sillah, J., Fielding, K., Alderson, M.R., Skeiky, Y.A., Dalemans, W., McAdam, K.P., Lienhardt, C., & Marchant, A. 2004. Immune responses to mycobacterial antigens in the Gambian population: implications for vaccines and immunodiagnostic test design. *Infection & Immunity*, 72, (1) 381-388
Ref ID: 1498

EXC-Not focused on diagnosis of LTBI (non-commercial IGRAs used)

32) Bergeron, K.G., Bonebrake, R.G., Allen, C., & Gray, C.J. 2003. Latent tuberculosis in pregnancy: screening and treatment. [Review] [28 refs]. *Current Women's Health Reports*, 3, (4) 303-308
Ref ID: 1585

EXC-Review

33) 2000. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society.[see comment]. [Review] [101 refs]. *Thorax*, 55, (11) 887-901
Ref ID: 1954

EXC-Guidelines

34) Scholten, J.N., Fujiwara, P.I., & Frieden, T.R. 1999. Prevalence and factors associated with tuberculosis infection among new school entrants, New York City, 1991-1993.[see comment]. *International Journal of Tuberculosis & Lung Disease*, 3, (1) 31-41
Ref ID: 2127

EXC-TST alone

35) Swaminathan, S., Umadevi, P., Shantha, S., Radhakrishnan, A., & Datta, M. 1999. Sero diagnosis of tuberculosis in children using two ELISA kits. *Indian Journal of Pediatrics*, 66, (6) 837-842
Ref ID: 2145

EXC-Focus on active TB

36) Soren, K., Saiman, L., Irigoyen, M., Gomez-Duarte, C., Levison, M.J., & McMahon, D.J. 1999. Evaluation of household contacts of children with positive tuberculin skin tests. *Pediatric Infectious Disease Journal*, 18, (11) 949-955
Ref ID: 2161

EXC-No IGRA used

37) Starke, J.R. 1997. Tuberculosis. An old disease but a new threat to the mother, fetus, and neonate. [Review] [101 refs]. *Clinics in Perinatology*, 24, (1) 107-127
Ref ID: 2353

EXC-Review

38) Starke, J.R. 1995. Universal screening for tuberculosis infection. School's out![comment]. *JAMA*, 274, (8) 652-653
Ref ID: 2549

EXC-Editorial

39) Snider, D.E., Jr., Rieder, H.L., Combs, D., Bloch, A.B., Hayden, C.H., & Smith, M.H. 1988. Tuberculosis in children. [Review] [41 refs]. *Pediatric Infectious Disease Journal*, 7, (4) 271-278
Ref ID: 3065

EXC-Review article

40) Sztajnbok, F.R., Boecha, N.L., Sztajnbok, D.C., Ribeiro, S.B., Oliveira, S.K., & Sant'Anna, C.C. 2009. The challenge of pediatric tuberculosis in face of new diagnostic techniques. *Jornal de Pediatria*, 85, (3) 183-193
Ref ID: 3431

EXC-Review article

41) Sharma, N. 2009. ELISpot as a predictor for development of tb in children with tb contact. *Thorax*, 64, (4) 320
Ref ID: 3466

EXC-Letter

42) Dominguez, J., Latorre, I., Altet, N., Mateo, L., De Souza-Galvao, M., Ruiz-Manzano, J., & Ausina, V. 2009. IFN-gamma-release assays to diagnose TB infection in the immunocompromised individual. *Expert Review of Respiratory Medicine*, 3, (3) 309-327
Ref ID: 3718

EXC-Review article

43) Pai, M., Dogra, S., & Narang, P. 2007. Interferon-gamma release assays in children - No better than tuberculin skin testing: Response to Ranganathan S et al. *Journal of Infection*, 54, (4) 414-415
Ref ID: 4264

EXC-Letter to editor

44) Castro-Rodriguez, J.A., Mallol, J., Andrade, R., Munoz, M., & Azzini, I. 2007. Comparison of tuberculin skin test response after three modalities of neonatal BCG vaccination. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 101, (5) 493-496
Ref ID: 4270

EXC-No IGRA used

45) Stark, J.R. 2006. Use of new TB test in children should be limited. *Indian Journal of Pediatrics*, 73, (5) 422
Ref ID: 4358

EXC-Review

46) Saiman, L. & Colson, P. 2004. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*, 114, (4) 1175-1201
Ref ID: 4740

EXC-Guidelines

47) Tapiero, B.F. & Lamarre, V. 2003. Tuberculosis in Canada: Global view and new challenges. *Paediatrics and Child Health*, 8, (3) 139-140
Ref ID: 5018

EXC-Review article/ commentary

48) Burke, M.G. 2009. Journal club. Are new assays useful for detecting TB? *Contemporary Pediatrics*, 26, (10) 20 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2010456021&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=847&accno=2010456021
Ref ID: 6224

EXC-Review article

49) Saiman, L., San Gabriel, P., Schulte, J., Vargas, M.P., Kenyon, T., & Onorato, I. 2001. Risk factors for latent tuberculosis infection among children in New York City. *Pediatrics*, 107, (5) 999-1003 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2001091821&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=783&accno=2001091821
Ref ID: 6283

EXC-IGRA not used

50) Molicotti, P., Bua, A., Mela, G., Olmeo, P., Delogu, R., Ortu, S., Sechi, L.A., & Zanetti, S. 2008. Performance of QuantiFERON-TB testing in a tuberculosis outbreak at a primary school. *Journal of Pediatrics*, 152, (4) 585-586
Ref ID: 500

EXC-No detailed analysis & no grading of exposure to TB

51) Muller, L.L., Bennet, R., Gaines, H., Zedenius, I., & Berggren, I. 2008. Complexity in estimating recent tuberculosis transmission among predominantly immigrant school children in Stockholm, Sweden 2006. *Scandinavian Journal of Infectious Diseases*, 40, (9) 709-714
Ref ID: 307

EXC-Focus on active TB

52) Higuchi, R., Mori, M., Ozawa, R., Miyamae, T., Imagawa, T., Nishimaki, S., Mitsuda, T., Aihara, Y., & Yokota, S. 2009. Whole blood interferon-gamma assay for tuberculosis in children in Japan. *Pediatrics International*, 51, (1) 97-102
Ref ID: 105

EXC-Assesses treatment effectiveness

Excluded Studies for Clinical Question 3 (contacts) and reason for exclusion

1) 2006. Blood test vs. skin test: are hospitals ready for the TB 'gold standard'? Hospitals consider secondary use of Quantiferon. *Hospital Employee Health*, 25, (2) 13-16 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009125764&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=507&accno=2009125764
Ref ID: 6130

EXC-Review article

2) Arend, S.M., Engelhard, A.C., Groot, G., de, B.K., Andersen, P., Ottenhoff, T.H., & van Dissel, J.T. 2001. Tuberculin skin testing compared with T-cell responses to Mycobacterium tuberculosis-specific and nonspecific antigens for detection of latent infection in persons with recent tuberculosis contact. *Clinical & Diagnostic Laboratory Immunology*, 8, (6) 1089-1096
Ref ID: 1812

EXC-PPD based IGRA

3) Aziz, N., Hasan, S., Munir, M., Tayyab, M., & Chaudrhy, N.A. 2008. Risk to household contacts of tuberculous patients based on Mantoux test and antibody titre. *Journal of Ayub Medical College, Abbottabad: JAMC*, 20, (2) 47-50
Ref ID: 96

EXC-Non-commercial IGRA used (antigens not specified)

4) Carvalho, A.C., Pezzoli, M.C., El-Hamad, I., Arce, P., Bigoni, S., Scarcella, C., Indelicato, A.M., Scolari, C., Carosi, G., & Matteelli, A. 2007. QuantiFERON-TB Gold test in the identification of latent tuberculosis infection in immigrants. *Journal of Infection*, 55, (2) 164-168
Ref ID: 709

EXC-Not contact investigation

5) Chee, C.B., Lim, L.K., Barkham, T.M., Koh, D.R., Lam, S.O., Shen, L., & Wang, Y.T. 2009. Use of a T cell interferon-gamma release assay to evaluate tuberculosis risk in newly qualified physicians in Singapore healthcare institutions. *Infection Control & Hospital Epidemiology*, 30, (9) 870-875
Ref ID: 22

EXC-Not focused on Latent TB Infection (definition of LTBI not adequate)

6) Cummings, K.J., Smith, T.S., Shogren, E.S., Khakoo, R., Nanda, S., Bunner, L., Smithmyer, A., Soccorsi, D., Kashon, M.L., Mazurek, G.H., Friedman, L.N., & Weissman, D.N. 2009. Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. *Infection Control & Hospital Epidemiology*, 30, (11) 1123-1126
Ref ID: 3420

EXC-Majority of new Health Care Workers had no risk factors for TB

7) Demissie, A., Ravn, P., Olobo, J., Doherty, T.M., Eguale, T., Geletu, M., Hailu, W., Andersen, P., & Britton, S. 1999. T-cell recognition of Mycobacterium tuberculosis culture filtrate fractions in tuberculosis patients and their household contacts. *Infection & Immunity*, 67, (11) 5967-5971
Ref ID: 2170

EXC-Not focused on diagnosis of LTBI

8) Detjen, A.K., Loebenberg, L., Grewal, H.M., Stanley, K., Gutschmidt, A., Kruger, C., Du, P.N., Kidd, M., Beyers, N., Walzl, G., & Hesseling, A.C. 2009. Short-term reproducibility of a commercial interferon gamma release assay. *Clinical & Vaccine Immunology: CVI*, 16, (8) 1170-1175
Ref ID: 48

EXC-Focuses on reproducibility of IGRA

9) Dosanjh, D.P., Hinks, T.S., Innes, J.A., Deeks, J.J., Pasvol, G., Hackforth, S., Varia, H., Millington, K.A., Gunatheesan, R., Guyot-Revol, V., & Lalvani, A. 2008. Improved diagnostic evaluation of suspected tuberculosis.[see comment][erratum appears in Ann Intern Med.2008 Apr 15;148(8):635]. *Annals of Internal Medicine*, 148, (5) 325-336
Ref ID: 515

EXC-Not focused on LTBI

10) Ewer, K., Deeks, J., Alvarez, L., Bryant, G., Waller, S., Andersen, P., Monk, P., & Lalvani, A. 2003. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak.[see comment]. *Lancet*, 361, (9364) 1168-1173
Ref ID: 1619

EXC-To be addressed in question focusing on children

11) Franchi, A., Diana, O., & Franco, G. 2009. Job-related risk of latent tuberculosis infection in a homogeneous population of hospital workers in a low incidence area. *American Journal of Industrial Medicine*, 52, (4) 297-303
Ref ID: 170

EXC-Used TST only

12) Franken, W.P., Timmermans, J.F., Prins, C., Slootman, E.J., Dreverman, J., Bruins, H., van Dissel, J.T., & Arend, S.M. 2007. Comparison of Mantoux and QuantiFERON TB Gold tests for diagnosis of latent tuberculosis infection in Army personnel. *Clinical & Vaccine Immunology: CVI*, 14, (4) 477-480
Ref ID: 792

EXC-Not contact tracing (no gradient of exposure to TB)

13) Haley, C.A., Cain, K.P., Yu, C., Garman, K.F., Wells, C.D., & Laserson, K.F. 2008. Risk-based screening for latent tuberculosis infection. *Southern Medical Journal*, 101, (2) 142-149
Ref ID: 491

EXC-TST only (no IGRA)

14) Hargreaves, S., Holmes, A., & Friedland, J.S. 2000. Refugees, asylum seekers, and general practice: room for improvement?[see comment]. *British Journal of General Practice*, 50, (456) 531-532
Ref ID: 1975

EXC-Editorial

15) Higuchi, K., Harada, N., Mori, T., & Sekiya, Y. 2007. Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. *Respirology*, 12, (1) 88-92
Ref ID: 849

EXC-To be addressed in question focussing on children

16) Higuchi, K., Kondo, S., Wada, M., Hayashi, S., Ootsuka, G., Sakamoto, N., & Harada, N. 2009. Contact investigation in a primary school using a whole blood interferon-gamma assay. *Journal of Infection*, 58, (5) 352-357
Ref ID: 164

EXC-To be addressed in question focussing on children

17) Hotta, K., Ogura, T., Nishii, K., Kodani, T., Onishi, M., Shimizu, Y., Kanehiro, A., Kiura, K., Tanimoto, M., & Tobe, K. 2007. Whole blood interferon-gamma assay for baseline tuberculosis screening among Japanese healthcare students. *PLoS ONE*, 2, (8)
Ref ID: 3967

EXC-Screening not contact (only one had contact with TB patient)

18) Jeffries, D.J., Hill, P.C., Fox, A., Lugos, M., Jackson-Sillah, D.J., Adegbola, R.A., & Brookes, R.H. 2006. Identifying ELISPOT and skin test cut-offs for diagnosis of Mycobacterium tuberculosis infection in The Gambia. *International Journal of Tuberculosis & Lung Disease*, 10, (2) 192-198
Ref ID: 1049

EXC-PPD based IGRA

19) Joshi, R., Patil, S., Kalantri, S., Schwartzman, K., Menzies, D., & Pai, M. 2007. Prevalence of abnormal radiological findings in health care workers with latent tuberculosis infection and correlations with T cell immune response. *PLoS ONE [Electronic Resource]*, 2, (8) e805
Ref ID: 3436

EXC-Not focused on diagnosis of Latent TB Infection (focus on inactive and active TB)

20) Lalvani, A., Pathan, A.A., Durkan, H., Wilkinson, K.A., Whelan, A., Deeks, J.J., Reece, W.H., Latif, M., Pasvol, G., & Hill, A.V. 2001. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Lancet*, 357, (9273) 2017-2021
Ref ID: 1850

EXC-PPD based IGRA

21) Miranda, C., Yen-Lieberman, B., Terpeluk, P., Tomford, J.W., & Gordon, S. 2009. Reducing the rates of indeterminate results of the QuantiFERON-TB Gold In-Tube test during routine preemployment screening for latent tuberculosis infection among healthcare personnel. *Infection Control & Hospital Epidemiology*, 30, (3) 296-298
Ref ID: 146

EXC-No gradient of exposure to TB

22) Molicotti, P., Bua, A., Mela, G., Olmeo, P., Delogu, R., Ortu, S., Sechi, L.A., & Zanetti, S. 2008. Performance of QuantiFERON-TB testing in a tuberculosis outbreak at a primary school. *Journal of Pediatrics*, 152, (4) 585-586
Ref ID: 500

EXC-To be addressed in question focussing on children

23) Muller, L.L., Bennet, R., Gaines, H., Zedenius, I., & Berggren, I. 2008. Complexity in estimating recent tuberculosis transmission among predominantly immigrant school children in Stockholm, Sweden 2006. *Scandinavian Journal of Infectious Diseases*, 40, (9) 709-714
Ref ID: 307

EXC-To be addressed in question focussing on children

24) Nguyen, M., Perry, S., & Parsonnet, J. 2005. QuantiFERON-TB predicts tuberculin skin test boosting in U.S. foreign-born. *International Journal of Tuberculosis & Lung Disease*, 9, (9) 985-991
Ref ID: 1147

EXC-PPD based Quantiferon

25) Nienhaus, A., Schablon, A., Bacle, C.L., Siano, B., & Diel, R. 2008. Evaluation of the interferon-gamma release assay in healthcare workers. *International Archives of Occupational & Environmental Health*, 81, (3) 295-300
Ref ID: 567

EXC-No grading of exposure to TB

26) Ozdemir, D., Annakkaya, A.N., Tarhan, G., Sencan, I., Cesur, S., Balbay, O., & Guclu, E. 2007. Comparison of the tuberculin skin test and the quantiferon test for latent Mycobacterium tuberculosis infections in health care workers in Turkey. *Japanese Journal of Infectious Diseases*, 60, (2-3) 102-105
Ref ID: 760

EXC-PPD based IGRA

27) Pai, M., Joshi, R., Dogra, S., Mendiratta, D.K., Narang, P., Dheda, K., & Kalantri, S. 2006. Persistently elevated T cell interferon-gamma responses after treatment for latent tuberculosis infection among health care workers in India: a preliminary report. *Journal of Occupational Medicine & Toxicology*, 1, 7
Ref ID: 3447

EXC-Focus on test after treatment

28) Sahni, R., Miranda, C., Yen-Lieberman, B., Tomford, J.W., Terpeluk, P., Quartey, P., Johnson, L.T., & Gordon, S.M. 2009. Does the implementation of an interferon-gamma release assay in lieu of a tuberculin skin test increase acceptance of preventive therapy for latent tuberculosis among healthcare workers? *Infection Control & Hospital Epidemiology*, 30, (2) 197-199
Ref ID: 257

EXC-Focuses on treatment

29) Schablon, A., Beckmann, G., Harling, M., Diel, R., & Nienhaus, A. 2009. Prevalence of latent tuberculosis infection among health care workers in a hospital for pulmonary diseases. *Journal of Occupational Medicine & Toxicology*, 4, 1
Ref ID: 3444

EXC-TST taken from medical history (time between tests too long).

30) Scholten, J.N., Fujiwara, P.I., & Frieden, T.R. 1999. Prevalence and factors associated with tuberculosis infection among new school entrants, New York City, 1991-1993.[see comment]. *International Journal of Tuberculosis & Lung Disease*, 3, (1) 31-41
Ref ID: 2127

EXC-Only TST used (no IGRA)

31) Shalabi, N.M. & Houssen, M.E. 2009. Discrepancy between the tuberculin skin test and the levels of serum interferon-gamma in the diagnosis of tubercular infection in contacts. *Clinical Biochemistry*, 42, (16-17) 1596-1601
Ref ID: 3725

EXC-Non-commercial IGRA (antigens not specified)

32) Soborg, B., Andersen, A.B., Larsen, H.K., Weldingh, K., Andersen, P., Kofoed, K., & Ravn, P. 2007. Detecting a low prevalence of latent tuberculosis among health care workers in Denmark detected by M. tuberculosis specific IFN-gamma whole-blood test. *Scandinavian Journal of Infectious Diseases*, 39, (6-7) 554-559
Ref ID: 734

EXC-No grading of exposure to TB

33) Stebler, A., Iseli, P., M++hlemann, K., & Bodmer, T. 2008. Letters to the editor. Whole-blood interferon-gamma release assay for baseline tuberculosis screening of healthcare workers at a Swiss university hospital. *Infection Control & Hospital Epidemiology*, 29, (7) 681-683 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009977130&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=195&accno=2009977130
Ref ID: 6228

EXC-No TST used as a comparator

34) Thijsen, S.F., van Rossum, S.V., Arend, S., Koster, B., Machiels, A.M., & Bossink, A.W. 2008. The value of interferon gamma release assays for diagnosis infection with Mycobacterium tuberculosis during an annual screening of health care workers. *Journal of Occupational & Environmental Medicine*, 50, (11) 1207-1208
Ref ID: 202

EXC-No gradient of exposure

35) Vekemans, J., Lienhardt, C., Sillah, J.S., Wheeler, J.G., Lahai, G.P., Doherty, M.T., Corrah, T., Andersen, P., McAdam, K.P., & Marchant, A. 2001. Tuberculosis contacts but not patients have higher gamma interferon responses to ESAT-6 than do community controls in The Gambia. *Infection & Immunity*, 69, (10) 6554-6557
Ref ID: 1828

EXC-PPD based IGRA

36) Yoshiyama, T., Harada, N., Higuchi, K., Nakajima, Y., & Ogata, H. 2009. Estimation of incidence of tuberculosis infection in health-care workers using repeated interferon-gamma assays. *Epidemiology & Infection*, 137, (12) 1691-1698
Ref ID: 2

EXC-Focuses on reproducibility of IGRA

37) Zhao, X., Mazlagic, D., Flynn, E.A., Hernandez, H., & Abbott, C.L. 2009. Is the QuantiFERON-TB blood assay a good replacement for the tuberculin skin test in tuberculosis screening? a pilot study at Berkshire Medical Center. *American Journal of Clinical Pathology*, 132, (5) 678-686
Ref ID: 3

EXC-TST taken from medical history (time between tests too long).

38) Lee, K., Han, M.K., Choi, H.R., Choi, C.M., Oh, Y.M., Lee, S.D., Kim, W.S., Kim, D.S., Woo, J.H., & Shim, T.S. 2009. Annual incidence of latent tuberculosis infection among newly employed nurses at a tertiary care university hospital.

Infection Control & Hospital Epidemiology, 30, (12) 1218-1222
Ref ID: 3406

EXC-No grading of exposure to TB

39) Demkow, U., Broniarek-Samson, B., Filewska, M., Lewandowska, K., Maciejewski, J., Zycinska, K., Zwolska, Z., & Kus, J. 2008. Prevalence of latent tuberculosis infection in health care workers in Poland assessed by interferon-gamma whole blood and tuberculin skin tests. *Journal of Physiology & Pharmacology*, 59, (Suppl 6) 209-217
Ref ID: 210

EXC-No grading of exposure to TB (details of correlations not given)

40) Choi, J.C., Shin, J.W., Kim, J.Y., Park, I.W., Choi, B.W., & Lee, M-K. (2008). The effect of previous tuberculin skin test on follow-up examination of the whole-blood interferon-γ assay in the screening for latent tuberculosis infection. *Chest*, 133, 1415-1420.

EXC-No grading of exposure to TB

41) Dominguez, J., Ruiz-Manzano, J., De Souza-Galvao, M., Latorre, I., Mila, C., Blanco, S., Jimenez, M.A., Prat, C., Lacoma, A., Altet, N., & Ausina, V. 2008. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clinical & Vaccine Immunology: CVI*, 15, (1) 168-171
Ref ID: 560

EXC-No grading of exposure to TB

42) Hill, P.C., Jeffries, D.J., Brookes, R.H., Fox, A., Jackson-Sillah, D., Lugos, M.D., Donkor, S.A., de Jong, B.C., Corrah, T., Adegbola, R.A., & McAdam, K.P. 2007. Using ELISPOT to expose false positive skin test conversion in Tuberculosis contacts. PLOS one, e183 (1). Ref ID: 3773

EXC-Non-commercial IGRA

43) Hill, P.C., Jackson-Sillah, D.J., Fox, A., Brookes, R.H., de Jong, B.C., Lugos, M.D., Adetifa, I.M., Donkor, S.A., Aikem, A.M., Howie, S.R., Corrah, T., McAdam, K.P., & Adegbola, R.A. 2008. Incidence of Tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. PLOS one, e1379 (1). Ref ID: 562

EXC-Non-commercial IGRA

Excluded Studies for Clinical Question 4 (immunocompromised) and reason for exclusion

Bellofiore, B., Matarese, A., Balato, N., Gaudiello, F., Scarpa, R., Atteno, M., Bocchino, M., & Sanduzzi, A. 2009. Prevention of tuberculosis in patients taking tumor necrosis factor-alpha blockers. *Journal of Rheumatology - Supplement*, 83, 76-77
Ref ID: 17

EXC-Focus on prevention

Lai, C.C., Tan, C.K., Liao, C.H., Chou, C.H., Huang, Y.T., & Hsueh, P.R. Diagnosis of pulmonary tuberculosis among dialysis patients by enzyme-linked immunospot assay for interferon-gamma.[comment]. *Nephrology Dialysis Transplantation*, 24, (8) 2605-2606
Ref ID: 18

EXC-Correspondence

Burgos, J.L., Kahn, J.G., Strathdee, S.A., Valencia-Mendoza, A., Bautista-Arredondo, S., Laniado-Laborin, R., Castaneda, R., Deiss, R., & Garfein, R.S. 2009. Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *International Journal of Tuberculosis & Lung Disease*, 13, (8) 962-968
Ref ID: 39

EXC-to be considered for cost-effectiveness

Mori, T. 2009. Usefulness of interferon-gamma release assays for diagnosing TB infection and problems with these assays. [Review] [106 refs]. *Journal of Infection & Chemotherapy*, 15, (3) 143-155
Ref ID: 65

EXC-Review

Kobashi, Y., Shimizu, H., Ohue, Y., Mouri, K., Obase, Y., Miyashita, N., & Oka, M. 2009. False negative results of QuantiFERON TB-2G test in patients with active tuberculosis. *Japanese Journal of Infectious Diseases*, 62, (4) 300-302
Ref ID: 71

EXC-Active TB

Triverio, P.A., Bridevaux, P.O., Roux-Lombard, P., Niksic, L., Rochat, T., Martin, P.Y., Saudan, P., & Janssens, J.P. 2009. Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. *Nephrology Dialysis Transplantation*, 24, (6) 1952-1956
Ref ID: 80

EXC-LTBI included patients with CXR scar

Inoue, T., Nakamura, T., Katsuma, A., Masumoto, S., Minami, E., Katagiri, D., Hoshino, T., Shibata, M., Tada, M., & Hinoshita, F. 2009. The value of QuantiFERON TB-Gold in the diagnosis of tuberculosis among dialysis patients.[see comment]. *Nephrology Dialysis Transplantation*, 24, (7) 2252-2257
Ref ID: 83

EXC-Diagnosing active TB

Ellertsen, L.K., Storla, D.G., Diep, L.M., Brokstad, K.A., Wiker, H.G., & Hetland, G. 2009. Allergic sensitisation in tuberculosis patients at the time of diagnosis and following chemotherapy. *BMC Infectious Diseases*, 9, 100
Ref ID: 94

EXC-Focus on allergic sensitisation

Acevedo-Vasquez, E., Ponce de, L.D., & Gamboa-Cardenas, R. 2009. Latent infection and tuberculosis disease in rheumatoid arthritis patients. [Review] [77 refs]. *Rheumatic Diseases Clinics of North America*, 35, (1) 163-181
Ref ID: 103

EXC-Overview of TB screening in RA patients on biologic therapy

Kobashi, Y., Sugiu, T., Mouri, K., Obase, Y., Miyashita, N., & Oka, M. 2009. Indeterminate results of QuantiFERON TB-2G test performed in routine clinical practice. *European Respiratory Journal*, 33, (4) 812-815
Ref ID: 121

EXC-Both active and latent TB

Syed Ahamed, K.B., Sikhamani, R., Swaminathan, S., Perumal, V., Paramasivam, P., & Raja, A. 2009. Role of interferon gamma release assay in active TB diagnosis among HIV infected individuals. *PLoS ONE [Electronic Resource]*, 4, (5) e5718
Ref ID: 123

EXC-Active TB

Villiger, P.M., Zellweger, J.P., & Moller, B. 2009. Novel screening tools for latent tuberculosis: time to leave an old friend?. [Review] [50 refs]. *Current Opinion in Rheumatology*, 21, (3) 238-243
Ref ID: 133

EXC-Overview of tests

Garfein, R.S., Lozada, R., Liu, L., Laniado-Laborin, R., Rodwell, T.C., Deiss, R., Alvelais, J., Catanzaro, A., Chiles, P.G., & Strathdee, S.A. 2009. High prevalence of latent tuberculosis infection among injection drug users in Tijuana, Mexico. *International Journal of Tuberculosis & Lung Disease*, 13, (5) 626-632
Ref ID: 140

EXC-No comparison with TST

Stavri, H., Ene, L., Popa, G.L., Duiculescu, D., Murgoci, G., Marica, C., Ulea, I., Cus, G., & Popa, M.I. 2009. Comparison of tuberculin skin test with a whole-blood interferon gamma assay and ELISA, in HIV positive children and adolescents with TB. *Romanian Archives of Microbiology & Immunology*, 68, (1) 14-19
Ref ID: 143

Not accessible

Lalvani, A. & Millington, K.A. 2008. Screening for tuberculosis infection prior to initiation of anti-TNF therapy. [Review] [39 refs]. *Autoimmunity Reviews*, 8, (2) 147-152
Ref ID: 144

EXC-Review

Dheda, K., Smit, R.Z., Badri, M., & Pai, M. 2009. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. [Review] [149 refs]. *Current Opinion in Pulmonary Medicine*, 15, (3) 188-200
Ref ID: 153

EXC-Review using active TB and low incidence as gold standard

Lauzardo, M. 2009. Will new TB tests be effective in HIV-infected individuals? *HIV Clinician*, 21, (2) 13-14
Ref ID: 156

EXC-Discussion

Bocchino, M., Bellofiore, B., Matarese, A., Galati, D., & Sanduzzi, A. 2009. IFN-gamma release assays in tuberculosis management in selected high-risk populations. [Review] [203 refs]. *Expert Review of Molecular Diagnostics*, 9, (2) 165-177
Ref ID: 166

EXC-Review article

Giardina, A.R., Accardo-Palumbo, A., Ciccia, F., Ferrante, A., Principato, A., Impastato, R., & Triolo, G. 2009. Blocking TNF in vitro with infliximab determines the inhibition of expansion and interferon gamma production of Vgamma9/Vdelta2 T lymphocytes from patients with active rheumatoid arthritis. A role in the susceptibility to tuberculosis? *Reumatismo,* 61, (1) 21-26
Ref ID: 175

EXC-PPD based study

Behar, S.M., Shin, D.S., Maier, A., Coblyn, J., Helfgott, S., & Weinblatt, M.E. 2009. Use of the T-SPOT.TB assay to detect latent tuberculosis infection among rheumatic disease patients on immunosuppressive therapy. *Journal of Rheumatology*, 36, (3) 546-551
Ref ID: 178

EXC-Indeterminate TST from history

Soysal, A., Bahceciler, N., Barlan, I., & Bakir, M. 2008. Lack of an inverse association between tuberculosis infection and atopy: by T-cell-based immune assay (RD1-ELISpot). *Pediatric Allergy & Immunology*, 19, (8) 709-715
Ref ID: 184

EXC-Non-commercial IGRA

Kobashi, Y., Sugiu, T., Shimizu, H., Ohue, Y., Mouri, K., Obase, Y., Miyashita, N., & Oka, M. 2009. Clinical evaluation of the T-SPOT.TB test for patients with indeterminate results on the QuantiFERON TB-2G test. *Internal Medicine*, 48, (3) 137-142
Ref ID: 187

EXC-Comparing QFT with T-SPOT

Lindemann, M., Dioury, Y., Beckebaum, S., Cicinnati, V.R., Gerken, G., Broelsch, C.E., Wrighton-Smith, P., & Grosse-Wilde, H. 2009. Diagnosis of tuberculosis infection in patients awaiting liver transplantation. *Human Immunology*, 70, (1) 24-28
Ref ID: 188

EXC-Comparing lymphocyte transformation test with TST

Wang, X., Barnes, P.F., Dobos-Elder, K.M., Townsend, J.C., Chung, Y.T., Shams, H., Weis, S.E., & Samten, B. 2009. ESAT-6 inhibits production of IFN-gamma by Mycobacterium tuberculosis-responsive human T cells. *Journal of Immunology*, 182, (6) 3668-3677
Ref ID: 190

EXC-Comparing antigens

Lalvani, A. & Millington, K.A. 2008. T-cell interferon-gamma release assays: can we do better?[comment]. *European Respiratory Journal*, 32, (6) 1428-1430
Ref ID: 191

EXC-Editorial

Pasquinelli, V., Townsend, J.C., Jurado, J.O., Alvarez, I.B., Quiroga, M.F., Barnes, P.F., Samten, B., & Garcia, V.E. 2009. IFN-gamma production during active tuberculosis is regulated by mechanisms that involve IL-17, SLAM, and CREB. *Journal of Infectious Diseases*, 199, (5) 661-665
Ref ID: 212

EXC-Focus on transcription propeptides of IGRA

Aichelburg, M.C., Rieger, A., Breitenecker, F., Pfistershammer, K., Tittes, J., Eltz, S., Aichelburg, A.C., Stingl, G., Makristathis, A., & Kohrgruber, N. 2009. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clinical Infectious Diseases*, 48, (7) 954-962
Ref ID: 217

EXC-Not comparing IGRA with TST

Hursitoglu, M., Cikrikcioglu, M.A., Tukek, T., Beycan, I., Ahmedova, N., Karacuha, S., Sansal, M., Ozkan, O., & Celik, V. 2009. Acute effect of low-flux hemodialysis process on the results of the interferon-gamma-based QuantiFERON-TB Gold In-Tube test in end-stage renal disease patients. *Transplant Infectious Disease*, 11, (1) 28-32
Ref ID: 263

EXC-No comparison with TST

Kim, S.H., Song, K.H., Choi, S.J., Kim, H.B., Kim, N.J., Oh, M.D., & Choe, K.W. 2009. Diagnostic usefulness of a T-cell-based assay for extrapulmonary tuberculosis in immunocompromised patients. *American Journal of Medicine*, 122, (2) 189-195
Ref ID: 267

EXC-Active TB used as gold standard

Oon, H.H., Chong, W.S., & Liew, C.F. 2008. Indeterminate results on the interferon-gamma release assay for tuberculosis screening should not be ignored.[comment]. *British Journal of Dermatology*, 159, (4) 992-993
Ref ID: 312

EXC-Correspondence

Rehman, A. & Irfanullah 2008. Interferon gamma assays for tuberculosis in children. [Review] [36 refs]. *JPMA - Journal of the Pakistan Medical Association*, 58, (9) 508-511
Ref ID: 351

EXC-Overview of use in children

Winthrop, K.L., Nyendak, M., Calvet, H., Oh, P., Lo, M., Swarbrick, G., Johnson, C., Lewinsohn, D.A., Lewinsohn, D.M., & Mazurek, G.H. 2008. Interferon-gamma release assays for diagnosing mycobacterium tuberculosis infection in renal dialysis patients. *Clinical Journal of The American Society of Nephrology: CJASN*, 3, (5) 1357-1363
Ref ID: 364

EXC-Active TB

Doherty, S.D., Van, V.A., Lebwohl, M.G., Korman, N.J., Young, M.S., Hsu, S., & National Psoriasis Foundation 2008. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. [52 refs]. *Journal of the American Academy of Dermatology*, 59, (2) 209-217
Ref ID: 392

EXC-Screening algorithm

Manuel, O. & Kumar, D. 2008. QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. [Review] [49 refs]. *Expert Review of Molecular Diagnostics*, 8, (3) 247-256
Ref ID: 400

EXC-Reviews of Quantiferon

Lalvani, A., Meroni, P.L., Millington, K.A., Modolo, M.L., Plebani, M., Tincani, A., Villalta, D., Doria, A., & Ghirardello, A. 2008. Recent advances in diagnostic technology: applications in autoimmune and infectious diseases. [Review] [46 refs]. *Clinical & Experimental Rheumatology*, 26, (1:Suppl 48) S62-S66
Ref ID: 414

EXC-Overview

Vilaplana, C., Ruiz-Manzano, J., Gil, O., Cuchillo, F., Montane, E., Singh, M., Spallek, R., Ausina, V., & Cardona, P.J. 2008. The tuberculin skin test increases the responses measured by T cell interferon-gamma release assays. *Scandinavian Journal of Immunology*, 67, (6) 610-617
Ref ID: 447

EXC-Examining whether TST might affect the monitoring of the immune response of vaccine

Greenberg, J.D., Reddy, S.M., Schloss, S.G., Kurucz, O.S., Bartlett, S.J., Abramson, S.B., & Bingham, C.O., III 2008. Comparison of an in vitro tuberculosis interferon-gamma assay with delayed-type hypersensitivity testing for detection of latent Mycobacterium tuberculosis: a pilot study in rheumatoid arthritis.[erratum appears in J Rheumatol. 2008 May;35(5):943]. *Journal of Rheumatology*, 35, (5) 770-775
Ref ID: 451

EXC-PPD based IGRA (1st generation QFT)

Lalvani, A. & Millington, K.A. 2008. T Cells and Tuberculosis: Beyond Interferon-gamma.[comment]. *Journal of Infectious Diseases*, 197, (7) 941-943
Ref ID: 471

EXC-Commentary

Desai, N., Raste, Y., Cooke, N.T., & Harland, C.C. 2008. QuantiFERON-TB Gold testing for tuberculosis in psoriasis patients commencing anti-tumour necrosis factor alpha therapy.[see comment]. *British Journal of Dermatology*, 158, (5) 1137-1138
Ref ID: 475

EXC-Correspondence

Hornum, M., Mortensen, K.L., Kamper, A.L., & Andersen, A.B. 2008. Limitations of the QuantiFERON-TB Gold test in detecting Mycobacterium tuberculosis infection in immunocompromised patients. *European Journal of Internal Medicine*, 19, (2)

137-139
Ref ID: 537

EXC-Case series

Gupta, A., Street, A.C., & Macrae, F.A. 2008. Tumour necrosis factor alpha inhibitors: screening for tuberculosis infection in inflammatory bowel disease. *Medical Journal of Australia*, 188, (3) 168-170
Ref ID: 539

EXC-Update

Leung, C.C., Yam, W.C., Yew, W.W., Ho, P.L., Tam, C.M., Law, W.S., Wong, M.Y., Leung, M., & Tsui, D. 2008. Comparison of T-Spot.TB and tuberculin skin test among silicotic patients. *European Respiratory Journal*, 31, (2) 266-272
Ref ID: 545

EXC-Screening

Zellweger, J.P. 2008. Latent tuberculosis: which test in which situation?. [Review] [74 refs]. *Swiss Medical Weekly*, 138, (3-4) 31-37
Ref ID: 551

EXC-Discussion paper

Dinser, R., Fousse, M., Sester, U., Albrecht, K., Singh, M., Kohler, H., Muller-Ladner, U., & Sester, M. 2008. Evaluation of latent tuberculosis infection in patients with inflammatory arthropathies before treatment with TNF-alpha blocking drugs using a novel flow-cytometric interferon-gamma release assay.[see comment]. *Rheumatology*, 47, (2) 212-218
Ref ID: 552

EXC-Using non-commercial novel flow cytometric IGRA

Karam, F., Mbow, F., Fletcher, H., Senghor, C.S., Coulibaly, K.D., LeFevre, A.M., Ngom Gueye, N.F., Dieye, T., Sow, P.S., Mboup, S., & Lienhardt, C. 2008. Sensitivity of IFN-gamma release assay to detect latent tuberculosis infection is retained in HIV-infected patients but dependent on HIV/AIDS progression. *PLoS ONE [Electronic Resource]*, 3, (1) e1441
Ref ID: 554

EXC-Non-commercial IGRA

Inui, N., Suda, T., & Chida, K. 2008. Use of the QuantiFERON-TB Gold test in Japanese patients with sarcoidosis. *Respiratory Medicine*, 102, (2) 313-315
Ref ID: 564

EXC-No comparison with TST

National Tuberculosis, A.C. 2007. Position statement on interferon-gamma release immunoassays in the detection of latent tuberculosis infection, October 2007. *Communicable Diseases Intelligence*, 31, (4) 404-405
Ref ID: 572

EXC-Position statement

Kaushik, V.V., Ambalavanan, S., & Binymin, K. Comment on: Use of the QuantiFERON TB Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-alpha agents: the Newcastle (UK) experience.[comment]. *Rheumatology*, 46, (12) 1863-1864
Ref ID: 597

EXC-Comment

Angus, J., Roberts, C., Kulkarni, K., Leach, I., & Murphy, R. 2007. Usefulness of the QuantiFERON test in the confirmation of latent tuberculosis in association with erythema induratum. *British Journal of Dermatology*, 157, (6) 1293-1294
Ref ID: 600

EXC-Correspondence

Sellam, J., Hamdi, H., Roy, C., Baron, G., Lemann, M., Puechal, X., Breban, M., Berenbaum, F., Humbert, M., Weldingh, K., Salmon, D., Ravaud, P., Emilie, D., Mariette, X., & RATIO (Research Axed on Tolerance of Biotherapies) Study Group 2007.

Comparison of in vitro-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy. *Annals of the Rheumatic Diseases*, 66, (12) 1610-1615
Ref ID: 607

EXC-Non-commercial assay

Grimes, C.Z., Hwang, L.Y., Williams, M.L., Austin, C.M., & Graviss, E.A. 2007. Tuberculosis infection in drug users: interferon-gamma release assay performance. *International Journal of Tuberculosis & Lung Disease*, 11, (11) 1183-1189
Ref ID: 622

EXC-Assessing risk factors associated with tests

Madariaga, M.G., Jalali, Z., & Swindells, S. 2007. Clinical utility of interferon gamma assay in the diagnosis of tuberculosis. [Review] [44 refs]. *Journal of the American Board of Family Medicine: JABFM*, 20, (6) 540-547
Ref ID: 631

EXC-Overview of utility of tests

Drobniewski, F., Cobelens, F., Zellweger, J.P., & EuroTB, W. 2007. Use of Gamma-interferon assays in low- and medium-prevalence countries in Europe: a consensus statement of a Wolfheze Workshop organised by KNCV/EuroTB, Vilnius Sept 2006. [7 refs]. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 12, (7) E070726
Ref ID: 661

EXC-Policy statement

Takahashi, H., Shigehara, K., Yamamoto, M., Suzuki, C., Naishiro, Y., Tamura, Y., Hirohashi, Y., Satoh, N., Shijubo, N., Shinomura, Y., & Imai, K. 2007. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. *Rheumatology International*, 27, (12) 1143-1148
Ref ID: 668

EXC-No detailed info

Passalent, L., Khan, K., Richardson, R., Wang, J., Dedier, H., & Gardam, M. 2007. Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.TB test, tuberculin skin test, and an expert physician panel. *Clinical Journal of The American Society of Nephrology: CJASN*, 2, (1) 68-73
Ref ID: 685

EXC-Comparison with expert panel

Silverman, M.S., Reynolds, D., Kavsak, P.A., Garay, J., Daly, A., & Davis, I. 2007. Use of an interferon-gamma based assay to assess bladder cancer patients treated with intravesical BCG and exposed to tuberculosis. *Clinical Biochemistry*, 40, (12) 913-915
Ref ID: 704

EXC-Comparing BCG patients with non-BCG

Martinez, L.C., Harrison-Balestra, C., Caeiro, J.P., & Nousari, C.H. 2007. The role of the QuantiFERON-TB Gold test as screening prior to administration of tumor necrosis factor inhibitors. *Archives of Dermatology*, 143, (6) 809-810
Ref ID: 735

EXC-Summary of cases

Pratt, A., Nicholl, K., & Kay, L. 2007. Use of the QuantiFERON TB Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-alpha agents: the Newcastle (UK) experience.[see comment]. *Rheumatology*, 46, (6) 1035-1036
Ref ID: 749

EXC-Letter

Pai, M., Dheda, K., Cunningham, J., Scano, F., & O'Brien, R. 2007. T-cell assays for the diagnosis of latent tuberculosis infection: moving the research agenda forward. [100 refs]. *The Lancet Infectious Diseases*, 7, (6) 428-438
Ref ID: 752

EXC-Overview of research agenda

Wallis, R.S. 2007. Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma. [Review] [51 refs]. *Journal of Investigative Dermatology*, Symposium, (1) 16-21
Ref ID: 767

EXC-Focus on antigen IP10 and the comparison of reactivation of LTBI with either infliximab or etanercept

Lalvani, A. & Millington, K.A. 2007. T cell-based diagnosis of childhood tuberculosis infection. [Review] [52 refs]. *Current Opinion in Infectious Diseases*, 20, (3) 264-271
Ref ID: 776

EXC-Indeterminate between ELISPOT and T-SPOT

Hoffmann, M., Reichmuth, M., Fantelli, K., Schoch, O.D., Fierz, W., Furrer, H., & Vernazza, P. 2007. Conventional tuberculin skin testing versus T-cell-based assays in the diagnosis of latent tuberculosis infection in HIV-positive patients.[comment]. *AIDS*, 21, (3) 390-392
Ref ID: 836

EXC-Comment

Efthimiou, P. & Sood, S. 2007. QuantiFERON TB Gold Test: the new standard for screening of latent tuberculosis in patients with rheumatoid arthritis?[comment]. *Annals of the Rheumatic Diseases*, 66, (2) 276
Ref ID: 839

EXC-Summary of cases

Lashley, M. 2007. A targeted testing program for tuberculosis control and prevention among Baltimore city's homeless population. *Public Health Nursing*, 24, (1) 34-39
Ref ID: 848

EXC-Identification of LTBI and care of TB infected cases

Kunst, H. 2006. Diagnosis of latent tuberculosis infection: the potential role of new technologies. [Review] [78 refs]. *Respiratory Medicine*, 100, (12) 2098-2106
Ref ID: 888

EXC-Discussion paper

Tsiouris, S.J., Coetzee, D., Toro, P.L., Austin, J., Stein, Z., & El-Sadr, W. 2006. Sensitivity analysis and potential uses of a novel gamma interferon release assay for diagnosis of tuberculosis. *Journal of Clinical Microbiology*, 44, (8) 2844-2850
Ref ID: 947

EXC-Combine active and latent TB

Brock, I., Ruhwald, M., Lundgren, B., Westh, H., Mathiesen, L.R., & Ravn, P. 2006. Latent tuberculosis in HIV positive, diagnosed by the M. tuberculosis specific interferon-gamma test. *Respiratory Research*, 7, 56
Ref ID: 953

EXC-No comparison with TST

Iseli, A., Hullstrung, H.D., Rodenhausen, S., Widmer, A.F., Tyndall, A., & Hasler, P. 2006. Detection of tuberculosis by extensive screening in a patient with rheumatoid arthritis prior to anti-TNF-alpha therapy. *Rheumatology*, 45, (8) 1049-1050
Ref ID: 958

EXC-Letter

Shah, S.S., McGowan, J.P., Klein, R.S., Converse, P.J., Blum, S., & Gourevitch, M.N. 2006. Agreement between Mantoux skin testing and QuantiFERON-TB assay using dual mycobacterial antigens in current and former injection drug users. *Medical Science Monitor*, 12, (4) MT11-MT16
Ref ID: 1005

EXC-PPD based IGRA

Wagstaff, A.J. & Zellweger, J.P. 1964. T-SPOT.TB: an in vitro diagnostic assay measuring T-cell reaction to Mycobacterium tuberculosis-specific antigens. *Molecular Diagnosis & Therapy*, 10, (1) 57-63
Ref ID: 1014

EXC-Review article

Sutherland, R., Yang, H., Scriba, T.J., Ondondo, B., Robinson, N., Conlon, C., Suttill, A., McShane, H., Fidler, S., McMichael, A., & Dorrell, L. 2006. Impaired IFN-gamma-secreting capacity in mycobacterial antigen-specific CD4 T cells during chronic HIV-1 infection despite long-term HAART. *AIDS*, 20, (6) 821-829
Ref ID: 1036

EXC-Investigating IFN-gamma secreting capacity

Piana, F., Codecasa, L.R., Besozzi, G., Migliori, G.B., & Cirillo, D.M. 2006. Use of commercial interferon-gamma assays in immunocompromised patients for tuberculosis diagnosis.[comment]. *American Journal of Respiratory & Critical Care Medicine*, 173, (1) 130-131
Ref ID: 1081

EXC-Correspondence

Dheda, K., Lalvani, A., Miller, R.F., Scott, G., Booth, H., Johnson, M.A., Zumla, A., & Rook, G.A. 2005. Performance of a T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count.[see comment]. *AIDS*, 19, (17) 2038-2041
Ref ID: 1118

EXC-Research letter

Berg, J., Nyamathi, A., Christiani, A., Morisky, D., & Leake, B. 2005. Predictors of screening results for depressive symptoms among homeless adults in Los Angeles with latent tuberculosis. *Research in Nursing & Health*, 28, (3) 220-229
Ref ID: 1217

EXC-Depressive symptoms of LTBI cases

Dheda, K., Udwadia, Z.F., Huggett, J.F., Johnson, M.A., & Rook, G.A. 2005. Utility of the antigen-specific interferon-gamma assay for the management of tuberculosis. [Review] [68 refs]. *Current Opinion in Pulmonary Medicine*, 11, (3) 195-202
Ref ID: 1234

EXC-Overview of test in different at risk groups

Pugliese, G. 1992. Screening for tuberculous infection: an update. *American Journal of Infection Control*, 20, (1) 37-40
Ref ID: 1305

EXC-Screening update

Valenti, W.M. 1992. Tuberculosis in the human immunodeficiency virus era: everything old is new again. *American Journal of Infection Control*, 20, (1) 35-36
Ref ID: 1306

EXC-Commentary

Bargman, C. 2004. TNF inhibitors and tuberculosis.[comment]. *American Journal of Nursing*, 104, (11) 15-16
Ref ID: 1352

EXC-Comment

Sester, M., Sester, U., Clauer, P., Heine, G., Mack, U., Moll, T., Sybrecht, G.W., Lalvani, A., & Kohler, H. 2004. Tuberculin skin testing underestimates a high prevalence of latent tuberculosis infection in hemodialysis patients. *Kidney International*, 65, (5) 1826-1834
Ref ID: 1458

EXC-Investigating PPD reactivity

Dahle, U.R. 2004. Compulsory screening of immigrants for TB and HIV: screening could detect latent infection.[comment]. *BMJ*, 328, (7444) 897
Ref ID: 1462

EXC-Comment

Coker, R. 2004. Compulsory screening of immigrants for tuberculosis and HIV.[see comment]. *BMJ*, 328, (7435) 298-300
Ref ID: 1487

EXC-Commentary

Long, R. & Gardam, M. 2003. Tumour necrosis factor-alpha inhibitors and the reactivation of latent tuberculosis infection. [Review] [32 refs]. *CMAJ Canadian Medical Association Journal*, 168, (9) 1153-1156
Ref ID: 1614

EXC-Review article

Chapman, A.L., Munkanta, M., Wilkinson, K.A., Pathan, A.A., Ewer, K., Ayles, H., Reece, W.H., Mwinga, A., Godfrey-Faussett, P., & Lalvani, A. 2002. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of Mycobacterium tuberculosis-specific T cells.[see comment]. *AIDS*, 16, (17) 2285-2293
Ref ID: 1675

EXC-PPD based IGRA

2000. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society.[see comment]. [Review] [101 refs]. *Thorax*, 55, (11) 887-901
Ref ID: 1954

EXC-Review

Kimura, M., Converse, P.J., Astemborski, J., Rothel, J.S., Vlahov, D., Comstock, G.W., Graham, N.M., Chaisson, R.E., & Bishai, W.R. 1999. Comparison between a whole blood interferon-gamma release assay and tuberculin skin testing for the detection of tuberculosis infection among patients at risk for tuberculosis exposure. *Journal of Infectious Diseases*, 179, (5) 1297-1300
Ref ID: 2124

EXC-PPD based IGRA

Sodhi, A., Gong, J., Silva, C., Qian, D., & Barnes, P.F. 1997. Clinical correlates of interferon gamma production in patients with tuberculosis. *Clinical Infectious Diseases*, 25, (3) 617-620
Ref ID: 2320

EXC-PPD based IGRA/ focus on active TB

Citron, K. 1996. Tuberculosis among homeless people. *Journal of Epidemiology & Community Health*, 50, (3) 382
Ref ID: 2407

EXC-Letter to editor

Barclay, D.M., III, Richardson, J.P., & Fredman, L. 1995. Tuberculosis in the homeless. [Review] [62 refs]. *Archives of Family Medicine*, 4, (6) 541-546
Ref ID: 2566

EXC-Control of TB

Adebajo, A.O., Cawston, T.E., & Hazleman, B.L. 1994. Rheumatoid factors in association with rheumatoid arthritis and infectious diseases in West Africans. *Journal of Rheumatology*, 21, (5) 968-969
Ref ID: 2648

EXC-Letters to the editor

1992. Guidelines for the identification, investigation and treatment of individuals with concomitant tuberculosis and human immunodeficiency virus infection. Canadian Thoracic Society, the Tuberculosis Directors of Canada and the Department of National Health and Welfare. *Canada Communicable Disease Report*, 18, (20) 155-160
Ref ID: 2768

EXC-Guideline

Lan, J.L. & Wu, C.H. 1992. Detection of Mycobacterium tuberculosis antigen in synovial fluid of patients with rheumatoid arthritis. *British Journal of Rheumatology*, 31, (9) 615-618
Ref ID: 2800

EXC-Focus on technique for detection of antigens in synovial fluid

Inanc, N., Aydin, S.Z., Karakurt, S., Atagunduz, P., Yavuz, S., & Direskeneli, H. 2009. Agreement between Quantiferon-TB gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. *Journal of Rheumatology*, 36, (12) 2675-2681
Ref ID: 3398

EXC- No stratifying immunosupressed patients to identify which patients were more at risk

Itty, S., Bakri, S.J., Pulido, J.S., Herman, D.C., Faia, L.J., Tufty, G.T., Bennett, S.R., & Falk, N.S. 2009. Initial results of QuantiFERON-TB Gold testing in patients with uveitis. *Eye*, 23, (4) 904-909
Ref ID: 3409

EXC-Case series

Valleala, H., Tuuminen, T., Repo, H., Eklund, K.K., & Leirisalo-Repo, M. 2009. A case of Poncet disease diagnosed with interferon-gamma-release assays. *Nature Reviews Rheumatology*, 5, (11) 643-647
Ref ID: 3412

EXC-Case series

Goodfellow, A., Keeling, D.N., Hayes, R.C., & Webster, D. 2009. Utility of an interferon-gamma release assay for latent tuberculosis diagnosis in a case of bullous pemphigoid. *Journal of Cutaneous Medicine & Surgery*, 13, (5) 280-282
Ref ID: 3416

EXC-Case study

Park, J.H., Seo, G.Y., Lee, J.S., Kim, T.H., & Yoo, D.H. 2009. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. *Journal of Rheumatology*, 36, (10) 2158-2163
Ref ID: 3417

EXC-Differential analysis for TST and IGRA

Cummings, K.J., Smith, T.S., Shogren, E.S., Khakoo, R., Nanda, S., Bunner, L., Smithmyer, A., Soccorsi, D., Kashon, M.L., Mazurek, G.H., Friedman, L.N., & Weissman, D.N. 2009. Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. *Infection Control & Hospital Epidemiology*, 30, (11) 1123-1126
Ref ID: 3420

EXC-To consider for contacts (screening)

Laffitte, E., Janssens, J.P., Roux-Lombard, P., Thielen, A.M., Barde, C., Marazza, G., Panizzon, R.G., & Saurat, J.H. 2009. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. *British Journal of Dermatology*, 161, (4) 797-800
Ref ID: 3422

EXC-Insufficient data analysis

Sztajnbok, F.R., Boecha, N.L., Sztajnbok, D.C., Ribeiro, S.B., Oliveira, S.K., & Sant'Anna, C.C. 2009. The challenge of pediatric tuberculosis in face of new diagnostic techniques. *Jornal de Pediatria*, 85, (3) 183-193
Ref ID: 3431

EXC-Review article

al-Orainey, I.O. 2009. Diagnosis of latent tuberculosis: Can we do better? *Annals of Thoracic Medicine*, 4, (1) 5-9
Ref ID: 3432

EXC-Review article

Lagrange, P.H. & Herrmann, J.L. 2008. Diagnosing Latent Tuberculosis Infection in the HIV Era. *The Open Respiratory Medicine Journal*, 2, 52-59
Ref ID: 3442

Inaccessible

Winthrop, K.L. & Daley, C.L. 2008. A novel assay for screening patients for latent tuberculosis infection prior to anti-TNF therapy.[comment]. *Nature Clinical Practice Rheumatology*, 4, (9) 456-457
Ref ID: 3445

EXC-Correspondence

Murakami, S., Takeno, M., Kirino, Y., Kobayashi, M., Watanabe, R., Kudo, M., Ihata, A., Ueda, A., Ohno, S., Watanuki, Y., Kaneko, T., & Ishigatsubo, Y. 2009. Screening of tuberculosis by interferon-gamma assay before biologic therapy for rheumatoid arthritis. *Tuberculosis*, 89, (2) 136-141
Ref ID: 3530

EXC-Non commercial IGRA

Davarpanah, M.A., Rasti, M., Mehrabani, D., Allahyari, S.S., Neirami, R., & Saberi-Firoozi, M. 2009. Association between PPD and quantiFERON gold TB Test in TB infection and disease among HIV-Infected individuals in Southern Iran. *Iranian Red Crescent Medical Journal*, 11, (1) 71-75
Ref ID: 3611

Inaccessible

Dominguez, J., Latorre, I., Altet, N., Mateo, L., De Souza-Galvao, M., Ruiz-Manzano, J., & Ausina, V. 2009. IFN-gamma-release assays to diagnose TB infection in the immunocompromised individual. *Expert Review of Respiratory Medicine*, 3, (3) 309-327
Ref ID: 3718

EXC-Overview

Dodig, S., Topic, R.Z., & Zivcic, J. 2008. Latent tuberculosis infection in a subject with diabetes mellitus - A case report. [Croatian, English]. *Biochemia Medica*, 18, (3) 368-373
Ref ID: 3769

Inaccessible

Pai, M. & O'Brien, R. 2008. New diagnostics for latent and active Tuberculosis: State of the art and future prospects. *Seminars in Respiratory and Critical Care Medicine*, 29, (5) 560-568
Ref ID: 3784

EXC-Overview of prospects of new diagnostic tests

Dominguez, J. & Latorre, I. 2008. Role of the T-cell interferon-gamma release assays in preventing reactivation of latent tuberculosis infection in immunosuppressed patients in treatment with anti-TNF agents. *Journal of Crohn's and Colitis*, 2, (3) 250-254
Ref ID: 3819

EXC-Comparing QFT with T-SPOT

Keane, J. & Cheallaigh, C.N. 2008. Making tumor necrosis factor blockers safer: A prescribed consumptive challenge. *Journal of Rheumatology*, 35, (7) 1238-1239
Ref ID: 3872

EXC-Editorial

Daley, P. & Chordia, P. 2008. What is the clinical utility of interferon-gamma release assays for the diagnosis of TB in high-TB-burden countries? *Therapy*, 5, (3) 367-375
Ref ID: 3908

EXC-Overview of risk factors in high burden countries

Balato, N., Ayala, F., Gaudiello, F., Monfrecola, G., Cimmino, G., Ponticiello, A., Bocchino, M., Matarese, A., & Sanduzzi, A. 2008. Comparison of tuberculin skin test and interferon-gamma assays in patients with moderate to severe psoriasis who are candidates for antitumour necrosis factor-alpha therapy. *British Journal of Dermatology*, 158, (4) 847-849
Ref ID: 3959

EXC-Correspondence

Arend, S.M., Leyten, E.M.S., Franken, W.P.J., Huisman, E.M., & van Dissel, J.T. 2007. A patient with de novo tuberculosis during anti-tumor necrosis factor-alpha therapy illustrating diagnostic pitfalls and paradoxical response to treatment. *Clinical Infectious Diseases*, 45, (11) 1470-1475
Ref ID: 3964

EXC-Case report

Beglinger, C., Dudler, J., Mottet, C., Nicod, L., Seibold, F., Villiger, P.M., & Zellweger, J.-P. 2007. Screening for tuberculosis infection before initiation of anti-TNF-alpha therapy. *Swiss Medical Weekly*, 137, (43-44) 621-622
Ref ID: 4063

EXC-Correspondence

Farris, A.B. & Branda, J.A. 2007. QuantiFERON-TB gold assay for tuberculosis infection. *Clinical Microbiology Newsletter*, 29, (17) 129-136
Ref ID: 4106

EXC-Evaluating 1st and 2nd generation IGRA

Visweswaran, R.K. 2007. What is the best way of screening hemodialysis patients for latent tuberculosis? *Nature Clinical Practice Nephrology*, 3, (6) 310-311
Ref ID: 4176

EXC-Commentary

Nelson, K. 2007. Tuberculin testing to detect latent tuberculosis in developing countries. *Epidemiology*, 18, (3) 348-349
Ref ID: 4235

EXC-Commentary

Markova, R., Terzieva, V., Drenska, R., Todorova, Y., Sapundjieva, E., Stefanova, D., Dimitrov, V., Kostov, K., Elenkov, I., & Yankova, M. 2006. Evaluation of a whole blood IFN-gamma assay in immunocompetent and immunocompromised Bulgarian patients with mycobacterium tuberculosis infection. *Clinical Application of Immunology*, 5, (1) 548-555
Ref ID: 4290

Inaccessible

Richeldi, L. 2006. T-cell-based assay versus tuberculin skin testing for diagnosis of Mycobacterium tuberculosis infection in imunocompetent and immunosuppressed patients. *Enfermedades Emergentes*, 8, (4) 249-250
Ref ID: 4297

EXC-Overview

Saliu, O.Y., Sofer, C., Stein, D.S., Schwander, S.K., & Wallis, R.S. 2006. Tumor-necrosis-factor blockers: Differential effects on mycobacterial immunity. *Journal of Infectious Diseases*, 194, (4) 486-492
Ref ID: 4385

EXC-Examining antibody effects of TNF blocker

Kehinde, A.O. 2006. T-SPOT[trademark].TB: An in vitro diagnostic assay measuring T-cell reaction to Mycobacterium tuberculosis-specific antigens: A viewpoint. *Molecular Diagnosis and Therapy*, 10, (1) 64
Ref ID: 4451

EXC-Commentary

Davies, P.D.O. 2006. T-SPOT[trademark].TB: An in vitro diagnostic assay measuring T-cell reaction to Mycobacterium tuberculosis-specific antigens: A viewpoint. *Molecular Diagnosis and Therapy*, 10, (1) 64
Ref ID: 4452

EXC-Commentary

Huizinga, T.W.J. & Arend, S.M. 2006. Is the tuberculin skin test an accurate method of detecting tuberculosis in patients with rheumatoid arthritis? *Nature Clinical Practice Rheumatology*, 2, (4) 188-189
Ref ID: 4465

EXC-Commentary

Rothel, J.S. & Radford, A.J. 2003. Comparison of tuberculosis tests: Finding truth or confirming prejudice? [4]. *Clinical Infectious Diseases*, 36, (9) 1206-1207
Ref ID: 5033

EXC-Commentary

Chan, E.D., Heifets, L., & Iseman, M.D. 2000. Immunologic diagnosis of tuberculosis: A review. *Tubercle and Lung Disease*, 80, (3) 131-140
Ref ID: 5351

EXC-Overview of diagnosis

Greveson, K. 2009. Can ELISpot replace the tuberculin skin test for latent tuberculosis? *British Journal of Nursing (BJN)*, 18, (20) 1248-1254 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2010470325&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=596&accno=2010470325
Ref ID: 6134

EXC-Overview

Corbett, E.L., Charalambous, S., Moloi, V.M., Fielding, K., Grant, A.D., Dye, C., De Cock, K.M., Hayes, R.J., Williams, B.G., & Churchyard, G.J. 2004. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *American Journal of Respiratory & Critical Care Medicine*, 170, (6) 673-679 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2005059588&site=ehost-live
Ref ID: 6202

EXC-Assessing prevalence and HIV as a risk factor for undiagnosed TB

Brassard, P., Lowe, A.M., Bernatsky, S., Kezouh, A., & Suissa, S. 2009. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis & Rheumatism*, 61, (3) 300-304 available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2010215564&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=1742&accno=2010215564
Ref ID: 6282

EXC-Treatment

Excluded studies for Occupational Health Screening

Bodenmann, P., Vaucher, P., Wolff, H., Favrat, B., de, T.F., Masserey, E., & Zellweger, J.P. 2009. Screening for latent tuberculosis infection among undocumented immigrants in Swiss healthcare centres; a descriptive exploratory study. *BMC Infectious Diseases*, 9, 34
Ref ID: 204

EXC-Not screening Healthcare workers

Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Ly, I.N., Harstad, I., Dyrhol-Riise, A.M., & Heldal, E. 2008. School based screening for tuberculosis infection in Norway: comparison of positive tuberculin skin test with interferon-gamma release assay. *BMC Infectious Diseases*, 8, 140
Ref ID: 350

EXC-Not screening Healthcare workers

Haley, C.A., Cain, K.P., Yu, C., Garman, K.F., Wells, C.D., & Laserson, K.F. 2008. Risk-based screening for latent tuberculosis infection. *Southern Medical Journal*, 101, (2) 142-149
Ref ID: 491

EXC-Did not use IGRA

Nienhaus, A., Schablon, A., Bacle, C.L., Siano, B., & Diel, R. 2008. Evaluation of the interferon-gamma release assay in healthcare workers. *International Archives of Occupational & Environmental Health*, 81, (3) 295-300
Ref ID: 567

EXC-Not a study on screening

Kobashi, Y., Obase, Y., Fukuda, M., Yoshida, K., Miyashita, N., Fujii, M., & Oka, M. 2007. Usefulness of QuantiFERON TB-2G, a diagnostic method for latent tuberculosis infection, in a contact investigation of health care workers. *Internal Medicine*, 46, (18) 1543-1549
Ref ID: 658

EXC-Focus on Diagnosis

Anderson, C., Abubakar, I., Maguire, H., & Sonnenberg, P. 2007. Survey of tuberculosis incidents in hospital healthcare workers, England and Wales, 2005. *Journal of Public Health*, 29, (3) 292-297
Ref ID: 680

EXC-Not screening

Drobniewski, F., Balabanova, Y., Zakamova, E., Nikolayevskyy, V., & Fedorin, I. 2007. Rates of latent tuberculosis in health care staff in Russia. *PLoS Medicine / Public Library of Science*, 4, (2) e55
Ref ID: 690

EXC-Used IGRA alone

Kirkpatrick, A., Bell, C., Petrovic, M., Woodhead, M., Barrett, A., Duffell, E., Verma, A., & Reynolds, F. 2006. Investigation of a tuberculosis cluster at a job centre in Manchester, United Kingdom. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 11, (11) 273-275
Ref ID: 871

EXC-Not a study on Healthcare workers

Coker, R.J., Bell, A., Pitman, R., Hayward, A., & Watson, J. 2004. Screening programmes for tuberculosis in new entrants across Europe. *International Journal of Tuberculosis & Lung Disease*, 8, (8) 1022-1026
Ref ID: 1411

EXC-Not a study on Healthcare workers

Skodric, V., Savic, B., Jovanovic, M., Pesic, I., Videnovic, J., Zugic, V., Rakovic, J., & Stojkovic, M. 2000. Occupational risk of tuberculosis among health care workers at the Institute for Pulmonary Diseases of Serbia.

International Journal of Tuberculosis & Lung Disease, 4, (9) 827-831
Ref ID: 1968

EXC-Study not focused on Latent tb

Appendix O – Evidence tables 2011

Evidence Tables: IGRA Testing on people from high prevalence countries

Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
Kik, S.V., Franken, W.P., Arend, S.M., Mensen, M., Cobelens, F.G., Kamphorst, M., van Dissel, J.T., Borgdorff, M.W., & Verver, S. 2009 (Ref ID 60)	Observational Retrospective study	821	Not specifically recorded.	Netherlands / South America, Asia, Sub saharan Africa	Participants aged above 16 years. Close contacts of sputum smear positive TB patients. Foreign born and second generation immigrants.	IGRA (QGIT, TSPOT.TB) (ESAT-6, CFP-10,TB7.7)	TST (Threshold 5mm 10mmand 15mm)	Associations between test results and remote exposure, defined as birth outside Europe and North America. Attributable Fraction to particular risk factors calculated. Overall kappa values TST 15mm 0.418 for QFT and 0.379 for TSPOT.TB. For 10mm they were 0.198 and 0.190 respectively. Agreement values were 71.3% and 69.9% for QFT and TSPOT.TB respectively for 15mm. For 10mm they were 62.1% and 64.9% respectively. The continent of birth was the only variable which was independently associated with a positive result for TST 10mm, p value for trend 0.031. Both QFT and TSPOT.tb also showed a positive result independently associated with continent of birth and age.	No data	Netherlands Organisation for Health Research and Development	Partial verification was performed on those with TST more than 5mm. Possibility of inclusion of patients with past active TB infections. Vague about the level of contact. Does not indicate duration of contact with infected individuals. Does not mention what they did with positive or negative CXRs. They don't mention how deduced LTBI
Nienhaus, A.,	Observation	1040	Incidence	Germany/	Study	IGRA	TST	Agreement 5mm 74.8%,	No data	No sponsor	Although study

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
Schablon, A., & Diel, R. 2008 (Ref ID 394)	al Cross sectional/ retrospective		of TB in Germany reported to be < 6/100000 and >20/100000 in countries from where the immigrants originated.	Germany Turkey, Eastern Europe and Africa	population 1040 healthy individuals. Mean age of 31.6 years 61.8% female, 25.4% foreign born, 43.4% had previous BCG vaccination. 41.8% HCW.	(QFTBG) Threshold level 0.35IU/ml Positive result 100/1033	(Threshold 5mm 311/1033(30.1 %) 10mm= 191/1033(18.5 %) 15mm=69/1033 (6.7%)	10mm 84.2%, 15mm 89.8%. Kappa Statistics 5mm(0.26) 10mm (0.37) 15mm (0.33.) BCG vacc. 5mm(0.12) 10mm(0.28) 15mm(0.34) No vacc 5mm(0.5) 10mm(0.54) 15mm(0.3) aOR for positive TST(10mm) for foreign birthplace was 4.6(3.21-6.53) as compared with German birth, for QFT it was 2.6(1.71-4.09)		reported	states the population consisted of health persons they have said nothing to rule out symptomless TB by chest Xray. TST at 10mm could possibly be confounded by gender foreign birthplace and BCG vaccination. QFT on could be confounded by age and foreign birthplace. TST+/QFT- discordance is associated with foreign birthplace. Authors explain that such discordance might be explained by resolved or old TB infections that are detected by TST and not QFT.
Carvalho, A.C., Pezzoli, M.C., El-Hamad, I., Arce, P., Bigoni, S., Scarcella, C., Indelicato, A.M., Scolari, C., Carosi, G., & Matteelli, A. 2007 (Ref ID 709)	Observational Cross sectional/ retrospective	130	Immigrants from countries with at least an incidence of 50 per 100000	Italy/ Sub saharan Africa, Northern Africa, Eastern Europe, Asia, Latin America	32 female 98 male. Median age 28 years (range 19-50). Immigrants from high incidence countries within the last 5 years.	IGRA (QFTBG) Threshold level 0.35IU/ml	TST (Threshold 10mm)	Association of Discordance/Concordance between two tests and BCG scar, sex, age, race, previous TB contact. Overall agreement was 71% kcoefficient= 0.37. 100% agreement between TST and IGRA for induration below 10mm.	No data	Lombardia Region grant no 286/98	BCG vaccination independently negatively associated with discordance between tests. 0.28 (0.1-0.77) p=0.01. BCG scar not always good indicator of BCG vaccination. Overall kcoefficient= 0.37. 100% agreement between TST and

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Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
											IGRA for induration below 10mm.
Franken, W.P., Timmermans, J.F., Prins, C., Slootman, E.J., Dreverman, J., Bruins, H., van Dissel, J.T., & Arend, S.M. 2007 (Ref ID 792)	Prospective Cross sectional study	909	Range from <10, 10-49,50-99,100-199>200) per 100000	Netherlands / Bosnia Kyrgystan Iraq and Afghanistan.	Army personnel who had returned from mission (738) in high incidence countries compared with new recruits (171) who had not been on mission.	IGRA QFGinTube (ESAT-6 CFP-10, TB7.7)	TST (Threshold 10mm and 15mm)	Discordance and concordance between tests. Overall concordance and kappa values were determined to be 82% and 0.19 respectively for 10mm cut off and 92.3% and 0.24 respectively for 15mm TST cut off.	No data		Study not clear with regard to the definition of LTBI.
Brodie, D., Lederer, D.J., Gallardo, J.S., Trivedi, S.H., Burzynski, J.N., & Schluger, N.W. 2008 (Ref ID 479)	Prospective	123	Not specifically recorded.	United States/ Does not mention countries of origin of immigrants	Patients over 5 years old. Study group were those who had had contact with active TB patients and controls were those who had not had any contact. A lot of the patients were recent immigrants with a high rate BCG vaccination	IGRA (ESAT-6 and CFP-10)	TST	Overall agreement between TSPOT.tb and TST was 64% and the kappa value was 0.33(0.19-0.48). For BCG vaccinated people it was 56%(43-68) and 0.22(0.06-0.37) respectively. In non vaccinated people it was 82%(68-96) and 0.64(0.38-0.91)	Yes	Oxford Immunotech	Does not mention how they determined either those with ATB or LTBI. Used contact status as surrogate for LTBI and used that as Gold standard. Does not give indication of prevalence or incidence of countries of origin of immigrants.
Porsa, E., Cheng, L., Seale, M.M., Delclos, G.L., Ma, X., Reich, R., Musser, J.M., & Graviss, E.A. 2006	Cross sectional/ Observational	474	TB prevalence in United States $<10/10^5$ of foreign born the prevalence reported	United States/ Mexico, Jamaica, Nicaragua, Ecuador, El Salvador, Honduras, The	Adult inmates above 18 years of age. 114 female, 295 male. 370 born in the United States 39 Foreign born. 344 patients	IGRA (ESAT-6 and CFP-10)(QFGInTube)	TST Induration 10mm	Kappa statistics for discordance and concordance between TST and QFGT.Adjusted Odds Ratios calculated to determine which factors including Ethnicity, Old age, foreign birth and	Not determined	Health Resources and Services Administration Bureau of health professions Grant. Kits provided by	On logistic regression African American ethnicity only variable associated with positive results for both assays. Mentioned that positive IGRA

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Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
(Ref ID 1070)			25-300/10^5	Philippines and Brazil.	had prior incarceration. There was a mix of Caucasian African-American and Hispanic ethnicities			prior incarceration were more associated with Discordance.		Cellestis	indicates more recent and ongoing infection while positive TST indicates a remote infection in the past. Hence sensitivity appeared better in TSTs than IGRAs
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Jeppesen, A.S., Harstad, I., Heier, B.T., & Heldal, E. 2008 (Ref ID 438)	Observational Cross sectional/ retrospective	1000	TB incidence rate in Norway 6.3/100000	Norway/ Iraq, Somalia, Russia, Iran, Eritrea, Afghanistan, Sub saharan Africa	Asylum seekers. At least 18 years of age. 75.1% male and 24.9% female.	IGRA (ESAT-6 and CFP-10)(QFGInTube)	TST (Threshold 6mm) 460/912(50.4%) 10mm 311/921(34.1%) 15mm(15.5%)	Agreement 72% for 6mm 79% 10mm 78% 15mm. Kappa 6mm 0.43(0.37-0.49) 10mm 0.51(0.45-0.57) 15mm 0.39(0.32-0.47) statistics 0.43(0.37-0.49). aOR continent of origin with Asia as baseline for TST 15mm 3.8 and 3.3 for QFT	Not determined		Definite prevalence or incidence not recorded for countries of origin. For QFT, BCG vaccination and gender were not independent predictors of a positive result while country of origin and age group and level of exposure independently predicted a positive test. For TST 15mm the variables which independently predicted a positive result were gender, country of origin and level of exposure
Diel, R., Nienhaus, A., Lange, C., Meywald-Walter, K., Forssbohm, M., & Schaberg, T. 2006	Observational prospective study.	311	TB incidence rate in Hamburg 12/100000. Immigrants from countries with	Germany/ 25 different countries including former Soviet Union and Turkey.	Close contacts of sputum-smear positive cases. Contacts with less than 40hours contact time were excluded. Mean age 28.5	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST 5mm= 137/309 TST (28/137 Positive by IGRA) 10mm=64/309 15mm= 25/309	Overall Kappa statistics 0.2 CI(0.14-0.23) Concordant results 197/309 (63.8%). Positive result 169/172(98.2%) Negative result 28/137 (20.4%) Concordance for 5mm between BCG	No data	No sponsor	For QFT only Origin is an independent predictor of a positive test result. For TST BCG vaccination also acts an independent predictor. Study

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Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
(Ref ID 982)			incidence of at least 20/100000		years Previous BCG vaccination 157 (50.8%) Foreign/German (27.1%/72.9)			vacc 38.9% k=0.08(0.026-0.08). Not vacc 89.5% k=0.58(0.4-0.68) for 10mm 77.1% k=0.35 (0.24-0.35)for No BCG and 94.1% k=0.68 (0.46-0.81) for BCG. For TST(5mm) OR = 5.4, TST(10mm) 7.3 and 4.7 QFT			does not mention how the specific countries or how recent migrants had been in the country.
Janssens, J.P., Roux-Lombard, P., Perneger, T., Metzger, M., Vivien, R., & Rochat, T. 2008 (Ref ID 268)	Observational prospective study.	295	TB Incidence $20/10^5$ in Geneva. Incidence in countries from which immigrants originated between (50->100)/10^5	Switzerland / Countries not specified but categorised by incidence	Mean age 40 years (range 16-83 years) Foreign born 73.9% (218) Contacts were exposed to Cavitary TB 105 (35.6%) Non-cavitary TB 168 (56.9%) Pulmonary TB 22 (7.5%)	IGRA (ESAT-6,CFP-10,) (T-SPOT.TB)	TST Induration 5mm 173(58.6%) 10mm 148(50.2%) 61mm(20.7%)	Overall concordant results showed 60.7% TST 5mm, 63.6% 10mm, 63.9% 15mm.Kappa values were 0.24, 0.27 and 0.19 respectively. BCG Non-vaccinated subjects concordant results were 78.4%, 76.5% and 78.4% respectively while kappa values were 0.47, 0.41 and 0.28 for 5mm, 10mm and 15mm respectively when comparing with IGRA .aOR for Gender, BCG and incidence in country of origin (<$50/10^5$ is used as baseline) showed these variables were independent predictors of a positive result 2.07 (1.22-3.51), 2.98 (1.39-6.41) 3.67 (1.40-1.90) respectively for TST 5mm. Only incidence in country of origin showed the significant association with a positive result for	Not determined	Ligue Pulmonaire Genevoise	Countries of origin of foreign born nationals not listed. Not very specific of exclusion of positive results if any of chest xray. In the analysis they did not mention if they adjusted for immunocompromised individuals. They were only 6%. The TB incidence of Geneva from where they recruited was $20/10^5$. They did not use that as the baseline value in calculations.

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Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
								TST 10mm 2.22 (1.15-4.27) and 3.84 (1.61-9.20) for 50-99/10^5 and >100/10^5 respectively. <50/10^5 was baseline. For IGRA , age by 10 year increments and incidence in country of origin were the independent predictors of a positive result. 1.30 (1.06-1.6) for age and 2.17 (1.13-4.15) and 2.62 (1.18-5.82) respectively for two categories of incidence.			
Diel, R., Loddenkemper, R., Meywald-Walter, K., Niemann, S., & Nienhaus, A. 2008 (Ref ID 455)	Observational prospective study.	1794	Incidence of TB in Hamburg, Germany reported to be 10.8/10^{5}.	Germany/ Noted as 'foreign born' but cases progressing to TB documented as from Turkey, Angola	Close contacts of sputum-smear positive cases with at least 40 hours exposure in a closed room. Age range between 0 to 60 years, with most (87.5%) falling between the 16 to 50 range. 28% were migrants from 29 different countries	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST (Threshold 5mm and 10mm)	Overall kappa statistics 0.276 and 0.119 and 0.616 for BCG vaccinated and non BCG respectively. For the concordance the values were 69.2%, 44.2% and 90.7% respectively. Odds Ratio for a positive test if foreign born adjusted for BCG vaccination, Age and exposure time were determined as follows. TST 5mm 5.81 (3.6-9.1), 10mm 5.2 (3.2-8.4), QFT 2.28 (1.3-3.9)	Not determined	No declared sponsor	Specific countries of origin of migrants not mentioned.

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Evidence Tables: Children

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Lighter, J., Rigaud, M., Eduardo, R., Peng, C.H., & Pollack, H. 2009(282)	Observational prospective	253 Children below 18 years (Mean age 9) Age stratified as follows <24 mo, 24-59mo, 60mo. Recruited from the well child clinic, paediatric chest clinic and paediatric inpatient ward. 42% were female.72 received a single vaccination, 59 had visible BCG scars	Level of exposure graded as **minimal** (No known risk), **low/moderate** risk factors (birth in or travel to a disease-endemic region and/or living with a household member with specific risks (emigrating from a disease-endemic region, having HIV, or having a history of imprisonment, homelessness, or intravenous drug use). **High**(Known direct contact with tuberculosis index case)	QFTG. Considered positive when > 0.35 IU/ml and >25% than nil control value	TST (Mantoux technique). Considered positive with induration of >10mm	Proportion of QFTG positive results for children with increasing gradients of M tuberculosis exposure **Minimal**- 0% of TST+and -ve **Low/moderate** 6% of TST-ve and 19% TST+ were QFTG+. **High** 0% of TST –ve and 100%of TST+ case were QFTG+.	Not determined	Pott's memorial foundation and the Thrasher Research Fund	Cut off of 0.35IU/ml not validated especially for very young children who produce on average less interferon gamma than school aged children and adults

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Higuchi, K., Harada, N., Mori, T., & Sekiya, Y. 2007(849)	Observational prospective. Japan. Japanese students all BCG vaccinated	349 15-16years. Patients were all male and previously BCG vaccinated. They attended the same high school as a student diagnosed with active tb	Students stratified into two groups those with close contact (sharing of classes with index case; 210) and those with limited contact (not attending classes with the index case; 139)	QFTG. Considered positive when > 0.35 IU/ml	TST (defined standard test dose of tuberculin PPD equivalent to 2.5 tuberculin units). Erythma used instead of induration. An erythma of >30mm considered positive for a BCG vaccinated individual	The distribution of TST responses in both close and limited contacts was similar. (p=0.20)	Follow up of 91 students with positive TST but negative QFGT showed no signs of active tb after 3.5 years of follow up	Ministry of Health Labour and Welfare Japan	Partial verification only patients with positive TST were tested with QFTG. Authors suggest that similar positive rates of TST in both strata of exposed groups suggest limited transmission of MTB.

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Chun, J.K., Kim, C.K., Kim, H.S., Jung, G.Y., Lee, T.J., Kim, K.H., & Kim, D.S. 2008(276)	Observational conducted in South Korea	Age up to 15 years. Patients visiting a children's hospital. All children but one had been BCG vaccinated.	Divided into four groups according to contact status. **1. Close contact group** residing in the same house as active tb index case**. 2. Casual contact group**; those with exposure outside household. **3. Control group**; TST positive healthy children with no contact history. **4**. **Children with symptoms suggestive of tuberculosis** as a potential cause	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Close contacts: Kappa 0.19 for 5mm and 0.529 for 10mm. (B) Kappa 0.378 for 10mm. A significantly higher rate of positive QFTG results was evident for the close contact group. 8/42, 19% as compared with the control group 3 subjects 1/65, 1.5% p<0.05. Majority of indeterminate QFTG results were from group 4 who were suffering from medical conditions that could be associated with impaired immune function at the time of testing	Not determined	Not reported	Authors found that in children with no exposure to TB, the QFTG was positive in only one of the 65 children, although all of them were positive by the TST at 5mm and 64.6% at 10mm. They also found that there was a significant relationship between higher responses to mitogen-positive control and increasing age of the children

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Tsiouris, S.J., Austin, J., Toro, P., Coetzee, D., Weyer, K., Stein, Z., & El-Sadr, W.M. 2006(941)	Observational/United States/ South Africa	1741 5-15years. Mean age of	Participants grouped according to the status of contact they were living with. **A.** Current case of active TB in the household. **B**. Past case of active TB.**C**. Current and past case of active TB.	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Univariate analysis showed the likelihood of having a positive IGRA increased with increasing age (p=0.011) as did having a TST > 10mm. Overall agreement increased with increasing cut off of TST 0.52, 0.56 and 0.62 for 5, 10 and 15mm respectively.	Not determined	Aeras Global TB vaccine foundation.	IGRA performed well without indeterminate results. The inability to obtain adequate blood specimen from 16.7% of participants is a drawback which is likely to be true of any whole-blood based paediatric test.

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Okada, K., Mao, T.E., Mori, T., Miura, T., Sugiyama, T., Yoshiyama, T., Mitarai, S., Onozaki, I., Harada, N., Saint, S., Kong, K.S., & Chhour, Y.M. 2008(393)	Observational / Japan	They used 161 index cases and 217 contacts 5 years and below.	Contacts stratified by varying risk of infection as classified by smear and culture result of index cases. **A**. Smear -ve with positive or negative culture. **B**. Smear positive grade 1+ including scanty smear. **C** Smear positive grade 2+ **D**. Smear positive grade 3+	IGRA(QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 2.5TU PPD-S	Measured concordance rates and kappa values by smear positivity of index cases and by age of children. Concordance 0.87, 0.906, 0.837, 0.893 and 0.877 overall, kappa 0.308, 0.711, 0.536, 0.774 and 0.626 overall. Also measured multivariate odds ratios for positive results for both TST and QFTG. The following covariates were analysed. Gender, age, BCG scar, Period from final contact and Smear positivity.	Not determined	Japan International Cooperation Agency	Smear positivity of index cases was the most important factor for positivity of both TST and QFTG

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Brock, I., Weldingh, K., Lillebaek, T., Follmann, F., & Andersen, P. 2004(1434)	Observational. Done in Denmark on Danish School population	125 Mean age of 17 years. 85 not BCG vaccinated. Subjects nearest contact case also 17 asked to participate	Stratified by high and low exposure**.** **High exposure** contained individuals with close contact to the index case either through household, school class or local choir that index case regularly attended. **Low exposure** was comprised of 40 students from 2 other classes at the school with no connection to the index case	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Determined concordance between the tests in both levels of exposure. And also in both BCG and non BCG vaccinated individuals. Overall kappa = 0.866	Not determined	Not reported	Study demonstrated that IGRA is similar in performance in to TST in detecting LTBI in young non BCG vaccinated individuals.
Connell, T.G., Curtis, N., Ranganathan, S.C., & Buttery, J.P. 2006(979)	Observational study. Australia. Some children born in high prevalence countries 52%	Children less than 18years with a high risk of latent TB infection.	Contact with high risk as defined by siblings or parents recently diagnosed with TB disease, clinical suspicion of TB disease and those recently immigrated from high prevalence of TB	IGRA(QFTG) 0.35IU/ml positive response	TST PPD 10 IU of tuberculin. Positive if 15mm in individuals with evidence of prior BCG, > 5mm in TB contacts regardless of BCG and > for all others	Concordance between TST and IGRA poor overall k=0.3. 70% of TST positives were negative by IGRA. 65% of TST positives had a known TB contact.	Not determined	John Burge Trust. Victoria Australia	Recommended further studies to clarify predictive values.

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Higuchi, K., Kondo, S., Wada, M., Hayashi, S., Ootsuka, G., Sakamoto, N., & Harada, N. 2009 (164)	Prospective Observational study Japan/ Participants from Japan BCG vaccination done	313 participants between the ages of 8-12 years. In a Japanese School	Participants were exposed to an index case in the school. Close contact participants were those who had daily contact (at 90hours contact. Casual participants: total of less than 18hours	IGRA (QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 3 TU PPD-S	QFTG positivity in close contacts 9.8% as compared with 1.8% in casual contacts p=0.02. TST(5mm) positivity in close contacts 52.6% as compared with 67.2% (p=0.078).TST (10mm) 34.2% compared with 28.7% (p=0.488)	Not recorded. No child with negative QFT result developed active TB after 3 years. 3 out of 298 QFT negatives had a positive after 1 year	Not recorded	Authors suggest that QFT has the same performance characteristics in 8-12 years olds as adults. Suggestion of testing contacts three months after the end of exposure as an appropriate and sensitive approach.
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Ly, I.N., Harstad, I., Dyrhol-Riise, A.M., & Heldal, E. 2008.(350)	Cross sectional study/Norway/ Determined by presence of scar	14-15 year olds	Factors associated with latent tb investigated include. Origin, gender, exposure to tuberculosis, travel history. Children grouped into western born, second generation and first generation	IGRA(QFTG) 0.35IU/ml positive	TST PPD RT23 (2 tuberculin units were used)	9% of 511 TST positive children were IGRA positive. They determined adjusted Odds ratios for a positive IGRA for origin of child and exposure. 0.9(0.3-2.4) and 3.3(1.6-6.2) for second generation and first generation respectively as compared with Western born. 2.9(1.1-7.6) Comparing exposure to non exposure of tb	Not determined	Division of infectious disease control at the Norwegian Institute of Public Health.	The authors conclude that factors other than tb infection are widely contributing to positive TST results in this group and indicate the improved IGRA specificity for latent tb

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Connell, T.G., Ritz, N., Paxton, G.A., Buttery, J.P., Curtis, N., & Ranganathan, S.C. 2008 (397)	Observational study. Australia/ Australia and some born in high prevalence countries. 52% BCG vaccinated	96 children from 6months of age to 19 years. Children who were at risk of latent tb or with suspected tb infection were eligible for inclusion. At risk was defined as a recent TB contact and/or recent immigration from a country of high prevalence of TB.	38 participants had LTBI TST positive with no additional symptoms. 49 patients TST negative with no confirmation of active TB. Contacts were either household or non household	IGRA(QFTG), T-SPOT.TB	TST PPD 10 IU of tuberculin. Positive >10mm in	Out of 100 patients, 38 were TST positive of which 16 were household contacts 6 non household contacts and 6 had no known contacts to active TB. 49 were TST negative, of which 10 were household contacts, 1 non-household contact and 38 had no known contacts with active TB.	Authors conclude the need for longitudinal studies for determination of predictive values	Not reported	Interesting how latent and uninfected participants were defined. LTBI: those who were TST positive but with no other symptoms and chest radiograph not suggestive of TB. Uninfected: defined as a well child with negative TST or child with symptoms potentially suggestive of TB but in whom investigations for TB were negative or a child with an alternative diagnosis and complete recovery in the absence of specific TB treatment

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Hansted, E., Andriuskeviciene, A., Sakalauskas, R., Kevalas, R., & Sitkauskiene, B. 2009 (3427)	Observational study done in Lithuania. All participants were BCG vaccinated	10 to 17 year olds	Study subjects who had been in contact with a case of infectious TB were divided into three groups. 1. Culture confirmed 2. High risk group; those living with a family member with infectious tb or having contact with such a person at school. Those this group were free from symptoms. Low risk; those who have no identifiable risk of TB(no known risk of contact with Tb patient, no symptoms and no complaints	IGRA(TSPOT.TB)	TST Mantoux test SSI PPD RT-23, 2TU positive if >10mm	60% high risk TST positive. 17.8% IGRA positive. Calculated RR 3.375. For the low risk 65.4% were TST positive while 9.6% were IGRA positive. Calculated RR 6.8 The total number of discordant results was 54 out of 97 subjects in both high risk and low risk populations. Out of 61 TST positive patients 51 were IGRA negative.	Not recorded	No records of funding	Authors conclude that identifying latent TB in children using this method is useful, especially in countries like Lithuania which have a high incidence of TB despite a high coverage with BCG vaccination

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Bibliographic Reference/ Ref ID	Study aim & type/Country of study	Definition and length of contact/ exposure	Number of participants/ Patient Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified	Positive and Negative Predictive values or Modified	Source of Funding	Additional comments
Lee, S.S., Liu, Y.C., Huang, T.S., Chen, Y.S., Tsai, H.C., Wann, S.R., & Lin, S.S. 2008. Ref ID: 473	To compare QFT-G and TST in the diagnosis of LTBI in BCG vaccinated HCWs/ Taiwan	Intensity of exposure graded by 1) **Duration of contact:** < 3h/wk, 3-8h/wk, >8 h/wk. 2) **Face-to face contact:** >1 hr. 3) **Staying in same room for >8hrs**. 4) **Personal protection during contact:** unmasked, surgical mask, N95 mask. **Intimate contact:** contact hours >8hrs and if duration of face-to-face contact was >1h.	Contact investigation in 39 HCW's with contact to case patient (smear positive, miliary TB). All BCG vaccinated. 12 male, 27 female. Mean age 35.1± 4.2 yrs (range 27-44yrs). None with symptoms and all had CXR negative for active disease-this persisted for up to 2 years after exposure ended.	QFT-G. **Conversion:** baseline <0.35 IU/ml and follow-up ≥ 0.35 IU/ml. **Repeated testing:** second QFT-G at >8 weeks in those initially QFT-G negtative.	TST (Mantoux). **Positive result:** ≥10mm. **Conversion:** increase in 10mm from negative initial TST.	**Initial testing:** 84.6% (33) TST+, 10.3% (4) QFT-G+ & 12.8% (5). QFT-G indeterminate. **Follow-up:** 32 tested. 33.3% (2/6) TST+. Using QFT-G ≥0.35, 12.5% (4/32) QFT-G+. **Initial concordance:** 18.0% (k= -0.03, CI -0.08 to 0.02, p=0.75). **Concordance between conversions**: 40%, (k= -0.40, p=0.82). Using 15mm and 18mm thresholds, agreement increased to 41.2% (k=0.04, CI -0.13 to 0.21, p=0.32) and 55.9% (k=0.12, CI -0.10 to 0.34, p=0.14) respectively.	**Risk factors for QFT-G conversion:** Intimate contact (OR 1.94, CI 0.18-21.12, p=0.59) and face-to-face contact >1hr (OR 9.20, CI 0.69-122.38, p=0.09) was associated with higher risk of QFT-G conversion, although non-significant.	National Health Research Institutes, Department of Health, Executive Yuan, Republic of China and Kaohsiung Veterans General Hospital.	Repeated testing. Used two thresholds of QFT-G (results not reported in evidence table). Active TB excluded using CXR. **Author's conclusion:** QFT-G conversion was more closely associated with intensity of exposure than TST conversion (although n.s). TST not useful in contact investigation with BCG vaccinated HCWs.

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Harada, N., Nakajima, Y., Higuchi, K., Sekiya, Y., Rothel, J., & Mori, T. 2006. Ref ID: 1009	To investigate the performance of QFT-G to detect LTBI by testing HCWs in a Japanese hospital where patients with and without TB are treated/ Japan	No specific definition of length of exposure but questionnaire included **history of employment in TB wards:** 1-4yrs, 5-9yrs, and ≥10 yrs, **history of employment in OPD TB clinic** (as above) and **job category**.	332 (approx 510 invited) HCWs working in Japanese hospital. No exclusion criteria. HCWs with and without TB contact. Mean age 41.4 yrs. 91.3% received at least 1 BCG, 15 non-BCG and 14 unknown. CXR in 98.2% showed 17 with evidence of healed/inactive TB & no cases of active TB.	QFT-G. **Positive result:** ≥0.35 IU/ml to neg control.	TST (Mantoux, 2.5 TU).	**TST & QFT-G results:** 9.9% had IFN-γ response to at least one antigen. 93.1% had TST≥ 10mm, 46.4% ≥20mm. **Other results:** 37.5% with TST ≥30mm had QFT-G+ compared to 7.4% with weaker TST ≤30mm (χ^2=5.8, p=0.02). No sig relationship between QFT-G+ and increasing induration of TST (χ^2=1.5, p=0.22).	**Risk factors for QFT-G+:** from multivariate regression-history of working in a TB ward (OR 2.9, p=0.03), history of working in the outpatient dept of TB clinic (OR 3.5, p=0.03). CXR consistent with past/ minimally severe TB also associated with increased OR (3.4) but this was n.s.	Japanese Ministry of Health, Labor and Welfare.	Active TB excluded using CXR-17 had evidence of 'healed or inactive TB' and these were not excluded from analyses. Some received more than 1 BCG.
Tripodi, D., Brunet-Court, Nael, V., Audrain, M., Chailleux, E., Germaud, P., Naudin, F., Muller, J.Y., Bourrut-Lacouture, M., Durand-Perdriel, M.H., Gordeeff, C., Guillaumin, G., Houdebine, M., Raffi, F., Boutoille, D., Biron, C., Potel, G., Roedlich, C., Geraut, C., Schablon, A., & Nienhaus, A. 2009. Ref ID: 3397	To compare the performance of TST and IGRA in French HCWs when using a high cut-off for TST/ Cross-sectional study/ France	All HCWs had unprotected contact to AFB positive patients- occurred in ED and lasted between 1-2 hours. Screening performed 8-10 weeks after exposure. No further details on length of exposure given. No specific analyses based on length of exposure.	148 HCWs working in French hospital & participating in TB screening due to contact to infectious TB. All French-born. 73.6% female. 100% BCG vaccinated (37.8% had one BCG, 62.2% had 2 or more). 47.3% worked in healthcare >10 yrs. No active TB in CXR of 60 HCWs.	QFT-GIT.	TST. **Positive result:** ≥10mm. **Old LTBI probable:** TST≥5-10mm. **Recent LTBI probable:** TST ≥10-<15mm. **Recent LTBI very probable:** TST≥ 15mm.	**QFT-GIT & TST results:** 18.9% QFT-GIT+, 65.5% TST≥10mm. Association between TST induration and QFT-GI+ was weak (p=0.081). **Calculated concordance:** 46.6%, k=0.11 (discordance 50% TST+/QFT- & 3.4% TST-/QFT+) when threshold ≥10mm compared to French definition of very probable recent LTBI (k=0.02).	**Logistic regression:** did not reveal association between QFT+ or TST+ and age, gender, BCG or yrs spent in healthcare.	Not reported	CXR to exclude active TB only used when TST ≤10 if no previous TST available for comparison. If previous TST available CXR performed when TST increased by >10mm (60 HCWs).

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Kang, Y.A., Lee, H.W., Yoon, H.I., Cho, B., Han, S.K., Shim, Y.S., & Yim, J.J. 2005. Ref ID: 1199	To compare the TST and IGRA in the diagnosis of LTBI according to intensity of exposure/ Korea (intermediate incidence)	4 groups: **1) Low risk of infection:** healthy medical students without identified risk for exposure. **2) Casual contacts:** healthy hospital staff with history of casual contact with active TB patients. **3) Close contacts**: household contact/ worked in same room as active case for ≥8 hrs/day. **4) Active TB.**	273 participants. 99 low risk (median age 25yrs, 59% male, 93% BCG scar), 72 casual contacts (median age 28, 67% male, 90% BCG scar), 48 close contacts (median age 41, 19% male, 67% BCG scar) & 54 active TB (median age 43, 59% male, 56% BCG scar). Exclusion: Group 1-3 with abnormal CXR, taken immunosuppressive drugs in past 3 months or if positive test for HIV.	QFTG. **Positive result:** ≥0.35 IU/ml	TST (Mantoux).	**TST (10mm cutoff) and QFT-G results:** Group 1 (51% TST+, 4% QFT+, k=0.08), Group 2 (60% TST+, 10% QFT+, k=0.14), Group 3 (71% TST+, 44% QFT+, k=0.17). **Overall agreement:** In groups 1-3 (k=0.16). **TST (15mm cutoff) and QFT-G results:** Group 1 (k=0.13), Group 2 (k=0.25), Group 3 (k=0.25). **Risk of infection with TST+ (10mm):** Adjusted OR (age, sex & BCG) Group 1 (OR 1.00), Group 2 (OR 1.48, CI 0.79-2.74), Group 3 (OR 3.13, CI 1.33-7.36). **Risk of infection with TST+ (15mm):** Adj OR Group1 (OR 1.00), Group 2 (OR 1.95, CI 1.02-3.72), Group 3 (OR 2.46, CI 1.10-5.50). **Risk of infection with QFT-G+:** Group 1 (OR 1.00), Group 2 (OR 2.48, CI 0.69-8.90), Group 3 (OR 8.98, CI 2.54-31.68).	Odds of positive result for each increase in risk across 4 groups increased by factor of 1.68 for 10mm TST (CI 1.24-2.26, p<0.001), by factor of 1.82 for 15mm TST (CI 1.38-2.41, p<0.001) and by factor of 4.23 for QFT-G (CI 2.79-6.41, p<0.001).	Seoul National University College of Medicine Research Fund.	QFT-G correlated significantly better with increased risk of infection across groups compared to TST using 10 and 15mm threshold (p<0.001).

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Pai, M., Gokhale, K., Joshi, R., Dogra, S., Kalantri, S., Mendiratta, D.K., Narang, P., Daley, C.L., Granich, R.M., Mazurek, G.H., Reingold, A.L., Riley, L.W., & Colford, J.M., jr. 2005. Ref ID: 1200	To estimate LTBI prevalence in HCWs using the TST and IGRA, to determine agreement between the tests and to compare their correlation with risk factors/ cross sectional/ India	Assessed **surrogate markers of exposure including:** year of training, years in health care profession, job category, direct contact with active TB (sufficient distance to allow conversation), training in internal medicine & household TB contact.	726 (1172 HCWs invited.) HCWs median age 22 yrs (range 18-61) 71% BCG scars, 48% medical/ nursing students, 2% attending physicians. 68% reported direct contact. Exclusion: <18 yrs, Pregnant, allergy to tuberculin, past active TB	QFT-GIT. **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using 1 TU. **Positive result:** ≥10mm (5 & 15 mm used for comparison)	**TST & QFT-GIT:** 41% TST+ (10mm), 23% TST+ (15mm), 40% QFT-GIT+. **Concordance:** TST 5mm (71.4%, k=0.45, CI 0.39-0.51), 10mm (81.4%, k=0.61, CI 0.56-0.67), 15mm (77.9%, k=0.51, CI 0.44-0.57). **Discordance:** TST+/QFT- (5mm 24.6%, 10mm 10%, 15mm 2.6%) & TST-/QFT+ (5mm 4%, 10mm 8.6%, 15mm 19.5%). **Risk factors for discordance:** From multivariate analysis- 2 covariates important but not significantly associated with discordance-job category (attending physicians/faculty vs. med students OR 3.9, CI 0.9-15.6) & increasing yrs in healthcare 2-5 yrs (OR 1.3, CI 0.6-2.8), 6-10 yrs (OR 2.01, CI 0.8-5.4), ≥10 yrs (OR 2.1, CI 0.6-7.5) compared to those with ≤1 yr.	**Risk factors for TST+:** age & no of yrs in HCP (≤1 yr adj OR 1.00, 6-10yrs OR 2.78, CI 1.23-6.25, >10 yrs OR 3.20, CI 1.08-9.45) sig in multivariate regression. **Risk factors for QGT+:** age, no of yrs in HCP (≤1 yr adj OR 1.00, 6-10 yrs OR 4.15, CI 1.81-9.50, > 10 yrs OR 3.34, CI 1.13-9.81) and job category (med student adj OR 1.00, orderlies OR 2.71, CI 1.25-5.86).	Fogarty AIDS International Training and Research Program.	Limited definition of length of exposure. Symptomatic participants or those positive by either test investigated for active TB.

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Mirtskhulava, V., Kempker, R., Shields, K.L., Leonard, M.K., Tsertvadze, T., del, R.C., Salakaia, A., & Blumberg, H.M. 2008. Ref ID: 472	To assess LTBI using both TST and QFT-3G diagnostic tests. To assess concordance between the two diagnostic tests/ Cross-sectional/ Georgia	**High occupational exposure:** HCWs direct contact with infectious TB patients (e.g. on daily basis). **Limited exposure:** HCWs in administration building and had no routine patient contact and those working at research centers. Questionnaire also assessed **community exposure to TB**.	281 (1231 HCWs eligible). HCWs working at National Centre for TB and Lung Disease (NTP) & affiliated centers. Data for 265-mean age 42 yrs, 86% female, median length of employment 8 yrs, 81% frequent daily contact with TB patients, 77.7% positive BCG history.	QFT-GIT. **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using 5 TU. **Positive result:** ≥10mm.	**TST & QFT-GIT:** 66.8% TST+, 60% QFT-G+. **Concordance: 5mm:** (73.2%, k=0.39, CI 0.29-0.50), **10mm**: (73.6%, k=0.43, CI 0.33-0.55) & **15mm**: (70.3%, k=0.40, CI 0.29-0.51). **Discordance: TST+/QFT-** (5mm 23.4%, 10mm 16.6%, 15mm 11.3%). **TST-/QFT+** (5mm 3.4%, 10mm 9.8%, 15mm 18.5%)	From multivariate analysis- **Risk factors for TST+:** employment as HCW >5 yrs (OR 5.09, CI 2.77-9.33) sig associated with increased risk of TST+. **Risk factors for QFT-GIT+:** Age>30yrs (OR 2.91, CI 1.32-6.43) & employment as HCW >5yrs (OR 2.26, CI 1.27-4.01).	National Institutes of Health/ Fogarty International Center.	Unknown history of BCG classified as negative history of BCG. Didn't collect info on possible multiple BCG vaccinations.

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Casas, I., Latorre, I., Esteve, M., Ruiz-Manzano, J., Rodriguez, D., Prat, C., Garcia-Olive, I., Lacoma, A., Ausina, V., & Dominguez, J. 2009. Ref ID: 3428	To investigate the performance of QFT-GIT and T-SPOT.TB and TST for detecting LTBI in HCWs, specifically looking at concordance between both test results and association with known risk factors for LTBI/ cross sectional/ Spain	Questionnaire included degree of occupational exposure to TB. **High exposure**: HCWs from wards with ≥5 contagious patients per year, those from microbiology lab and autopsy wards and from ED. **Medium exposure:** HCWs from wards with 2-4 active cases/yr. **Low exposure:** HCWs from wards with max 1 active TB case.	147 participants. Median age 43.3 yrs, 76.9% female, 15.6% BCG vaccination, 2% unknown BCG, 10.9% high exposure, 42.8% medium exposure, 46.3% low exposure. 64.4% had previous positive TST and not re-tested.	T-SPOT.TB (spots counted by automated plate reader). QFT-GIT (ELISA). **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) in those without previous documented result. **Positive result:** ≥5mm (≥15mm in BCG vaccinated).	**TST, QFT-GIT & T-SPOT results:** 71.1% TST+, 38.8% T-SPOT+, 29.3% QFT-GIT+. **Concordance: TST vs. T-SPOT:** in all participants (62.9%, k=0.32, SE=0.06), no BCG (64.9%, k=0.35, SE=0.07) & in BCG vaccinated (47.8%, k=0.17, SE=0.09). **TST vs. QFT-GIT:** in all (58.7%, k=0.29, SE=0.05), in no BCG (63.2%, k=0.35, SE=0.06) & in BCG vaccinated (34.7%, k=0.09, SE=0.05). **T-SPOT vs. QFT-GIT:** in all (86.0%, k=0.69, SE=0.06), in no BCG (86.3%, k=0.70, SE=0.07) & in BCG vaccinated (86.9%, k=0.65, SE=0.18)	From univariate analysis of all participants- **Risk factors for TST+:** age & years in HCP (OR 1.12, CI 1.06-1.18, p=0.0001). From multivariate analysis- **Risk factors for T-SPOT+:** High occupational exposure (adj OR 3.67, CI 1.07-12.59). **Risk factors for QFT-GIT+:** none sig-occupational exposure important but n.s (OR 2.62, CI 0.81-8.42).	Sociedad Espanola de Neumologia y Cirugua Toracica, SOCAP & FUCAP.	Unable to confirm accuracy of previous TST performed in other institutions but didn't repeat TST in those with previous positive result. Unsure if active TB ruled out. Author's also reported concordance for participants with and without previous positive TST (not reported in evidence table).

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Kobashi, Y., Obase, Y., Fukuda, M., Yoshida, K., Miyashita, N., Fuji, M., & Oka, M. 2007. Ref ID: 658	To evaluate the usefulness of QFT-2G for detecting LTBI in contact investigation of HCWs/ Japan	Contact score =infectivity (of index) x time (hrs) of exposure. 3 groups based on 'contact score': **mild, moderate, severe**. This score qualifies duration of exposure to index case as well as degree of infectivity of index case.	190 Medical staff members who had recent contact history with 4 index cases of TB. 46 males, 144 females. Average age 30.6 yrs. 2 had clinical symptoms at time of investigation. 78% BCG. Past history of positive TST+ (≥10mm) 43%. No one had used mask during contact. Exclusion: history of TB or prior exposure to patient with TB.	QFT-2G (ESAT-6, CFP-10). **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using equivalent of 3TU. **Positive result:** ≥30mm.	**TST & QFT-2G:** TST+ (22% mild contact score, 31% moderate, 33% severe). QFT-2G+ (0% mild, 4% moderate, 33% severe). Significantly more participants in severe group had QFT-2G+ compared to mild and moderate contacts (both $p<0.05$). **Follow-up:** Those with QFT-2G+ given anti TB drugs-no active TB in these 5 cases. 2/4 converted from positive to negative at 6 & 9 months respectively after starting treatment.	N/A	Not reported	Used high TST cut off. Analyses not adjusted for BCG. **Author's conclusion:** The QFt-2G test showed significant relationship with the contact score when compared with the TST.

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Topic, R.Z., Dodig, S., & Zoricic-Letoja, I. 2009. Ref ID: 226	To assess the occupational risk of LTBI in HCWs at a children's hospital in country of intermediate prevalence of TB and to assess the association of LTBI with concentration of immunoglobulins, CRP & hematological changes/ Croatia	**<u>Group A (high risk):</u>** HCWs from TB ward & were exposed directly to TB patients during office hours over period of >5yrs. **<u>Group B (low risk):</u>** Controls from non TB ward without direct exposure to TB patients	54 Clinically healthy medical staff. Mean age 44 yrs, 27 group A (26 females) & 27 in group B (25 females). All BCG vaccinated x2. <u>Exclusions</u>: history of TB.	QFT-GIT. **<u>Positive result:</u>** ≥0.35 IU/ml.	TST (Mantoux).	**<u>TST & QFT-GIT:</u>** TST+ (5mm 83%, 10mm 63%, 15mm 35%). 31% QFT-GIT+ (high risk 20.4%, low risk 11.1%). **<u>Calculated concordance:</u>** TST 5mm 48%, 10mm 61%, 15mm 74%. Highest concordance when TST≥15mm (74%, k=0.418, CI=0.155-0.680). **<u>Other results:</u>** size of TST induration sig higher in those with positive IGRA (p=0.0006). Proportion of QFT-GIT+ participants differed between TB wards (64% school children & adolescents, 15% infants & children, p=0.028)	N/A	Not reported.	Calculated concordance for 5mm & 10mm (not clearly reported in results). Reported all participants 'healthy' but unsure what investigations used to exclude active TB.

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Storla, D.G., Kristiansen, I., Oftung, F., Korsvold, G.E., Gaupset, M., Gran, G., Overby, A.K., Dyrhol-Riise, A.M., & Bjune, G.A. 2009. Ref ID: 154	To assess the risk for HCWs of acquiring M.tubercuolosis after exposure to patients with sputum smear positive pulmonary TB at 3 university hospitals/ Norway.	**Close contact:** stay in same room with smear positive TB patient in non-protected manner for min 1 hr**.** **Low exposure:** 1-8 cumulative hours of close contact. **High exposure:** >8 hours cumulative contact.	155 HCWs (48 controls). TB exposure HCWs from 3 university hospitals. Mean age 39 yrs, Controls had no known prior exposure & were non-clinical staff. Mean age 41 yrs. In total all but one had BCG scar. 10 participants from high endemic countries	T-SPOT.TB (spots counted manually using telescope).	TST (Mantoux) using 2TU. **Positive result:** an increase of ≥10mm or of ≥15mm if previous TST unknown	**TST & T-SPOT**: 27% TST+ (17% newly infected, 10% previous TST+). 3% T.SPOT+ (3 from newly infected & 2 from previous TST+: one was born in TB endemic country and one had previous treatment for TB). **Concordance:** TST+/T.SPOT+ (5/42, 12%) in both newly and previously infected participants. In only newly infected (3/42, 7%). **Exposure results:** High exposure (51), low exposure (104). No correlation between length of exposure and TST results, no correlation between T.SPOT+ and TST results. Only 1/3 infected had high exposure.	N/A	Financed by participating hospitals & Norwegian Institute of Public Health.	Not sure if those with previous TST+ were tested with TST again. No mention of X-ray results (how many normal vs. abnormal or indicative of active TB). No k values for concordance.

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Khana, P., Nikolayevskyy, V., Warburton, F., Dobson, E., & Drobniewski, F. 2009. Ref ID: 112.	To analyse the prevalence of LTBI in a new nursing entrant cohort at a large London hospital/ UK/	No specific active case as screening. Used **<u>surrogate markers of TB exposure:</u>** country of birth, employment history, BCG status, past TB diagnosis and past treatment for TB & previous direct contact with TB case.	171 nurses screened. 44.4% born in UK, 44.4% Africa, 2.3% India, 2.9% Caribbean. Median age 26 yrs, 82.5% BCG vaccinated, 11 reported direct contact with active case.	QFT-GIT	TST. **<u>Positive result:</u>** ≥15mm	**<u>TST & QFT-GIT:</u>** 16.2% (24/148) TST+ & 7.6% (13/171) QFT-GIT+. **<u>Calculated concordance:</u>** 87.8%. **<u>Discordance:</u>** 12.2% (3 TST-/QFT+, 15 TST+/QFT-). Those with TST-/QFT+ were all born in Africa & had BCG. 2 had direct contact with TB case & 1 received diagnosis of TB followed by treatment.	From univariate analysis-**<u>Risk factors for TST+:</u>** Birth in Africa (p=0.02), birth in high prevalence country (p=0.02) & >2 yrs in HCP (p=0.003). **<u>Risk factors for QFT-GIT+:</u>** Birth in Africa (p=0.02), birth in high prevalence country (p=0.009) & >2 yrs in HCP (p=0.003).	HPA Mycobacterium Reference Unit (UK).	Only 11 nurses reported direct contact with TB case. Multivariate data non-significant but data not shown in paper. Calculated concordance as not shown in paper-no k values reported.
Vinton, P., Mihrshahi, S., Johnson, P., Jenkin, G.A., Jolley, D., & Biggs, B.A. 2009. Ref ID: 147.	To evaluate the QFT-GIT by comparing it with TST as a method for screening HCWs for LTBI in hospitals in Australia/ 66.5% born in Australia.	No specific active case. **<u>Defined 5 groups with high risk for exposure to TB:</u>** 1) born in high prevalence countries. 2) History of travel to high prevalence country for >12 months. 3) Occupation includes high likelihood of TB contact. 4) High risk occupational contact (>10hrs contact time with TB patient). 5) Household contacts of active TB case.	481 hospital staff members. Median age 42 yrs, 89.6% female, 78% BCG vaccinated. 12.7% high risk occupational exposure, 9% household contact.	QFT-GIT	TST (Mantoux). **<u>Positive test:</u>** ≥10mm	**<u>TST & QFT-GIT:</u>** TST+ (33% 10mm, 20% 15mm, 10.7% 20mm). 6.7% QFT-GIT+. **<u>Concordance:</u> Overall:** TST 10mm (71%, k=0.16) TST 15mm (82%, k=0.23) & TST 20mm (89%, k=0.25). **Non-BCG:** 10mm (92%, k=-0.03), 15mm (97%, k=-0.02. **BCG vaccinated:** 10mm (66%, k=0.15), 15mm (79%, k=0.22). From multivariate analysis-**<u>Risk factors for discordance TST-/QFT+:</u>** High risk occupational exposure (OR 31.1, CI 1.30-746, p=0.034). **<u>Risk factors for TST+/QFT-:</u>** BCG (OR 7.11, CI 2.04-24.7, p=0.002) & occupation	From multivariate analysis-**<u>Risk factors for TST+:</u>** receipt of BCG (OR 1.04, CI1.01-1.06, p=0.003), occupation involving patient contact (OR 2.58, CI 1.23-5.40, p=0.012) & greater no yrs lived in high prevalence country. **<u>Risk factors for QFT-GIT+:</u>** birth in high prevalence country, no yrs lived in high prevalence country & high risk occupational contact (OR 5.60, CI 1.42-22.0, p=0.014).	Department of Human Services Victoria, National Health and Medical Council, Edgar Tattnall Memorial Trust.	Small numbers of those with occupational risk and household contact.

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						with patient contact (OR 3.96, CI 1.74-9.02, p=0.001).			
Girardi, E., Angeletti, C., Puro, V., Sorrentino, R., Magnavita, N., Vincenti, D., Carrara, S., Butera, O., Ciufoli, A.M., Squarcione, S., Ippolito, G., & Goletti, D. 2009. Ref ID: 3408.	To analyse data on HCWs in Italy who were tested by TST, in house ELISPOT, QFT-GIT & T-SPOT.TB and validate the use of these tests in this population by assessing association with occupational risk and to estimate their sensitivity and specificity by using latent class analysis/ cross sectional/ Italy	Wards routinely treated TB patients. **<u>Ward or service of employment:</u> High risk:** (>1 patient with TB cared for per year e.g. wards for infectious disease & respiratory disease) & **Low risk:** this not the case, e.g. pediatrics, internal medicine & epidemiology.	115 HCWs. Median age 41 yrs, BCG documented in 37.4%. 66.1% employed in wards with low risk of exposure to TB & 33.9% employed in wards with high risk of exposure to TB.	In-house ELISPOT (ESAT-6, CFP-10), T-SPOT.TB. QFT-GIT. **<u>Positive result:</u>** >0.35 IU/ml	TST (Mantoux). **<u>Positive result:</u>** ≥10mm.	**<u>TST & IGRA:</u>** 53% TST+, 36.5% T-SPOT+, 25.2% QFT-GIT+. Estimated sensitivity and specificity using latent class analysis. **<u>Sensitivity:</u>** TST (99.9%), T-SPOT (96.7%, CI 69.3-99.7), QFT-GIT (76.3%, CI 55.9-89.1). **<u>Specificity:</u>** TST (64.2%, CI 53.0-74.1), T-SPOT (85.6%, CI 75.3-92.0), QFT-GIT (93.6%, CI 85.4-97.3)	From multivariate analyses-**<u>Risk factors for TST+:</u>** BCG (OR 4.32, CI 1.56-11.95), age & physician lower risk of TST+ (OR 0.20, CI 0.04-0.92). **<u>Risk factors for T-SPOT+:</u>** worked in high risk TB services (OR 3.10, CI 1.28-7.48) & age. **<u>Risk factors for QFT-GIT+:</u>** age, physicians lower risk (OR 0.07, CI 0.01-0.70) compared to nurse assistants.	Not reported.	Active TB not excluded with investigations but there is some reference to the population as 'healthy' in discussion. Paper reports estimated sensitivity & specificity values for non-BCG group (not in evidence table). Latent class analysis used.

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Alvarez-Leon, E.E., Espinosa_Vega, E., Santana-Rodriguez, E., Molina-Cabrillana, J.M., Perez-Arellano, J.L., Caminero, J.A., & Serrano-Aguilar, P. 2009. Ref ID: 23	To compare how the TST and IGRA (QFT-G In-Tube) tests work in Spanish HCWs in order to improve procedures for the detection of LTBI/ Cross sectional/ Spain	Hospital departments classified as **high risk:** any HCW received diagnosis of TB in previous 10 yrs. **Intermediate risk:** >5 TB patients treated during previous yr. **Low risk:** 1-5 TB patients treated in previous yr. **Very low risk:** rest of departments. Also gained info on years working in direct patient contact, direct contact with TB cases, household contact with TB & high risk procedures in active TB cases.	134 HCWs working at Spanish hospital (50-60 TB patients admitted annually). 101 (75.4%) female, mean age=33.4 years. 57 (42.5%) HCWs had direct contact with TB patients and 28 (49.1%) of these reported respiratory protection not always used. 47 (35.1%) had BCG.	QFT-GIT.	TST **Positive result:** (≥5mm in non-BCG, ≥15mm with BCG).	**TST & QFT-GIT:** 8.96% TST+ & 5.97% QFT-GIT+. **Concordance:** **All HCWs:** (positive 59%, negative 97%, overall 94%, k=0.56, CI 0.27-0.85). **Non-BCG:** (positive 57%, negative 96%, overall 93%, k=0.53, CI 0.20-0.86). **BCG vaccinated:** (positive 67%, negative 99%, overall 98%, k=0.65, CI 0.03-1.00). **Discordance:** TST+/QFT- (3% all HCWs, 5% non-BCG, 0 BCG vaccinated). TST-/QFT+ (2% all HCWs, 2% non-BCG, 3% BCG vaccinated.)	From multivariate analysis **Risk factors for TST+:** working as an orderly (OR 21.5, CI 2-234, p<0.05). **Risk factors for QFT-GIT+:** age (OR 1.20 for every increased year of age p<.05).	Fondo de Investigaciones Sanitarias (FIS) & Evaluation of Sanitary Technologies (ETES).	2 step TST used.CXR to exclude active TB in HCWs with positive tests.
Hesseling, A.C., Mandalakas, A.M., Kirchner, H.L., Chegou, N.N., Marais, B.J., Stanley, K., Zhu, X., Black, G., Beyers, N., & Walzl, G. 2009. Ref ID: 15	To assess the agreement of two commercially available IGRAs in relation to TST and to investigate the impact of exposure and age on TST and IGRA responses to detect infection/ Cross sectional/ South Africa	Modified M tuberculosis contact score. **Low exposure:** < 4. **High exposure:** ≥4.	82 (29 children, 53 adults) household contacts of Pulmonary TB index case. Overall Mean age 22.8, 75.6% BCG vaccination. Mean contact score 6.4 & 59.8% high exposure.	T-SPOT.TB & QFT-G	TST (Mantoux). **Positive result** ≥10mm	**TST, QFT-G & T-SPOT:** **All contacts** (69.2% TST+, 40.9% QFT+, 75% T-SPOT+). **Adults** (78% TST+, 39.6% QFT-G+, 66% T-SPOT +. **Concordance:** **All contacts:** TST vs. T-SPOT (65.8%, k=0.12, CI -0.11-0.36), TST vs. QFT-G (70.6%, k=0.45, CI 0.28-0.62), T-SPOT vs. QFT-G (31.9%, k=0.38, CI 0.21-0.55). **Adults:** TST vs. T-SPOT (76%, k=0.38, CI 0.10-0.66), TST vs. QFT-G (60%, k=0.34, CI 0.16-0.52), T-SPOT vs. QFT-G (74%, k=0.50, CI 0.31-0.70).	From logistic regression contact score ≥4 associated with positive TST (adj OR 3.83, CI 1.05-14.03), positive T-SPOT (adj OR 38.40, CI 7.59-616.11) & positive QFT-G (adj OR 14.94, CI 4.02-55.58).	South African National Research Foundation & Bill and Melinda Gates Foundation through Grand Challenges in Global Health grant & Norwegian Centre or Cooperation in Higher Education.	Information extracted for overall results & adults only. Discordant results not in evidence table. 2 children excluded based on abnormal CXR-infer CXR done for all participants. No details of normal CXR given.

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Pai, M., Joshi, R., Dogra, S., Zwerling, A.A., Gajalakshmi, D., Goswami, K., Reddy, M.V., Kalantri, A., Hill, P.C., Menzies, D., & Hopewell, P.c. 2009. Ref ID: 250	To determine the incidence of TST and QFT conversions and to assess whether different tests and variations in definitions are likely to produce different rates of conversion and estimated rates of QFT reversions/ India	No specific definitions given. Results include **sleeping proximity** to index case (same house, different house to index), **relationship to index** & **average amount of time spent with index** case per day (< 3hrs, 3-6hrs, >6hrs).	250 household contacts of smear positive index case (culture and HIV results not available for most patients as tests not routinely performed). 57% female, median age 25. 60% BCG scar present. At baseline 80% slept in same house as index, 20% in different house. 46% spent < 3hrs with index per day, 41% 3-6 hrs & 13% >6hrs. Participants followed up at 12 months.	QFT-GIT (ELISA) **positive result**: ≥0.35 IU/ml. Defined **uncertainty zone**: (0.20-0.50). <0.2 IU/ml= definitely negative, >0.5 IU/ml= definitely positive. **Conversion rates:** calculated for those TST-/QFT- or TST+/QFT- at baseline.	TST (Mantoux). **Positive result:** ≥10mm	**Baseline TST & QFT-GIT:** 46% TST+, 54% QFT-GIT+. **Baseline concordance:** 82%, k=0.63. **Follow-up conversion:** estimated rates of conversion using 4 definitions (range 11.8%-21.2%). **Concordance between TST & QFT-GIT conversions:** Range from 83%-93%. Highest concordance (93%, k=0.53, CI 0.20-0.86) with TST increase of 10mm & most stringent QFT definition. **QFT-GIT reversion:** 6.4% of participants QFT-GIT+ at baseline reverted to QGT-GIT-. No new cases of active TB at follow-up.	N/A	Canadian Institutes of Health Research	Unknown immunosupression. Active TB not excluded. Used 2 step TST 'Uncertainty zone' chosen arbitrarily (those in this range considered to have uncertain status). No separate analyses for adults and children. No analysis based on length of exposure.
Adetifa, I.M., Lugos, M.D., Hammond, A., Jeffries, D., Donkor, S., Adegbola, R.A., & Hill, P.C. 2007. Ref ID: 577	To compare the diagnostic performance of an ex vivo ELISPOT and the QFT-GIT for the diagnosis of LTBI and active TB disease in The Gambia/ West Africa	Contacts categorised by **where they slept in relation to an active case:** in the same bedroom, a different bedroom in the same house or in a different house in the same compound.	320 (194 household contacts, 80 active TB cases). Data for 178 contacts. Same room (mean age 34.3 yrs, 51.2% female, 25% BCG scar & 8.3% uncertain BCG). Separate room (mean age 30 yrs, 66.9% female, 53.7% BCG scar &2.7% uncertain BCG, 2.6% HIV pos). Separate house (mean age 29.7 yrs, 52.6% female, 44.4% BCG scar).	QFT-GIT. **Positive test:** ≥0.35 IU/ml. Ex-vivo ELISPOT assay (ESAT-6, CFP-10)	PPD skin test.	**Concordance: Overall:** between TST & QFT-GIT (71.1%, k=0.43, CI 0.29-0.57) there was significant discordance (p=0.007) 18.8% TST+/QFT-GIT-, 36.2% TST-/QFT-GIT+. **Non-BCG:** (68.2%, k=0.37, CI 0.17-0.58, discordance p=0.02). **BCG vaccinated:** (76.5%, k=0.52, CI 0.31-0.73, discordance p=0.11).	**Risk factors for QFT-GIT+:** in those sleeping in same room (adj OR 3.8, CI 1.2-12.5). **Risk factors for TST+:** in those sleeping in same room (adj OR 4.8, CI 1.3-17.1)	Medical Research Council (UK).	Results for in house IGRA not reported in evidence table. CXR only given to those with positive TST. Those with symptoms underwent clinical assessment. 6/187 CXR had radiological abnormalities but were asymptomatic. One had previous TB treatment & 2 were diagnosed with active TB. 3 were HIV pos. Unsure if these were included in analysis.

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Brodie, D., Lederer, D.J., Gallardo, J.S., Trivedi, S.H., Burzynski, J.N., & Schluger, N.W. 2008. Ref ID: 479	To compare the use of T-SPOT.TB test with TST in detecting LTBI in high risk individuals as well as discriminating LTBI from BCG vaccination/ USA	**<u>Close contacts</u>**: ≥8 hrs of contact with active TB patient per week. **<u>Other than close contact:</u>** contact <8 hrs per week. **<u>Non-contacts:</u>** not contacts of patients with active TB.	96 (123 enrolled but 27 excluded. 58% close contacts (mean age 33 yrs, 70% male, 68% BCG, 48% HIV status unknown). 42% controls-includes 3 'other than close contact' (mean age 34 yrs, 50% male, 75% BCG, 35% HIV status unknown). Close contacts: 73% foreign born. Controls: 80% foreign born.	T-SPOT.TB (spots counted manually & with automated plate reader).	TST (Mantoux) using 5 TU.	**<u>TST & T-SPOT:</u>** TST+ (63% close contacts, 78% control) T-SPOT+ (45% close contacts, 25% controls). **<u>Concordance:</u> Overall:** (64%, k=0.33, CI 0.19-0.48), **BCG vaccinated:** (56%, k=0.22, CI 0.06-0.37). **Non-BCG:** (82%, k=0.64, CI 0.38-0.91). **<u>Sensitivity:</u>** (all contacts) T-SPOT (45%, CI 31-59), TST (62%, CI 49-75). **<u>Specificity:</u>** (all contacts) T-SPOT (75%, CI 59-87), TST (23% (CI 11-38).	**<u>Risk factors for TST+:</u>** close contacts with BCG (adj OR 0.1, CI 0.001-0.5, p=0.01) & non-BCG (adj OR 9.1, CI 1.2-67, p=0.03). **<u>Risk factors for T-SPOT+:</u>** close contacts (adj OR 2.9, CI 1.1-7.4, p=0.03). **<u>PPV:</u>** (all contacts) T-SPOT (71%, CI 54-85), TST (53%, CI 40-65). **<u>NPV:</u>** (all contacts) T-SPOT (49%, CI 36-62), TST (30%, CI 15-49). **<u>Diagnostic accuracy:</u>** (all contacts) T-SPOT (57%, CI 47-67) & TST (46%, CI 36-56).	Stony Wold Herbert Fund Inc, NIH, National Heart, Lung & Blood Institute, Oxford Immunotec Ltd.	Included 3 'other than close contacts' with control group. May have included children. No mention of excluding active TB. Sensitivity, specificity, PPV & NPV values also reported for BCG and non-BCG groups but not reported in evidence table.
O'Neal, S., Hedburg, K., Markum, A., & Schafer, S. 2009. Ref ID: 137	To report a worksite TB contact investigation in which TST and QFT-G were used in same people to compare the results of the two tests/ USA (Oregon).	No specific definition given for length of exposure-all contacts were co-workers of active case of cavitary pulmonary TB. Provide info on **work site**-index case worked in cutting area (adjacent to packaging/ boxing areas).	74 (127 employees invited). 61 employees of active case received both TST and QFT-G & 13 received TST alone. 46 males, 15 females, US born (25), Mexico (28), Asia (5), Other (3). 14 had BCG, 29 without BCG, 18 unknown BCG. 34 worked in cutting (same as index), packaging (6), boxing (4), Other (17).	QFT-G (ESAT-6, CFP-10). **<u>Positive result:</u>** ≥0.35 IU/ml.	TST. **<u>Positive result</u>**: ≥5mm.	**<u>TST & QFT-G:</u>** 57% TST+, 28% QGT-G+. **<u>Discordance:</u>** at TST ≥5mm discordance 30% (18), proportion agreement 69.5%, k= 41.9. TST+ (15mm)/ QFT-G- occurred in 11 (61%) discordant cases; one had QFT-G+/TST-. 40.7% with robust TST (≥15mm) had QFT-G-. **<u>Risk factors of discordance:</u>** not correlated with age, sex, BCG or worksite (logistic regression data not shown in paper).	Calc NPV of QFT-G at varying estimates of infection prevalence using pooled estimates of 78% sensitivity, 96% specificity. NPV decreases as prevalence increases (at 57% prevalence, NPV=77%).	Not reported.	No exclusion of active TB.

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Porsa, E., Cheng, L., Seale, M.M., Delclos, G.L., Ma, X., Reich, R., Musser, J.M., & Graviss, E.A. 2006. Ref ID: 1070	To evaluate the performance of IGRA compared to TST for TB screening in a moderate-risk population in the US/ cross-sectional/ USA.	No specific active case or definition of length of contact. Info also gained relating to **known TB contact, prior incarceration, lived in shelter** & whether participants were **intravenous drug user.**	409 (533 invited) adult inmates in county jail. 72.1% male, mean age 31 yrs, 84.1% prior incarceration, 12.5% had prior TB contact, 20.3% lived in shelter, 13% intravenous drug user 90.5% US born. Exclusion: known history of LTBI (prior pos TST, current active TB, use of immunosuppressive drugs. All tested for HIV.	QFT-G (ELISA).	TST (5TU). **Positive result:** ≥10mm.	**Concordance:** 90% (CI 87.1-93.0), k=0.25 (CI 0.10-0.41). TST+/QFT+ (2.2%), TST-/QFT- (87.8%). **Discordance:** participants were more likely to be TST+/QFT-G- (6.8%) than TST-/QFT-G+ (3.2%). From multivariate regression- **Risk factors for concordance:** African-American ethnicity (adj OR 0.29, CI 0.11-0.77), foreign birth (OR 0.23, CI 0.07-0.80), prior incarceration (OR 0.06, CI 0.01-0.50). These factors more likely to be associated with discordance.	From multivariate analysis- **Risk factors for TST+:** older age (OR 1.04, CI 1.01-1.08), African-American ethnicity (OR 4.97, CI 1.58-15.68), foreign birth (OR 20.20, CI 4.21-97.02) & prior incarceration (OR 6.19, CI 1.48-25.95). **Risk factors for QFT-G+:** African-American ethnicity (OR 5.58, CI 1.16-26.74).	Health Resources and Services Administration Bureau of Health Professions & E.A.G & E.P have received research support from Oxford Immunotec Ltd.	Active TB not excluded.
Kik, S.V., Franken, W.P., Arend, S.M., Mensen, M., Cobelens, F.G., Kamphorst, M., van Dissel, J.T., Borgdorff, M.W., & Verver, S. 2009. Ref ID: 60	To assess whether QFT-GIT, T-SPOT.TB and TST responses were influenced by remote exposure to TB among immigrants with recent contact with sputum smear case of TB/ Netherlands	**Close contacts:** frequent (min 3 times/week) and/or intensive contact (contact within small closed space or physically nearby) with index case. Recent contact also separated into **household contact, non-household contact, unknown contact** during analysis.	433 (715 eligible) immigrant close contacts of index case, aged ≥16 yrs, born in high TB endemic country. Also included second generation immigrants if BCG vaccinated & at least one of parents born in TB endemic country.	QFT-GIT. **Positive test:** ≥0.35 IU/ml. T-SPOT.TB (spots counted using magnifying glass).	TST (2TU). **Positive result:** ≥5mm. If TST negative repeated 3 months later.	**TST, QFT-GIT & T-SPOT:** (322/433, 74.4%) TST+, 53.9% (152/282) QFT-GIT+ & 59.6% T-SPOT+. **Concordance: QFT-GIT & TST:** 10mm (62.1%, k=0.198) & 15mm (71.3%, k=0.418). **T-SPOT.TB & TST:** 10mm (64.9%, k=0.190) & 15mm (69.9%, k=0.379). **QFT-GIT & T-SPOT:** 84.4%, k=0.683.	From multivariate analysis- **Risk factors for TST+:** TST results did not differ between household contacts and non-contacts (OR 0.96, CI 0.48-1.92, p=0.9). After adj: origins from sub-Saharan Africa (adj OR=6.00, CI=1.32-27.24, p=0.018). **Risk factors for QFT-GIT+ & T-SPOT+:** QFT-GIT (adj OR=2.97, CI=1.40-6.27, p=0.001) & T.SPOT.TB (adj OR=2.40, CI=1.13-5.10, p<0.001).	The Netherlands organisation for Health Research and Development.	IGRA only done with positive TST. Not sure if 2 step TST approach was used. Adjusted OR's for age, sex & degree of contact. **Author's conclusion:** When IGRAs are used to determine LTBI infection in foreign born individuals, positive findings not only relate to recent TB infection, but also reflect prior TB exposure in their country of origin.

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Zellweger, J.P., Zellweger, A., Ansermet, S., de, S.B., & Wrighton-Smith, P. 2005. Ref ID: 1101	To investigate how well T-SPOT.TB and TST results correlate with level of exposure to the index case and to examine whether prior BCG vaccination undermines the utility of either test in determining who should received treatment/ Switzerland/ 69.2% born in Switzerland.	**Duration of exposure to index case:** <3hrs, 3-8hrs, >8hrs. **Intensity of exposure:** Close exposure (>1hr face-to-face in the same room at <2m distance) or not close. Results classified into: **High exposure:** any participant with exposure of long duration (>8hrs) or close exposure. **Low exposure:** all combinations of exposure.	92 (143 invited) residents and staff at institution for alcoholic patients in Switzerland. 55% residents & 45% staff. 86% BCG vaccinated. Results of both tests available for 91 participants.	T-SPOT.TB	TST (Mantoux). **Positive result:** >10mm.	**TST & T-SPOT:** 44% TST+ & 15% T-SPOT+. **Concordance**: 65% concordance (59/91), level of agreement low (k=0.232, p=0.0021). 6/11 with positive concordance was initially TST+. 5 initially T-SPOT+/TST- but received 2nd TST month later. **Discordance:** TST+/T-SPOT.TB- (29/91, 31.9%), TST-/T-SPOT.TB+ (3/91, 3.3%) with non-sig results for T-SPOT.TB.	**Risk factors for TST+:** Age (OR 2.66, CI 1.02-6.92, p=0.04) & associated with BCG (p=0.0003). Being in high exposure group n.s (OR 1.85, CI 0.78-4.36, p=0.16). **Risk factors for T.SPOT+:** Being in high exposure group (OR 5.00, CI 1.05-23.86, p=0.03). **Risk of infection (defined by TST+):** 42.9% (< 3hrs exposure), 28.6% (3-8hrs), 64.3% (>8hrs). 50% (with close contact) & 37.2% (no close contact). **Risk of infection (T-SPOT+):** 7.1% (<3hrs), 8.6% (3-8hrs) & 32.1% (>8hrs). 20.8% (close contact), 9.3% (no close contact).	Vaud County Section of the Swiss Lung Association.	No mention of whether everyone with initial TST- given further TST. No mention of excluding active TB.

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Arend, S.M., Thijsen, S.F., Leyten, E.M., Bouwman, J.J., Franken, W.P., Koster, B.F., Cobelens, F.G., van Houte, A.J., & Bossink, A.W. 2007. Ref ID: 808	To compare TST, QFT-GIT & T-SPOT.TB in BCG unvaccinated contacts and correlate results with measures of recent exposure/ The Netherlands/	Participants visited the supermarket at least once monthly. Results include: **duration of exposure (months):** 0-3, 4-6, 7-9, ≥10. **Frequency of shopping:** ≤1x/mo, >1x/mo and <1x/wk, 1x/wk, >1x/wk. **Average shopping time (min):** 1-15, 16-30, 31-60, >60. **Cumulative exposure time (min):** 1-300, 301-600, 601-1200, 1201-2400, >2400.	785 from contact investigation of supermarket employee. All unvaccinated.	QFT-GIT & T-SPOT.TB	TST (Mantoux)	**TST, QFT-GIT & T-SPOT:** 10.3% QFT-GIT+, 18.7% T-SPOT+. **Concordance**: **TST & QFT-GIT** at 5mm (67.3%, k=0.26), at 10mm (75.4%, k=0.33) & 15mm (86.5%, k=0.49). **TST & T-SPOT** at 5mm (69.7%, k=0.34), 10mm (75%, k=0.37) & 15mm (81.8%, k=0.42). **QFT-GIT & T-SPOT** (89.6%, k=0.59). **Sensitivity: QFT-GIT** (5mm=23.8%, 10mm=28.5%, 15mm=42.2%). **T-SPOT** (5mm= 36.7%, 10mm= 40.6%, 15mm= 51.3%). **Specificity: QFT-GIT** (5mm=99.8%, 10mm=98.7%, 15mm=97.9%). **T-SPOT** (5mm= 95.1%, 10mm=92.3%, 15mm= 89.7%).	From multivariate analysis-**Risk factors for TST+:** Age is positive factor. Not associated with any measure of exposure. **Risk factors for IGRA+: QFT-GIT+** associated with cumulative shopping time (adj OR 1.48, CI 1.19-1.84, p<0.001). **T-SPOT+** also associated with cumulative shopping time (adj OR 1.30, CI 1.10-1.53, p=0.002).	Mr Willem Bakhuys Roozeboom Foundation, KNCV Tuberculosis Foundation, The Hague, Research Fund of Diakonessehuis	Contact tracing in supermarket. Active TB not excluded.

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Diel, R., Loddenkemper, R., Meywald-Walter, K., Gottschalk, R., & Nienhaus, A. 2009. Ref ID: 205	To assess the use of T-SPOT.TB head to head with QFT in prospective community based study of contacts with recent exposure to infectious TB/ Hamburg	**<u>Close contacts:</u>** people exposed to culture positive TB during their infectious stage. Results separated into **<u>contact type</u>**: household/intimate contact, coworkers, pupils/teachers, HCWs, non-intimate friends, co-patients in hospital, members of sports clubs. **<u>Close contact to coughing index & contact time:</u>** ≤8hrs, 8-40hrs, >40hrs.	1989 (no history of prior TST). 812 TST+ contacts had complete results available for QFT and T-SPOT.TB. 53.3% male, 55.8% with BCG, 51.7% foreign born. 39.5% household/intimate contact, 26.5% close contact to coughing index, mean cumulative exposure time 138.6 hrs.	QFT-GIT & T-SPOT.TB	TST (Mantoux). **<u>Positive result:</u>** >5mm.	**<u>TST, QFT-GIT & T-SPOT:</u>** 40.8% (812/1989) TST+, 30.2% QFT-GIT+ & 28.7% T-SPOT+. **<u>Concordance:</u> QFT-GIT & T-SPOT** (93.9%, k=0.852, CI 0.78-0.92). Assuming positivity to both IGRA's as true infection, **sensitivity** of TST at 10mm= 72% and at 15mm= 39.7%.	From multivariate analysis- **<u>Risk factors for IGRA+:</u>** increasing age, foreign origin, AFB smear positivity, source case coughing & exposure time 8-40hrs for QFT-GIT (OR 1.8, CI 1.0-3.2) & >40hrs for QFT-GIT+ (OR 5.7, CI 3.5-9.3, p<0.001) & for T-SPOT+ (OR 4.9, CI 3.0-8.0).	Not reported.	See online supplement for details of definition of contacts. Only those with TST+ had IGRA tests. No mention of excluding active TB. Sample includes some children but limited separate analyses based on age.
Diel, R., Loddenkemper, R., Meywald-Walter, K., Niemann, S., 7 Nienhaus, A. 2008. Ref ID: none	To compare the QFT-GIT with TST in recently exposed close contacts of active TB cases with respect to their development of TB disease within 2 years/ Germany	Only close contacts included. **<u>Close contact:</u>** aggregate exposure time, before diagnosis of respective active case of min of 40 hrs in closed rooms. **<u>Exposure time:</u>** 40-<60 hrs, 60-<100 hrs, 100-<200 hrs & 200+ hrs. **<u>Excluded:</u>** contacts with unclear/occasional and contact <40 hrs during period of infectiousness.	601 contacts included with complete results for TST & QFT. 50.7% female, 46% BCG vaccinated, 28% foreign born. Mean age 27.7 yrs, 216 household/ intimate contacts, 165 colleagues of source, 155 pupils/ teachers, 50 HCWs & 21 sports club members. 53 children <15 yrs (18 preschool age).	QFT-GIT	TST (Mantoux). **<u>Positive result:</u>** ≥5mm.	**<u>TST & QFT-GIT:</u>** 40.4% TST+ & 11% QFT-GIT+. **<u>Concordance:</u> All participants** (69.2%, k=0.276, CI 0.22-0.33), **BCG vaccinated** (44.2%, k=0.119,) & **non-BCG** (90.7%, k=0.616). **<u>Follow-up:</u>** Those with QFT+ offered prevention treatment. 6 active cases found. 6/41 (14.6%) of QFT-GIT+ participants who refused treatment developed active TB by 09/2007. 5/219 (2.3%) participants with TST >5mm without treatment developed active TB. Significantly lower rate than that found for QFT-GIT (p<0.003). Only one case had BCG (relative	From multiple regression- **<u>Risk factors for TST+:</u>** At 10mm BCG (adj OR 4.6, CI 2.8-7.6), age, origin outside Germany (OR 5.2, CI 3.2-8.4) & exposure time (OR 1.001, CI 1.00-1.003, p=0.03) all sig associated. **<u>Risk factors for QFT-GIT+:</u>** Age (OR 1.04, CI 1.016-1.064), origin (OR 2.28, CI 1.3-3.9) & cumulative exposure time (OR 1.002, CI 1.001-1.003).	Not reported.	Follow-up at 2 years. Adults and children included. No mention of excluding active TB at start of study.

<u>Key:</u> CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

						risk reduction 76.4% p=0.15, n.s).			
Machado, a., Jr., Emodi, K., Takenami, I., Finkmoore, B.C., Barbosa, T., Carvalho, J., Cavalcanti, L., Santos, G., Tavares, M., Mota, M., Barreto, F., Reis, M.G., Arruda, S., & Riley, L.W. 2009. Ref ID: 161	To analyse factors associated with discordance between TST and IGRA results among household contacts of patients with Pulmonary TB/ Cross sectional/ Brazil	**Household contact**: resided in same household & spent min 100 hours with index case during symptomatic period. Also collected data on if contact **sleeps in same room** as index case & **length of exposure** as ≤1 month & >1 month.	301 household contacts of index case in public chest disease hospital. BCG scar in 228/301 (76%)- median age for these 22.0 years. Median age for those without BCG scar =33.5 years. Female 181 (60%).	QFT-GIT **Positive result:** ≥0.35 international units	TST. **Positive result:** ≥10mm.	**TST & QFT-GIT:** 145/261 (55.6%) TST+ & 27/298 (43.1%) QFT-GIT+. **Concordance:** TST+/QFT+ (39.2%), TST-/QFT- (36.8%). Agreement =76%, k= 0.53, CI 0.43-0.63. **Discordance:** 72% TST+/IGRA- & 28% TST-/IGRA+.	From multiple regression- **Risk factors for discordance:** Compared to negative concordant group, CXR showing old scar (adj OR 6.8, CI 1.3-35, p=0.02) was significantly associated with TST+/QFT- discordance. Also less likely for TST-/QFT+ to be associated with index case with CXR of cavitary disease (OR 0.2, CI 0.05-0.9, p=0.04) and reported length of exposure >1 month (OR 7.2, CI 1.7-29.3, p<0.01).	Fogarty International Center, National Institutes of Health	CXR used to exclude active TB.

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Kik et al 2009	To determine the positive predictive value for progression to TB of two IGRA in immigrant contacts/ Longitudinal study/ Netherlands	**Incident cases:** contacts diagnosed with TB at least 3 months after diagnosis of index case. **Co-prevalent case:** contacts diagnosed within first 3 months-these were excluded from analysis. No specific distinctions between levels of exposure.	339 close contacts of active TB who were ≥16 years old and were born in TB endemic country. Diagnosis of active disease based on CXR, symptoms, smear and/or culture results. Contacts with TST ≥5mm (or positive past TST) followed up at 6, 12, 18 and 24 months-when contacts did not show up for follow-up after several initiations, they were interviewed by phone where possible.	QFT-GIT **Positive result:** ≥0.35 IU/ml & T-SPOT (as defined by manufacturers criteria)	TST. **Positive result:** ≥5mm	Sensitivity and specificity values calculated using progression to active TB. Follow-up until 1st August 2008 **Sensitivity:** 100% for TST ≥10mm, 88% for TST ≥15mm, 63% for QFT-GIT & 75% for T-SPOT. **Specificity:** 15%, 44%, 46% & 40% respectively. Secondary analysis for progression to disease within first 12 months before August 1st 2008. **Sensitivity:** 100%, 86%, 50% & 67% respectively. **Specificity:** 15%, 43%, 45% & 39% respectively.	339 contacts followed up for median follow-up of 1.83 year. Follow-up until 1st August 2008. **PPV for progression to active TB:** 3.1% for TST ≥10mm, 3.8% for TST ≥15mm, 2.8% for QFT-GIT & 3.3% for T-SPOT. **NPV:** 100%, 99.3%, 98% & 98.3% respectively. Secondary analysis for progression to disease within first 12 months before August 1st 2008. **PPV:** 2.5%, 3.3%, 1.7% & 2.2% respectively. **NPV:** 100%, 99.3%, 98% & 98.3% respectively.	Netherlands organization for health research and development (ZonMw).	All contacts had CXR to exclude active TB.

Evidence Tables: Contacts

Evidence Tables: Immunocompromised

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Balcells, M.E., Perez, C.M., Chanqueo, L., Lasso, M.,	Observational study of individuals from Chile.HIV Positive	TST (Mantoux method. 2TU	IGRA(QFT)	Correlation between TST and IGRA results in HIV positive individuals | | IGRA+ | IGRA- | TOT |	Not determined	Supported by a grant from the	Authors observed that, multivariate analysis confirmed

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Villanueva, M., Espinoza, M., Villarroel, L., & Garcia, P. 2008 (294)	patients Mean CD4 Count 393/µl (range 100-977) 116 mean age 38.8years (Range 21-71). Older age, history of previous tb disease, previous known exposure to a case of active pulmonary tb, healthcare workers or individuals working with homeless people, residence in prison,	dose of PPD RT23)		TST+ 9 2 11 TST- 8 90 98 17 92 109 They also performed univariate analysis for a positive LTBI test depending on several factors TB risk factors.		Department of the Pontificia University of Chile. IGRA were supplied at reduced price by Cellestis	that past TB was independently associated with a positive TST (p=0.016) as well as a higher CD4 count (p=0.044). For IGRA past tb was the only factors significantly associated with a positive result. (p=0.041)

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Luetkemeyer, A.F., Charlebois, E.D., Flores, L.L., Bangsberg, D.R., Deeks, S.G., Martin, J.N., & Havlir, D.V. 2007 (797)	294 HIV infected patients sampled from two cohorts based in the United States. 55% of participants had lived or worked in homeless shelter, prison, hospital, or a drug rehab unit or were born in a country with high TB incidence, or had had contact with an active tb case.	TST (5TU PPD)	IGRA (QFT)	196 participants with both TST and IGRA results valid had the following overall result. (see tables below)	Not determined	Not recorded	Authors noted that until further data are available on the implication of discordant TST and IGRA results, a strategy of simultaneous TST and QFT testing where feasible would maximize potential LTBI diagnoses in HIV infected patients

	TST			
IG		+	-	TOT
	+	8	11	19
	-	10	167	177
	TOT	18	178	196

Results were also stratified by CD4 count.

CD4+	STRATA (cells/mm3)			
	<100	100-350	>350	tot
IG+	0	6	19	25
IG-	26	101	127	254
IG(I)	5	4	6	15
TOT	31	111	152	294
TST+	0	7	12	19
TST-	21	76	89	186
TOT	21	83	101	205

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Talati, N.J., Seybold, U., Humphrey, B., Aina, A., Tapia, J., Weinfurter, P., Albalak, R., & Blumberg, H.M. 2009 (253)	336 HIV positive patients of mean age of 42 years. Patients had a past med history of LTBI, diabetes mellitus, chronic renal insufficiency, history of malignancy, anytime smoker and Intravenous drug use. Study done in the US.	TST 0.1ml (5TU) of Siebert PPD	IGRA (TSPOT.TB AND QFT)	Reported a CD4 count of < 200 as associated with an indeterminate result for both IGRAs OR= 3.6(1.9,6.8)	Not determined	Partly supported by Centers for Disease Control and Prevention (CDC)	Authors commented that given the results of the study and the limited data currently available it was unclear if IGRAs can be used alone for the diagnosis of LTBI in HIV infected individuals

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<tr><td>Jones, S., de, G.D., Wallach, F.R., Gurtman, A.C., Shi, Q., & Sacks, H. 2007 (621)</td><td>207 HIV infected individuals with a mean age of 47 years. 52% were male. They were also stratified according to CD4 count <100, 19; 101-199, 24; 200-499, 88; >500, 70. Study conducted in Mount Sinai medical centre in New York. United States</td><td>TST 0.1ml (5TU PPD)</td><td>IGRA (QFT)</td><td>Overall concordance between IGRA and TST results
<table>
<tr><td></td><td colspan="4">IGRA</td></tr>
<tr><td></td><td>Ind</td><td>-</td><td>+</td><td>Tot</td></tr>
<tr><td>TST-</td><td>10</td><td>172</td><td>6</td><td>188</td></tr>
<tr><td>TST+</td><td>0</td><td>8</td><td>5</td><td>13</td></tr>
<tr><td></td><td>10</td><td>180</td><td>11</td><td>201</td></tr>
</table>

Ind = Indeterminate</td><td>Not determined</td><td>QuantiFERON kits donated by Cellestis</td><td>IGRA is able to distinguish between indeterminate tests and those that are truly negative. In contrast, a negative TST does not differentiate between individuals who are anergic and those who might have a truly negative TST.</td></tr>
</table>

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<tr><td>Mandalakas, A.M., Hesseling, A.C., Chegou, N.N., Kirchner, H.L., Zhu, X., Marais, B.J., Black, G.F., Beyers, N., & Walzl, G. 2008 (486)</td><td>43 HIV infected participants were enrolled in this study. 23 children and 20 adults. The mean age of adults was 18.7 years where as the mean for children was 4.4years. Study was conducted in South Africa</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA (QFT & T.SPOT))</td><td>Discordant results for TST and IGRAs<table><tr><td></td><td>TSPOT +</td><td>TSPOT -</td></tr><tr><td></td><td>TST -</td><td>TST +</td></tr><tr><td>All</td><td>29.7</td><td>10.8</td></tr><tr><td>Children</td><td>39.1</td><td>13.0</td></tr><tr><td>Adults</td><td>14.3</td><td>7.1</td></tr></table><table><tr><td></td><td>QFT+</td><td>QFT-</td></tr><tr><td></td><td>TST -</td><td>TST+</td></tr><tr><td>All</td><td>0</td><td>26.9</td></tr><tr><td>Children</td><td>0</td><td>25.0</td></tr><tr><td>Adults</td><td>0</td><td>28.6</td></tr></table></td><td>Not determined</td><td>Funded by Bill and Melinda Gates Foundation</td><td>Authors commented that no indeterminate results were observed in children with a CD4 count higher than adults. Adults with indeterminate results tended to have low CD4 counts and negative TST results.</td></tr>
</table>

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<tr><td>Vassilopoulos, D., Stamoulis, N., Hadziyannis, E., & Archimandritis, A.J. 2008 (347)</td><td>Observational study Some were on DMARD and various other immunosuppressive medicines such as steroids.

70 participants with various rheumatic diseases with a mean age 60years. The study was conducted in an Outpatients rheumatology clinic in Athens Greece</td><td>TST (Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (T.SPOT.TB</td><td>Overall results showing discordant and concordant results between tests<table>
<tr><td></td><td colspan="4">TST</td></tr>
<tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr>
<tr><td>+</td><td>12</td><td>4</td><td>16</td></tr>
<tr><td>-</td><td>15</td><td>39</td><td>54</td></tr>
<tr><td></td><td>27</td><td>43</td><td>70</td></tr>
</table></td><td>Not determined</td><td>Not recorded</td><td>Authors concluded that at this point based on the available data, replacement of the TST by the TSPOT cannot definitely be recommended. More data examining the tests cost, feasibility and reproducibility as well as the outcome of anti TNF treated rheumatic patients with discordant TST/TSPOT results are needed before recommendations can be made.</td></tr>
</table>

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<tr><td>Ponce de, L.D., Acevedo-Vasquez, E., Alvizuri, S., Gutierrez, C., Cucho, M., Alfaro, J., Perich, R., Sanchez-Torres, A., Pastor, C., Sanchez-Schwartz, C., Medina, M., Gamboa, R., & Ugarte, M. 2008 (450)</td><td>Cross sectional study conducted in Peru. 106 Rheumatoid arthritis patients, of whom 73% were receiving methotrexate and 91%, were receiving prednisolone at a dose of less than 10mg daily. They also recruited 97 controls</td><td>TST(Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (QFT)</td><td>Overall results showing TST and IGRA results of immunosuppressed patients and controls

RA patients
<table>
<tr><td></td><td colspan="4">TST</td></tr>
<tr><td>IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr>
<tr><td></td><td>+</td><td>21</td><td>24</td><td>45</td></tr>
<tr><td></td><td>-</td><td>6</td><td>50</td><td>56</td></tr>
<tr><td></td><td></td><td>27</td><td>74</td><td>101</td></tr>
</table>

Control
<table>
<tr><td></td><td colspan="4">TST</td></tr>
<tr><td>IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr>
<tr><td></td><td>+</td><td>50</td><td>5</td><td>55</td></tr>
<tr><td></td><td>-</td><td>11</td><td>27</td><td>38</td></tr>
<tr><td></td><td></td><td>61</td><td>32</td><td>93</td></tr>
</table>

RA= Rheumatoid arthritis</td><td>Not determined</td><td>Not recorded</td><td>Authors concede that a limitation of the study was the lack of a gold standard method for diagnosing LTBI. They attempted to compensate for this by evaluating both diagnostic tests in RA patients and matched controls. Data indicate that IGRA more accurate than the TST in RA patients but cannot determine absolute sensitivity of both tests</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Bartalesi, F., Vicidomini, S., Goletti, D., Fiorelli, C., Fiori, G., Melchiorre, D., Tortoli, E., Mantella, A., Benucci, M., Girardi, E., Cerinic, M.M., & Bartoloni, A. 2009 (82)</td><td>398 participants with rheumatic diseases requiring the use of biological drugs in Italy. Participants were treated with systemic corticosteroids, conventional DMARDs, and TNF alpha inhibitors. Risk factors associated with LTBI included birth or residence in high prevalence area, close contact with to patients with sputum positive TB.</td><td>TST(5units PPD)</td><td>IGRA(QFT)</td><td>Overall results
<table>
<tr><td></td><td>IGRA</td><td></td><td></td></tr>
<tr><td></td><td>+</td><td>-</td><td>Tot</td></tr>
<tr><td>TST+</td><td>39</td><td>35</td><td>74</td></tr>
<tr><td>TST-</td><td>13</td><td>306</td><td>319</td></tr>
<tr><td>Tot</td><td>52</td><td>341</td><td>393</td></tr>
</table>
Also presented Odds ratios adjusting for the association of risk factors for Tb infection and IGRA and TST positivity
<table>
<tr><td>No of Risks</td><td>IGRA +</td><td>p-val</td><td>TST +</td><td>P-val</td></tr>
<tr><td></td><td>OR</td><td></td><td>OR</td><td></td></tr>
<tr><td>0</td><td>1</td><td></td><td>1</td><td></td></tr>
<tr><td>1</td><td>3.3</td><td><0.05</td><td>2.57</td><td><0.05</td></tr>
<tr><td>>2</td><td>5.71</td><td><0.05</td><td>5.35</td><td><0.05</td></tr>
</table></td><td>Not determined</td><td>Not recorded</td><td>Until further data are available on the implication of discordant TST/IGRA results, a strategy of simultaneous TST and IGRA testing in populations with low prevalence of BCG vaccination should maximise the sensitivity of LTBI diagnosis</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Cobanoglu, N., Ozcelik, U., Kalyoncu, U., Ozen, S., Kiraz, S., Gurcan, N., Kaplan, M., Dogru, D., Yalcin, E., Pekcan, S., Kose, M., Topaloglu, R., Besbas, N., Bakkaloglu, A., & Kiper, N. 2007 (623)	106 divided into groups 1 and 2. Group 1 (38 healthy individuals), Group 2 (68 patients with chronic inflammatory diseases) 87% of these patients were on immunosuppressive medications such as methotrexate, methylprednisolone , prednisolone. The study was conducted in the University Faculty of Medicine in Ankara Turkey	TST 0.1ml (5TU) of PPD	IGRA(QFT)	Results stratified by age to adjust for supposed BCG effect. < 25years (57 participants) Group 1 9/25 Discordant results All TST+ IGRA – Group 2 17/32 Discordant results 16 (TST+ IGRA -) 1 (TST- IGRA +) >25years (40 participants) Group1 4/11 Discordant results 3(TST+ IGRA -) 1(TST- IGRA+) Group 2 13/29 Discordant results All 13 (TST+ IGRA-) 9 had IGRA indeterminate results of whom 7 were immunocompromised	Not determined	Not recorded	Authors say study should be accepted as a basis for the design of future studies that will be helpful for physicians to decide whether the IGRA is more sensitive than TST to detect LTBI before the use of TNF α blockers.

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<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Piana, F., Ruffo, C.L., Baldan, R., Miotto, P., Ferrarese, M., & Cirillo, D.M. 2007 (975)</td><td>138 immunosuppressed haematology patients in Italy. All patients were identified as nosocomial contacts of a case of smear positive TB. No information on graded exposure. Study was conducted in a Chemotherapy unit in Italy.</td><td>TST 0.1ml (5TU) of Siebert PPD</td><td>IGRA (T.SPOT.TB)</td><td>Overall result
<table>
<tr><td></td><td colspan="5">IGRA</td></tr>
<tr><td></td><td>+</td><td>-</td><td>Ind</td><td>Ins T cell</td><td>Tot</td></tr>
<tr><td>TST+</td><td>21</td><td>3</td><td>0</td><td>0</td><td>24</td></tr>
<tr><td>TST-</td><td>34</td><td>57</td><td>5</td><td>2</td><td>98</td></tr>
<tr><td>No res</td><td>6</td><td>8</td><td>1</td><td>1</td><td>16</td></tr>
<tr><td>Tot</td><td>61</td><td>68</td><td>6</td><td>3</td><td>138</td></tr>
</table>
Ind =Indeterminate
Ins= Insufficient
No res= No result
Results also stratified by pathological WBC count.
Pathological (<4.3x10^3 or>10.8X10^3 WBC.mm^{-3})
IGRA 44.3% +VE TST 14.5% +VE
Non Pathological
IGRA 44.6% +VE TST 25.9+VE</td><td>Not determined</td><td>T-SPOT.TB kits provided by Oxford Immunotech</td><td>It was important to determine whether the higher apparent prevalence of infection found with IGRA was due to the TST being falsely negative due to anergy, or to the IGRA being falsely positive in a number of patients.</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Richeldi, L., Losi, M., D'Amico, R., Luppi, M., Ferrari, A., Mussini, C., Codeluppi, M., Cocchi, S., Prati, F., Paci, V., Meacci, M., Meccugni, B., Rumpianesi, F., Roversi, P., Cerri, S., Luppi, F., Ferrara, G., Latorre, I., Gerunda, G.E., Torelli, G., Esposito, R., & Fabbri, L.M. 2009 (107)	369 participants who were prospectively enrolled into the following immunosuppressed groups. Liver transplantation candidates, Chronically HIV infected patients and patients with hematologic malignancies. Study participants were evaluated in a referral centre in Italy. Only about 3.6% patients were BCG vaccinated.	TST(5iu PPD)	IGRA (T-SPOT.TB) & (QFT)	Overall results | | LTC | HIV | HM | | | 120 | 116 | 95 | | TST + | 20 | 6 | 10 | | TST - | 100 | 110 | 85 | | TSP+ | 32 | 4 | 25 | | TSP- | 87 | 112 | 69 | | TSP.I | 1 | 0 | 1 | | QFT+ | 28 | 5 | 17 | | QFT- | 80 | 104 | 73 | | QFT.I | 12 | 7 | 5 | LTC Liver Transplantation Candidates HM Hematologic Malignancies HIV Human Immunodeficiency Virus TSP T.SPOT.TB TSP.I Indeterminate result QFT.I Indeterminate result	Not determined	Not recorded	Study shows that the performance of IGRA, both in terms of rates of positive results and in diagnostic agreement varies greatly across different categories of patients who are at increased risk of TB reactivation. Because of the importance of targeting such high-risk groups, for effective TB control, we advise caution when interpreting the results of IGRA among immunosuppressed patients.

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<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Soborg, B., Ruhwald, M., Hetland, M.L., Jacobsen, S., Andersen, A.B., Milman, N., Thomsen, V.O., Jensen, D.V., Koch, A., Wohlfahrt, J., & Ravn, P. 2009 (6)</td><td>302 patients with inflammatory disease were included. 153 had rheumatoid arthritis, 40 spondyloarthropathies 51 sarcoidosis, and 58 participants presenting with other conditions such as psoriatic arthritis. Patients either received DMARDS or corticosteroid treatment. The study was conducted in Rheumatology department of the Heart centre in Copenhagen Denmark</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Results presented as risk ratios which determined the associations between factors relevant to TB infection and test reactivity to either IGRA or TST.
<u>CORTICOSTEROID TREATMENT (YES, NO)</u>
RR IGRA = 0.5(0.1-1.6)
RR TST = 0.4(0.1-1.0)
<u>DMARDS TREATMENT (YES, NO)</u>
RR IGRA= 0.7(0.3-1.7)
RR TST = 1.3(0.7-2.3)
<u>CD4 COUNT (<500 >500)</u>
RR IGRA = 1 (0.2-3.2)
RR TST = 1.5(0.7-3.3)
Danish Guideline
<table>
<tr><td></td><td>TST -</td><td>TST+</td></tr>
<tr><td>IGRA-</td><td>180</td><td>36</td></tr>
<tr><td>IGRA +</td><td>9</td><td>9</td></tr>
</table>
US Guideline
<table>
<tr><td></td><td>TST-</td><td>TST+</td></tr>
<tr><td>IGRA-</td><td>159</td><td>57</td></tr>
<tr><td>IGRA+</td><td>9</td><td>9</td></tr>
</table>
</td><td>Not recorded</td><td>Not recorded</td><td>Interesting that authors stated that study was not designed to address the question of disease progression, as protocol recommended prophylactic treatment to test-positive patients.</td></tr>
</table>

<u>Key:</u> CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Matulis, G., Juni, P., Villiger, P.M., & Gadola, S.D. 2008 (565)</td><td>142 participants of which 126 received immunosuppressive therapy. 50% were female. Anti TNF, DMARDS and corticosteroids were the medicines they received. The mean age was 48years. Study was conducted in a University Hospital in Berne Switzerland.</td><td>TST (2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table>
<tr><th></th><th>TST+</th><th>TST-</th><th>Un</th><th>tot</th></tr>
<tr><td>IG+</td><td>10</td><td>5</td><td>2</td><td>17</td></tr>
<tr><td>IG-</td><td>34</td><td>60</td><td>23</td><td>117</td></tr>
<tr><td>Ind</td><td>2</td><td>4</td><td>2</td><td>8</td></tr>
<tr><td>Tot</td><td>46</td><td>69</td><td>27</td><td>142</td></tr>
</table>
Multivariate analysis were presented as Odds ratios
<u>CORTICOSTEROID TREATMENT (YES, NO)</u>
OR IGRA = 1.11(0.30-4.14)
OR TST = 0.74(0.32-1.72)
<u>DMARDS TREATMENT (YES, NO)</u>
OR IGRA= 2.34(0.52-10.6)
OR TST = 0.75(0.32-1.77)
<u>TNFα INHIBITORS</u>
OR IGRA = 0.19 (0.05-0.76)</td><td>Not determined</td><td>Study funded by Swiss commission for Rheumatic Disease and the Swiss National Science Foundation</td><td>They did a multivariate analysis which did not include analysis for the participants which had two or more immunosuppressant medications</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Schoepfer, A.M., Flogerzi, B., Fallegger, S., Schaffer, T., Mueller, S., Nicod, L., & Seibold, F. 2008 (310)</td><td>212 participants consisting of 114 crohns disease, 44 ulcerative colitis 10 indeterminate colitis and 44 controls. Study was conducted in Switzerland</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table><tr><td>Diag</td><td>N</td><td>BCG</td><td>Igra+</td><td>Tst+</td></tr><tr><td>IBD</td><td>168</td><td>+ve</td><td>12/ 118</td><td>27/ 118</td></tr><tr><td></td><td></td><td>-ve</td><td>2/50</td><td>3/50</td></tr><tr><td>Cont</td><td>44</td><td>+ve</td><td>3/33</td><td>17/ 33</td></tr><tr><td></td><td></td><td>-ve</td><td>1/11</td><td>2/11</td></tr></table>
IBD= Inflammatory Bowel Disease</td><td>Not determined</td><td>Not recorded</td><td>Authors concluded that the application of TST for detecting LTBI is limited in RA patients by the frequent presence of anergy. Combined IGRA assay and TST can aid in detecting LTBI in RA patients receiving adalimumab therapy</td></tr>
<tr><td>Manuel, O., Humar, A., Preiksaitis, J., Doucette, K., Shokoples, S., Peleg, A.Y., Cobos, I., & Kumar, D. 2007 (615)</td><td>153 patients with chronic liver disease who were candidates for liver transplant. Patients had various risk factors such as contact with active tb patient, born or stay in country with high prevalence tb. Study was conducted in a preliver transplant clinic in Canada</td><td>TST</td><td>IGRA (QFT)</td><td>Overall results
5mm cut off<table><tr><td></td><td>TST+</td><td>TST-</td><td>Total</td></tr><tr><td>IGRA+</td><td>25</td><td>9</td><td>34</td></tr><tr><td>IGRA-</td><td>12</td><td>95</td><td>107</td></tr><tr><td>Total</td><td>37</td><td>104</td><td>141</td></tr></table>
10mm cut off<table><tr><td></td><td>TST+</td><td>TST-</td><td>Total</td></tr><tr><td>IGRA+</td><td>18</td><td>16</td><td>34</td></tr><tr><td>IGRA-</td><td>9</td><td>98</td><td>107</td></tr><tr><td>Total</td><td>27</td><td>114</td><td>141</td></tr></table></td><td>Not determined</td><td>Test kits provided by Cellestis Ltd</td><td>Authors conclude that study demonstrates that IGRA and TST performed similarly for the diagnosis of LTBI in a population with end stage liver disease.</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
				Indeterminate IGRA result 12/153= 7.8%			

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<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Shovman, O., Anouk, M., Vinnitsky, N., Arad, U., Paran, D., Litinsky, I., Caspi, D., & Elkayam, O. 2009 (3413)</td><td>Study performed in Israel. 35 rheumatoid arthritis patients and 15 controls</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results
<table>
<tr><td></td><td colspan="3">TST results as percentage</td></tr>
<tr><td></td><td>+ve</td><td>-ve</td><td>Anergy</td></tr>
<tr><td>RA</td><td>45</td><td>17</td><td>37</td></tr>
<tr><td>Control</td><td>15</td><td>7</td><td>78</td></tr>
</table>
<table>
<tr><td></td><td colspan="3">IGRA results by percentage</td></tr>
<tr><td></td><td>+ve</td><td>-ve</td><td>ind</td></tr>
<tr><td>RA</td><td>11.4</td><td>60</td><td>28.6</td></tr>
<tr><td>Control</td><td>13</td><td>87</td><td>0</td></tr>
</table>
RA = Rheumatoid Arthritis</td><td>Not determined</td><td>Not recorded</td><td>The authors commented that the high rate of indeterminate results reduces the clinical utility of IGRA and questions its use in the diagnosis of LTBI in rheumatoid arthritis patients.</td></tr>
</table>

Evidence Tables: Screening

Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
Harada, N., Nakajima, Y., Higuchi, K., Sekiya, Y., Rothel, J., & Mori, T. 2006 (Ref ID 1009)	332 Japanese Healthcare workers of mean age 41.4 years. 15 participants were BCG naive while 14 had unknown BCG status. 95% of participants had been vaccinated. Some of the participants were employed on a tuberculosis ward while the others were employed on the outpatients' tuberculosis	TST	IGRA (QFT)	The authors conducted univariate and multivariate analysis. They found that age relative to persons aged over 30 years, for each decade of increased age, history of working in a tuberculosis ward, and history of working in the outpatient department of the hospitals tuberculosis clinic were significantly associated with a positive IGRA result. The measure of effect was the odds ratio.	Japanese Ministry of health, labour and welfare	Authors comment that for a small number of HCW who had TST reactions of 30mm and above, the rate of QFT positivity was significantly higher, suggesting that such strong tuberculin reactions may more likely represent tuberculosis. However there was no significant correlation

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Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
	clinic. These participants were not newly employed.					between QFT positivity and tuberculin reaction size for HCW with a diameter less than 30mm.
Alvarez-Leon E et al 2009 (Ref ID 23)	Cross sectional study of 134 Healthcare workers of mean age 33.4 years in Spain in an 800-bed university hospital to which 50 to 60 tuberculosis patients are admitted annually.35 % of participants had been	TST	IGRA (QFT)	Multivariate analysis confirmed that the only significant risk factor for a positive TST result was working as an orderly, whereas only age (yearly increase in age) remained as a significant risk factor associated with a positive QFT result. Variables such as age, sex, employment category, and number of years in healthcare profession were adjusted for.	Evaluation of Sanitary Technologies	Authors note that a positive IGRA results with high interferon gamma levels should be taken into account. They note however that in the absence of long term follow up data, it could be too early

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Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
	BCG vaccinated.					to replace the TST with IGRA in HCW for LTBI screening.
Storla, D.G., Kristiansen, I., Oftung, F., Korsvold, G.E., Gaupset, M., Gran, G., Overby, A.K., Dyrhol-Riise, A.M., & Bjune, G.A. 2009 (Ref ID 60)	155 **exposed** HCWs and 48 healthy controls. All but one of them had a visible scar from BCG vaccination.	TST	IGRA (T.SPOT.TB)	Measured concordance between IGRA and TST.	Study financed by participating hospitals and Norwegian Institute of Public Health	The authors found that the risk of a positive TST result was associated with prior BCG vaccination.

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<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type and Population Screened</th><th>Reference Test</th><th>Index Test</th><th>Measure of effect</th><th>Source of funding</th><th>Authors Comments</th></tr>
<tr>
<td>Hotta, K., Ogura, T., Nishii, K., Kodani, T., Onishi, M., Shimizu, Y., Kanehiro, A., Kiura, K., Tanimoto, M., & Tobe, K. 2007(Ref ID 3967)</td>
<td>Prospective study of participants enrolled at the beginning of their clinical training. The participants consisted of medical, nursing and dental students. The study was conducted in Japan. Most students had been BCG vaccinated</td>
<td>TST</td>
<td>IGRA</td>
<td>Measured concordant results stratified by cut off point of TST.
<table>
<tr><td>• Result</td><td>• >5</td><td>• >10</td><td>• >15</td></tr>
<tr><td>• Tst+/igra+</td><td>• 1.4%</td><td>• 1.4%</td><td>• 1.4%</td></tr>
<tr><td>• Tst-/igra-</td><td>• 17.4%</td><td>• 39.6%</td><td>• 71.0%</td></tr>
<tr><td>• Tst+/igra-</td><td>• 78.7%</td><td>• 56.5%</td><td>• 25.1%</td></tr>
<tr><td>• Tst-/igra+</td><td>• 0</td><td>• 0</td><td>• 0</td></tr>
</table>
•</td>
<td>Not recorded</td>
<td>The authors conclude that IGRA and TST results were quite discordant in a medical university setting, probably because of the influence of BCG vaccination on the TST results.</td>
</tr>
</table>

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<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type and Population Screened</th><th>Reference Test</th><th>Index Test</th><th>Measure of effect</th><th>Source of funding</th><th>Authors Comments</th></tr>
<tr><td>Zhao, X., Mazlagic, D., Flynn, E.A., Hernandez, H., & Abbott, C.L. 2009 (Ref ID 3)</td><td>Cross sectional study. Pilot of 40 HCWs 20 of whom had tested positive to TST and 20 negative. Study was based in a hospital in United States.</td><td>TST</td><td>IGRA (QFT)</td><td>Measured discordance between TST and IGRA
<table><tr><th></th><th>Igra+</th><th>Igra-</th><th>Tot</th></tr><tr><td>TST+</td><td>10</td><td>10</td><td>20</td></tr><tr><td>TST-</td><td>0</td><td>20</td><td>20</td></tr><tr><td>Tot</td><td>10</td><td>30</td><td>40</td></tr></table></td><td>Not recorded</td><td>Paper mentions that participants were interviewed about confounding factors. However the proportion of BCG vaccinated individuals is not stated.</td></tr>
</table>

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Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
Cummings, K.J., Smith, T.S., Shogren, E.S., Khakoo, R., Nanda, S., Bunner, L., Smithmyer, A., Soccorsi, D., Kashon, M.L., Mazurek, G.H., Friedman, L.N., & Weissman, D.N. 2009(Ref ID 3420)	Observational study looking at **newly** hired HCWs in a hospital in the United States. 96% were born in the US and had a median age of 28years. 93% did not report having a risk factor for TB or BCG vaccination. •	TST	IGRA (QFT)	Discordance and concordance between the tests were measured. The overall agreement between the TST result and the 1st IGRA results was 96% but the agreement on positive results was 0%.	The work was financially supported by the National Institute of Environmental Health Services.	Paper was very inclusive about the advantages of IGRA over TST. The authors also said that in low risk populations where the pre test probability of a negative result is high, reanalysis of positive results may improve the test's diagnostic efficiency.

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7.1 Appendix O – Evidence tables 2011

Evidence Tables: IGRA Testing on people from high prevalence countries

Bibliographic Reference (Ref ID)	Stud Typ	Number of Participants	Prevalence/ Incidence	Country of Study/ Origin of participants	Participant Characteristics	Type of Test	Reference Standard	Sensitivity and Specificity/ Modified Measure of Effect	Positive/ Negative Predictive values or Modified	Source of Funding	Additional comments
Kik, S.V., Franken, W.P., Arend, S.M., Mensen, M., Cobelens, F.G., Kamphorst, M., van Dissel, J.T., Borgdorff, M.W., & Verver, S. 2009 (Ref ID 60)	Observational Retrospective study	821	Not specifically recorded.	Netherlands/ South America, Asia, Sub saharan Africa	Participants aged above 16 years. Close contacts of sputum smear positive TB patients. Foreign born and second generation immigrants.	IGRA (QGIT, TSPOT.TB) (ESAT-6, CFP-10,TB7.7)	TST (Threshold 5mm 10mmand 15mm)	Associations between test results and remote exposure, defined as birth outside Europe and North America. Attributable Fraction to particular risk factors calculated. Overall kappa values TST 15mm 0.418 for QFT and 0.379 for TSPOT.TB. For 10mm they were 0.198 and 0.190 respectively. Agreement values were 71.3% and 69.9% for QFT and TSPOT.TB respectively for 15mm. For 10mm they were 62.1% and 64.9% respectively. The continent of birth was the only variable which was independently associated with a positive result for TST 10mm, p value for trend 0.031. Both QFT and TSPOT.tb also showed a positive result independently associated with continent of birth and	No data	Netherlands Organisation for Health Research and Development	Partial verification was performed on those with TST more than 5mm. Possibility of inclusion of patients with past active TB infections. Vague about the level of contact. Does not indicate duration of contact with infected individuals. Does not mention what they did with positive or negative CXRs. They don't mention how deduced LTBI

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								age.			
Nienhaus, A., Schablon, A., & Diel, R. 2008 (Ref ID 394)	Observational Cross sectional/ retrospective	1040	Incidence of TB in Germany reported to be < 6/100000 and >20/100000 in countries from where the immigrants originated.	Germany/ Germany Turkey, Eastern Europe and Africa	Study population 1040 healthy individuals. Mean age of 31.6 years 61.8% female, 25.4% foreign born, 43.4% had previous BCG vaccination. 41.8% HCW.	IGRA (QFTBG) Threshold level 0.35IU/ml Positive result 100/1033	TST (Threshold 5mm 311/1033(30.1%) 10mm= 191/1033(18.5%) 15mm=69/1033 (6.7%)	Agreement 5mm 74.8%, 10mm 84.2%, 15mm 89.8%. Kappa Statistics 5mm(0.26) 10mm (0.37) 15mm (0.33.) BCG vacc. 5mm(0.12) 10mm(0.28) 15mm(0.34) No vacc 5mm(0.5) 10mm(0.54) 15mm(0.3) aOR for positive TST(10mm) for foreign birthplace was 4.6(3.21-6.53) as compared with German birth, for QFT it was 2.6(1.71-4.09)	No data	No sponsor reported	Although study states the population consisted of health persons they have said nothing to rule out symptomless TB by chest Xray. TST at 10mm could possibly be confounded by gender foreign birthplace and BCG vaccination. QFT on could be confounded by age and foreign birthplace. TST+/QFT- discordance is associated with foreign birthplace. Authors explain that such discordance might be explained by resolved or old TB infections that are detected by TST and not QFT.
Carvalho, A.C., Pezzoli, M.C., El-Hamad, I., Arce, P.,	Observational Cross sectional/ retrospective	130	Immigrants from countries with at least an incidence	Italy/ Sub saharan Africa, Northern Africa, Eastern	32 female 98 male. Median age 28 years (range 19-50). Immigrants	IGRA (QFTBG) Threshold level 0.35IU/ml	TST (Threshold 10mm)	Association of Discordance/Concordance between two tests and BCG scar, sex, age, race, previous TB contact.	No data	Lombardia Region grant no 286/98	BCG vaccination independently negatively associated with discordance between tests.

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Bigoni, S., Scarcella, C., Indelicato, A.M., Scolari, C., Carosi, G., & Matteelli, A. 2007 (Ref ID 709)			of 50 per 100000	Europe, Asia, Latin America	from high incidence countries within the last 5 years.			Overall agreement was 71% kcoefficient= 0.37. 100% agreement between TST and IGRA for induration below 10mm.			0.28 (0.1-0.77) p=0.01. BCG scar not always good indicator of BCG vaccination. Overall kcoefficient= 0.37. 100% agreement between TST and IGRA for induration below 10mm.
Franken, W.P., Timmermans, J.F., Prins, C., Slootman, E.J., Dreverman, J., Bruins, H., van Dissel, J.T., & Arend, S.M. 2007 (Ref ID 792)	Prospective Cross sectional study	909	Range from <10, 10-49,50-99,100-199>200) per 100000	Netherlands/ Bosnia Kyrgystan Iraq and Afghanistan.	Army personnel who had returned from mission (738) in high incidence countries compared with new recruits (171) who had not been on mission.	IGRA QFGinTube (ESAT-6 CFP-10, TB7.7)	TST (Threshold 10mm and 15mm)	Discordance and concordance between tests. Overall concordance and kappa values were determined to be 82% and 0.19 respectively for 10mm cut off and 92.3% and 0.24 respectively for 15mm TST cut off.	No data		Study not clear with regard to the definition of LTBI.
Brodie, D., Lederer, D.J., Gallardo, J.S., Trivedi, S.H., Burzynski, J.N., & Schluger, N.W. 2008 (Ref ID 479)	Prospective	123	Not specifically recorded.	United States/ Does not mention countries of origin of immigrants	Patients over 5 years old. Study group were those who had had contact with active TB patients and controls were those who had not had any contact.	IGRA (ESAT-6 and CFP-10)	TST	Overall agreement between TSPOT.tb and TST was 64% and the kappa value was 0.33(0.19-0.48). For BCG vaccinated people it was 56%(43-68) and 0.22(0.06-0.37) respectively. In non vaccinated people it was 82%(68-96) and 0.64(0.38-0.91)	Yes	Oxford Immunotech	Does not mention how they determined either those with ATB or LTBI. Used contact status as surrogate for LTBI and used that as Gold standard. Does not give indication of prevalence or

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					A lot of the patients were recent immigrants with a high rate BCG vaccination						incidence of countries of origin of immigrants.
Porsa, E., Cheng, L., Seale, M.M., Delclos, G.L., Ma, X., Reich, R., Musser, J.M., & Graviss, E.A. 2006 (Ref ID 1070)	Cross sectional/ Observational	474	TB prevalence in United States $<10/10^5$ of foreign born the prevalence reported 25-$300/10^5$	United States/ Mexico, Jamaica, Nicaragua, Ecuador, El Salvador, Honduras, The Philippines and Brazil.	Adult inmates above 18 years of age. 114 female, 295 male. 370 born in the United States 39 Foreign born. 344 patients had prior incarceration. There was a mix of Caucasian African-American and Hispanic ethnicities	IGRA (ESAT-6 and CFP-10)(QFGInTube)	TST Induration 10mm	Kappa statistics for discordance and concordance between TST and QFGT.Adjusted Odds Ratios calculated to determine which factors including Ethnicity, Old age, foreign birth and prior incarceration were more associated with Discordance.	Not determined	Health Resources and Services Administration Bureau of health professions Grant. Kits provided by Cellestis	On logistic regression African American ethnicity only variable associated with positive results for both assays. Mentioned that positive IGRA indicates more recent and ongoing infection while positive TST indicates a remote infection in the past. Hence sensitivity appeared better in TSTs than IGRAs
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Jeppesen, A.S., Harstad, I., Heier, B.T., & Heldal, E.	Observational Cross sectional/ retrospective	1000	TB incidence rate in Norway 6.3/100000	Norway/ Iraq, Somalia, Russia, Iran, Eritrea, Afghanistan, Sub saharan Africa	Asylum seekers. At least 18 years of age. 75.1% male and 24.9% female.	IGRA (ESAT-6 and CFP-10)(QFGInTube)	TST (Threshold 6mm) 460/912(50.4%) 10mm 311/921(34.1%) 15mm(15.5%)	Agreement 72% for 6mm 79% 10mm 78% 15mm. Kappa 6mm 0.43(0.37-0.49) 10mm 0.51(0.45-0.57) 15mm 0.39(0.32-0.47) statistics 0.43(0.37-0.49). aOR continent of origin with Asia as baseline for TST 15mm 3.8 and 3.3 for	Not determined		Definite prevalence or incidence not recorded for countries of origin. For QFT, BCG vaccination and gender were not independent predictors of a positive result

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2008 (Ref ID 438)								QFT			while country of origin and age group and level of exposure independently predicted a positive test. For TST 15mm the variables which independently predicted a positive result were gender, country of origin and level of exposure
Diel, R., Nienhaus, A., Lange, C., Meywald-Walter, K., Forssbohm, M., & Schaberg, T. 2006 (Ref ID 982)	Observational prospective study.	311	TB incidence rate in Hamburg 12/100000. Immigrants from countries with incidence of at least 20/100000	Germany/ 25 different countries including former Soviet Union and Turkey.	Close contacts of sputum-smear positive cases. Contacts with less than 40hours contact time were excluded. Mean age 28.5 years Previous BCG vaccination 157 (50.8%) Foreign/German (27.1%/72.9)	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST 5mm= 137/309 TST (28/137 Positive by IGRA) 10mm=64/309 15mm= 25/309	Overall Kappa statistics 0.2 CI(0.14-0.23) Concordant results 197/309 (63.8%). Positive result 169/172(98.2%) Negative result 28/137 (20.4%) Concordance for 5mm between BCG vacc 38.9% k=0.08(0.026-0.08). Not vacc 89.5% k=0.58(0.4-0.68) for 10mm 77.1% k=0.35 (0.24-0.35)for No BCG and 94.1% k=0.68 (0.46-0.81) for BCG. For TST(5mm) OR = 5.4, TST(10mm) 7.3 and 4.7 QFT	No data	No sponsor	For QFT only Origin is an independent predictor of a positive test result. For TST BCG vaccination also acts an independent predictor. Study does not mention how the specific countries or how recent migrants had been in the country.
Janssens,	Observatio	295	TB	Switzerlan	Mean age 40	IGRA	TST	Overall concordant	Not	Ligue	Countries of origin

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J.P., Roux-Lombard, P., Perneger, T., Metzger, M., Vivien, R., & Rochat, T. 2008 (Ref ID 268)	nal prospective study.		Incidence $20/10^5$ in Geneva. Incidence in countries from which immigrants originated between $(50->100)/10^5$	d/ Countries not specified but categorised by incidence	years (range 16-83 years) Foreign born 73.9% (218) Contacts were exposed to Cavitary TB 105 (35.6%) Non-cavitary TB 168 (56.9%) Pulmonary TB 22 (7.5%)	(ESAT-6,CFP-10,) (T-SPOT.TB)	Induration 5mm 173(58.6%) 10mm 148(50.2%) 61mm(20.7%)	results showed 60.7% TST 5mm, 63.6% 10mm, 63.9% 15mm.Kappa values were 0.24, 0.27 and 0.19 respectively. BCG Non-vaccinated subjects concordant results were 78.4%, 76.5% and 78.4% respectively while kappa values were 0.47, 0.41 and 0.28 for 5mm, 10mm and 15mm respectively when comparing with IGRA .aOR for Gender, BCG and incidence in country of origin ($<50/10^5$ is used as baseline) showed these variables were independent predictors of a positive result 2.07 (1.22-3.51), 2.98 (1.39-6.41) 3.67 (1.40-1.90) respectively for TST 5mm. Only incidence in country of origin showed the significant association with a positive result for TST 10mm 2.22 (1.15-4.27) and 3.84 (1.61-9.20) for $50-99/10^5$ and $>100/10^5$ respectively. $<50/10^5$ was baseline. For IGRA , age by 10 year	determined	Pulmonaire Genevoise	of foreign born nationals not listed. Not very specific of exclusion of positive results if any of chest xray. In the analysis they did not mention if they adjusted for immunocompromised individuals. They were only 6%. The TB incidence of Geneva from where they recruited was $20/10^5$. They did not use that as the baseline value in calculations.

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								increments and incidence in country of origin were the independent predictors of a positive result. 1.30 (1.06-1.6) for age and 2.17 (1.13-4.15) and 2.62 (1.18-5.82) respectively for two categories of incidence.			
Diel, R., Loddenkemper, R., Meywald-Walter, K., Niemann, S., & Nienhaus, A. 2008 (Ref ID 455)	Observational prospective study.	1794	Incidence of TB in Hamburg, Germany reported to be $10.8/10^{5.}$	Germany/ Noted as 'foreign born' but cases progressing to TB documented as from Turkey, Angola	Close contacts of sputum-smear positive cases with at least 40 hours exposure in a closed room. Age range between 0 to 60 years, with most (87.5%) falling between the 16 to 50 range. 28% were migrants from 29 different countries	IGRA (ESAT-6, CFP-10) (QFTGinTube)	TST (Threshold 5mm and 10mm)	Overall kappa statistics 0.276 and 0.119 and 0.616 for BCG vaccinated and non BCG respectively. For the concordance the values were 69.2%, 44.2% and 90.7% respectively. Odds Ratio for a positive test if foreign born adjusted for BCG vaccination, Age and exposure time were determined as follows. TST 5mm 5.81 (3.6-9.1), 10mm 5.2 (3.2-8.4), QFT 2.28 (1.3-3.9)	Not determined	No declared sponsor	Specific countries of origin of migrants not mentioned.

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Evidence Tables: Children

Bibliography Reference (Ref ID)	Study type/Country of study/Origin of participants/BCG vaccination.	Number/Age /Patient Characteristics	Exposure Status/Contact/Gradient	Type of Test	Reference standard	Sensitivity and Specificity Modified measure of effect	Positive and Negative predictive values	Source of Funding	Additional Comments
Lighter, J., Rigaud, M., Eduardo, R., Peng, C.H., & Pollack, H. 2009(282)	Observational prospective	253 Children below 18 years (Mean age 9) Age stratified as follows <24 mo, 24-59mo, 60mo. Recruited from the well child clinic, paediatric chest clinic and paediatric inpatient ward. 42% were female.72 received a single vaccination, 59 had visible BCG scars	Level of exposure graded as **minimal** (No known risk), **low/moderate** risk factors (birth in or travel to a disease-endemic region and/or living with a household member with specific risks (emigrating from a disease-endemic region, having HIV, or having a history of imprisonment, homelessness, or intravenous drug use). **High**(Known direct contact with tuberculosis index case)	QFTG. Considered positive when > 0.35 IU/ml and >25% than nil control value	TST (Mantoux technique). Considered positive with induration of >10mm	Proportion of QFTG positive results for children with increasing gradients of M tuberculosis exposure **Minimal**- 0% of TST+and -ve **Low/moderate** 6% of TST-ve and 19% TST+ were QFTG+. **High** 0% of TST –ve and 100%of TST+ case were QFTG+.	Not determined	Pott's memorial foundation and the Thrasher Research Fund	Cut off of 0.35IU/ml not validated especially for very young children who produce on average less interferon gamma than school aged children and adults

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Higuchi, K., Harada, N., Mori, T., & Sekiya, Y. 2007(849)	Observational prospective. Japan. Japanese students all BCG vaccinated	349 15-16years. Patients were all male and previously BCG vaccinated. They attended the same high school as a student diagnosed with active tb	Students stratified into two groups those with close contact (sharing of classes with index case; 210) and those with limited contact (not attending classes with the index case; 139)	QFTG. Considered positive when > 0.35 IU/ml	TST (defined standard test dose of tuberculin PPD equivalent to 2.5 tuberculin units). Erythma used instead of induration. An erythma of >30mm considered positive for a BCG vaccinated individual	The distribution of TST responses in both close and limited contacts was similar. (p=0.20)	Follow up of 91 students with positive TST but negative QFGT showed no signs of active tb after 3.5 years of follow up	Ministry of Health Labour and Welfare Japan	Partial verification only patients with positive TST were tested with QFTG. Authors suggest that similar positive rates of TST in both strata of exposed groups suggest limited transmission of MTB.

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Chun, J.K., Kim, C.K., Kim, H.S., Jung, G.Y., Lee, T.J., Kim, K.H., & Kim, D.S. 2008(276)	Observational conducted in South Korea	Age up to 15 years. Patients visiting a children's hospital. All children but one had been BCG vaccinated.	Divided into four groups according to contact status. **1. Close contact group** residing in the same house as active tb index case**. 2. Casual contact group**; those with exposure outside household. **3. Control group**; TST positive healthy children with no contact history. **4**. **Children with symptoms suggestive of tuberculosis** as a potential cause	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Close contacts: Kappa 0.19 for 5mm and 0.529 for 10mm. (B) Kappa 0.378 for 10mm. A significantly higher rate of positive QFTG results was evident for the close contact group. 8/42, 19% as compared with the control group 3 subjects 1/65, 1.5% $p<0.05$. Majority of indeterminate QFTG results were from group 4 who were suffering from medical conditions that could be associated with impaired immune function at the time of testing	Not determined	Not reported	Authors found that in children with no exposure to TB, the QFTG was positive in only one of the 65 children, although all of them were positive by the TST at 5mm and 64.6% at 10mm. They also found that there was a significant relationship between higher responses to mitogen-positive control and increasing age of the children

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Tsiouris, S.J., Austin, J., Toro, P., Coetzee, D., Weyer, K., Stein, Z., & El-Sadr, W.M. 2006(941)	Observational/United States/ South Africa	1741 5-15years. Mean age of	Participants grouped according to the status of contact they were living with. **A.** Current case of active TB in the household. **B**. Past case of active TB.**C**. Current and past case of active TB.	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Univariate analysis showed the likelihood of having a positive IGRA increased with increasing age (p=0.011) as did having a TST > 10mm. Overall agreement increased with increasing cut off of TST 0.52, 0.56 and 0.62 for 5, 10 and 15mm respectively.	Not determined	Aeras Global TB vaccine foundation.	IGRA performed well without indeterminate results. The inability to obtain adequate blood specimen from 16.7% of participants is a drawback which is likely to be true of any whole-blood based paediatric test.

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Okada, K., Mao, T.E., Mori, T., Miura, T., Sugiyama, T., Yoshiyama, T., Mitarai, S., Onozaki, I., Harada, N., Saint, S., Kong, K.S., & Chhour, Y.M. 2008(393)	Observational / Japan	They used 161 index cases and 217 contacts 5 years and below.	Contacts stratified by varying risk of infection as classified by smear and culture result of index cases. **A**. Smear -ve with positive or negative culture. **B**. Smear positive grade 1+ including scanty smear. **C** Smear positive grade 2+ **D**. Smear positive grade 3+	IGRA(QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 2.5TU PPD-S	Measured concordance rates and kappa values by smear positivity of index cases and by age of children. Concordance 0.87, 0.906, 0.837, 0.893 and 0.877 overall, kappa 0.308, 0.711, 0.536, 0.774 and 0.626 overall. Also measured multivariate odds ratios for positive results for both TST and QFTG. The following covariates were analysed. Gender, age, BCG scar, Period from final contact and Smear positivity.	Not determined	Japan International Cooperation Agency	Smear positivity of index cases was the most important factor for positivity of both TST and QFTG

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Brock, I., Weldingh, K., Lillebaek, T., Follmann, F., & Andersen, P. 2004(1434)	Observational. Done in Denmark on Danish School population	125 Mean age of 17 years. 85 not BCG vaccinated. Subjects nearest contact case also 17 asked to participate	Stratified by high and low exposure**.** **High exposure** contained individuals with close contact to the index case either through household, school class or local choir that index case regularly attended. **Low exposure** was comprised of 40 students from 2 other classes at the school with no connection to the index case	IGRA(QFTG)	TST PPD RT23 (2 tuberculin units were used)	Determined concordance between the tests in both levels of exposure. And also in both BCG and non BCG vaccinated individuals. Overall kappa = 0.866	Not determined	Not reported	Study demonstrated that IGRA is similar in performance in to TST in detecting LTBI in young non BCG vaccinated individuals.
Connell, T.G., Curtis, N., Ranganathan, S.C., & Buttery, J.P. 2006(979)	Observational study. Australia. Some children born in high prevalence countries 52%	Children less than 18years with a high risk of latent TB infection.	Contact with high risk as defined by siblings or parents recently diagnosed with TB disease, clinical suspicion of TB disease and those recently immigrated from high prevalence of TB	IGRA(QFTG) 0.35IU/ml positive response	TST PPD 10 IU of tuberculin. Positive if 15mm in individuals with evidence of prior BCG, > 5mm in TB contacts regardless of BCG and > for all others	Concordance between TST and IGRA poor overall k=0.3. 70% of TST positives were negative by IGRA. 65% of TST positives had a known TB contact.	Not determined	John Burge Trust. Victoria Australia	Recommended further studies to clarify predictive values.

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Higuchi, K., Kondo, S., Wada, M., Hayashi, S., Ootsuka, G., Sakamoto, N., & Harada, N. 2009 (164)	Prospective Observational study Japan/ Participants from Japan BCG vaccination done	313 participants between the ages of 8-12 years. In a Japanese School	Participants were exposed to an index case in the school. Close contact participants were those who had daily contact (at 90hours contact. Casual participants: total of less than 18hours	IGRA (QFTG) 0.35IU/ml positive response	TST 0.1ml(PPD NIPPON BCG Manufacturing Tokyo Japan) Equivalent to 3 TU PPD-S	QFTG positivity in close contacts 9.8% as compared with 1.8% in casual contacts p=0.02. TST(5mm) positivity in close contacts 52.6% as compared with 67.2% (p=0.078).TST (10mm) 34.2% compared with 28.7% (p=0.488)	Not recorded. No child with negative QFT result developed active TB after 3 years. 3 out of 298 QFT negatives had a positive after 1 year	Not recorded	Authors suggest that QFT has the same performance characteristics in 8-12 years olds as adults. Suggestion of testing contacts three months after the end of exposure as an appropriate and sensitive approach.
Winje, B.A., Oftung, F., Korsvold, G.E., Mannsaker, T., Ly, I.N., Harstad, I., Dyrhol-Riise, A.M., & Heldal, E. 2008.(350)	Cross sectional study/Norway/ Determined by presence of scar	14-15 year olds	Factors associated with latent tb investigated include. Origin, gender, exposure to tuberculosis, travel history. Children grouped into western born, second generation and first generation	IGRA(QFTG) 0.35IU/ml positive	TST PPD RT23 (2 tuberculin units were used)	9% of 511 TST positive children were IGRA positive. They determined adjusted Odds ratios for a positive IGRA for origin of child and exposure. 0.9(0.3-2.4) and 3.3(1.6-6.2) for second generation and first generation respectively as compared with Western born. 2.9(1.1-7.6) Comparing exposure to non exposure of tb	Not determined	Division of infectious disease control at the Norwegian Institute of Public Health.	The authors conclude that factors other than tb infection are widely contributing to positive TST results in this group and indicate the improved IGRA specificity for latent tb

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Connell, T.G., Ritz, N., Paxton, G.A., Buttery, J.P., Curtis, N., & Ranganathan, S.C. 2008 (397)	Observational study. Australia/ Australia and some born in high prevalence countries. 52% BCG vaccinated	96 children from 6months of age to 19 years. Children who were at risk of latent tb or with suspected tb infection were eligible for inclusion. At risk was defined as a recent TB contact and/or recent immigration from a country of high prevalence of TB.	38 participants had LTBI TST positive with no additional symptoms. 49 patients TST negative with no confirmation of active TB. Contacts were either household or non household	IGRA(QFTG), T-SPOT.TB	TST PPD 10 IU of tuberculin. Positive >10mm in	Out of 100 patients, 38 were TST positive of which 16 were household contacts 6 non household contacts and 6 had no known contacts to active TB. 49 were TST negative, of which 10 were household contacts, 1 non-household contact and 38 had no known contacts with active TB.	Authors conclude the need for longitudinal studies for determination of predictive values	Not reported	Interesting how latent and uninfected participants were defined. LTBI: those who were TST positive but with no other symptoms and chest radiograph not suggestive of TB. Uninfected: defined as a well child with negative TST or child with symptoms potentially suggestive of TB but in whom investigations for TB were negative or a child with an alternative diagnosis and complete recovery in the absence of specific TB treatment

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Hansted, E., Andriuskeviciene, A., Sakalauskas, R., Kevalas, R., & Sitkauskiene, B. 2009 (3427)	Observational study done in Lithuania. All participants were BCG vaccinated	10 to 17 year olds	Study subjects who had been in contact with a case of infectious TB were divided into three groups. 1. Culture confirmed 2. High risk group; those living with a family member with infectious tb or having contact with such a person at school. Those this group were free from symptoms. Low risk; those who have no identifiable risk of TB(no known risk of contact with Tb patient, no symptoms and no complaints	IGRA(TSPOT.TB)	TST Mantoux test SSI PPD RT-23, 2TU positive if >10mm	60% high risk TST positive. 17.8% IGRA positive. Calculated RR 3.375. For the low risk 65.4% were TST positive while 9.6% were IGRA positive. Calculated RR 6.8 The total number of discordant results was 54 out of 97 subjects in both high risk and low risk populations. Out of 61 TST positive patients 51 were IGRA negative.	Not recorded	No records of funding	Authors conclude that identifying latent TB in children using this method is useful, especially in countries like Lithuania which have a high incidence of TB despite a high coverage with BCG vaccination

Evidence Tables: Contacts

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Lee, S.S., Liu, Y.C., Huang, T.S., Chen, Y.S., Tsai, H.C., Wann, S.R., & Lin, S.S. 2008. Ref ID: 473	To compare QFT-G and TST in the diagnosis of LTBI in BCG vaccinated HCWs/ Taiwan	Intensity of exposure graded by 1) **Duration of contact:** < 3h/wk, 3-8h/wk, >8 h/wk. 2) **Face-to face contact:** >1 hr. 3) **Staying in same room for >8hrs**. 4) **Personal protection during contact:** unmasked, surgical mask, N95 mask. **Intimate contact:** contact hours >8hrs and if duration of face-to-face contact was >1h.	Contact investigation in 39 HCW's with contact to case patient (smear positive, miliary TB). All BCG vaccinated. 12 male, 27 female. Mean age 35.1± 4.2 yrs (range 27-44yrs). None with symptoms and all had CXR negative for active disease-this persisted for up to 2 years after exposure ended.	QFT-G. **Conversion:** baseline <0.35 IU/ml and follow-up ≥ 0.35 IU/ml. **Repeated testing:** second QFT-G at >8 weeks in those initially QFT-G negtative.	TST (Mantoux). **Positive result:** ≥10mm. **Conversion:** increase in 10mm from negative initial TST.	**Initial testing:** 84.6% (33) TST+, 10.3% (4) QFT-G+ & 12.8% (5). QFT-G indeterminate. **Follow-up:** 32 tested. 33.3% (2/6) TST+. Using QFT-G ≥0.35, 12.5% (4/32) QFT-G+. **Initial concordance:** 18.0% (k= -0.03, CI -0.08 to 0.02, p=0.75). **Concordance between conversions**: 40%, (k= -0.40, p=0.82). Using 15mm and 18mm thresholds, agreement increased to 41.2% (k=0.04, CI -0.13 to 0.21, p=0.32) and 55.9% (k=0.12, CI -0.10 to 0.34, p=0.14) respectively.	**Risk factors for QFT-G conversion:** Intimate contact (OR 1.94, CI 0.18-21.12, p=0.59) and face-to-face contact >1hr (OR 9.20, CI 0.69-122.38, p=0.09) was associated with higher risk of QFT-G conversion, although non-significant.	National Health Research Institutes, Department of Health, Executive Yuan, Republic of China and Kaohsiung Veterans General Hospital.	Repeated testing. Used two thresholds of QFT-G (results not reported in evidence table). Active TB excluded using CXR. **Author's conclusion:** QFT-G conversion was more closely associated with intensity of exposure than TST conversion (although n.s). TST not useful in contact investigation with BCG vaccinated HCWs.
Harada, N., Nakajima, Y., Higuchi, K., Sekiya, Y., Rothel, J., & Mori, T. 2006. Ref ID: 1009	To investigate the performance of QFT-G to detect LTBI by testing HCWs in a Japanese hospital where patients with and without TB are treated/ Japan	No specific definition of length of exposure but questionnaire included **history of employment in TB wards:** 1-4yrs, 5-9yrs, and ≥10 yrs, **history of employment in OPD TB clinic** (as above) and **job category**.	332 (approx 510 invited) HCWs working in Japanese hospital. No exclusion criteria. HCWs with and without TB contact. Mean age 41.4 yrs. 91.3% received at least 1 BCG, 15 non-BCG and 14 unknown. CXR in 98.2% showed 17 with evidence of healed/inactive TB & no cases of active TB.	QFT-G. **Positive result:** ≥0.35 IU/ml to neg control.	TST (Mantoux, 2.5 TU).	**TST & QFT-G results:** 9.9% had IFN-γ response to at least one antigen. 93.1% had TST≥ 10mm, 46.4% ≥20mm. **Other results:** 37.5% with TST ≥30mm had QFT-G+ compared to 7.4% with weaker TST ≤30mm (χ^2=5.8, p=0.02). No sig relationship between QFT-G+ and increasing induration of TST (χ^2=1.5, p=0.22).	**Risk factors for QFT-G+:** from multivariate regression-history of working in a TB ward (OR 2.9, p=0.03), history of working in the outpatient dept of TB clinic (OR 3.5, p=0.03). CXR consistent with past/ minimally severe TB also associated with increased OR (3.4) but this was n.s.	Japanese Ministry of Health, Labor and Welfare.	Active TB excluded using CXR-17 had evidence of 'healed or inactive TB' and these were not excluded from analyses. Some received more than 1 BCG.

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Tripodi, D., Brunet-Court, Nael, V., Audrain, M., Chailleux, E., Germaud, P., Naudin, F., Muller, J.Y., Bourrut-Lacouture, M., Durand-Perdriel, M.H., Gordeeff, C., Guillaumin, G., Houdebine, M., Raffi, F., Boutoille, D., Biron, C., Potel, G., Roedlich, C., Geraut, C., Schablon, A., & Nienhaus, A. 2009. Ref ID: 3397	To compare the performance of TST and IGRA in French HCWs when using a high cut-off for TST/ Cross-sectional study/ France	All HCWs had unprotected contact to AFB positive patients- occurred in ED and lasted between 1-2 hours. Screening performed 8-10 weeks after exposure. No further details on length of exposure given. No specific analyses based on length of exposure.	148 HCWs working in French hospital & participating in TB screening due to contact to infectious TB. All French-born. 73.6% female. 100% BCG vaccinated (37.8% had one BCG, 62.2% had 2 or more). 47.3% worked in healthcare >10 yrs. No active TB in CXR of 60 HCWs.	QFT-GIT.	TST. **Positive result:** ≥10mm. **Old LTBI probable:** TST≥5-10mm. **Recent LTBI probable:** TST ≥10-<15mm. **Recent LTBI very probable:** TST≥ 15mm.	**QFT-GIT & TST results:** 18.9% QFT-GIT+, 65.5% TST≥10mm. Association between TST induration and QFT-GI+ was weak ($p=0.081$). **Calculated concordance:** 46.6%, k=0.11 (discordance 50% TST+/QFT- & 3.4% TST-/QFT+) when threshold ≥10mm compared to French definition of very probable recent LTBI (k=0.02).	**Logistic regression:** did not reveal association between QFT+ or TST+ and age, gender, BCG or yrs spent in healthcare.	Not reported	CXR to exclude active TB only used when TST ≤10 if no previous TST available for comparison. If previous TST available CXR performed when TST increased by >10mm (60 HCWs).

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Kang, Y.A., Lee, H.W., Yoon, H.I., Cho, B., Han, S.K., Shim, Y.S., & Yim, J.J. 2005. Ref ID: 1199	To compare the TST and IGRA in the diagnosis of LTBI according to intensity of exposure/ Korea (intermediate incidence)	4 groups: **1) Low risk of infection:** healthy medical students without identified risk for exposure. **2) Casual contacts:** healthy hospital staff with history of casual contact with active TB patients. **3) Close contacts**: household contact/ worked in same room as active case for ≥8 hrs/day. **4) Active TB.**	273 participants. 99 low risk (median age 25yrs, 59% male, 93% BCG scar), 72 casual contacts (median age 28, 67% male, 90% BCG scar), 48 close contacts (median age 41, 19% male, 67% BCG scar) & 54 active TB (median age 43, 59% male, 56% BCG scar). Exclusion: Group 1-3 with abnormal CXR, taken immunosuppressive drugs in past 3 months or if positive test for HIV.	QFTG. **Positive result:** ≥0.35 IU/ml	TST (Mantoux).	**TST (10mm cutoff) and QFT-G results:** Group 1 (51% TST+, 4% QFT+, k=0.08), Group 2 (60% TST+, 10% QFT+, k=0.14), Group 3 (71% TST+, 44% QFT+, k=0.17). **Overall agreement:** In groups 1-3 (k=0.16). **TST (15mm cutoff) and QFT-G results:** Group 1 (k=0.13), Group 2 (k=0.25), Group 3 (k=0.25). **Risk of infection with TST+ (10mm):** Adjusted OR (age, sex & BCG) Group 1 (OR 1.00), Group 2 (OR 1.48, CI 0.79-2.74), Group 3 (OR 3.13, CI 1.33-7.36). **Risk of infection with TST+ (15mm):** Adj OR Group1 (OR 1.00), Group 2 (OR 1.95, CI 1.02-3.72), Group 3 (OR 2.46, CI 1.10-5.50). **Risk of infection with QFT-G+:** Group 1 (OR 1.00), Group 2 (OR 2.48, CI 0.69-8.90), Group 3 (OR 8.98, CI 2.54-31.68).	Odds of positive result for each increase in risk across 4 groups increased by factor of 1.68 for 10mm TST (CI 1.24-2.26, p<0.001), by factor of 1.82 for 15mm TST (CI 1.38-2.41, p<0.001) and by factor of 4.23 for QFT-G (CI 2.79-6.41, p<0.001).	Seoul National University College of Medicine Research Fund.	QFT-G correlated significantly better with increased risk of infection across groups compared to TST using 10 and 15mm threshold (p<0.001).

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Pai, M., Gokhale, K., Joshi, R., Dogra, S., Kalantri, S., Mendiratta, D.K., Narang, P., Daley, C.L., Granich, R.M., Mazurek, G.H., Reingold, A.L., Riley, L.W., & Colford, J.M., jr. 2005. Ref ID: 1200	To estimate LTBI prevalence in HCWs using the TST and IGRA, to determine agreement between the tests and to compare their correlation with risk factors/ cross sectional/ India	Assessed **surrogate markers of exposure including:** year of training, years in health care profession, job category, direct contact with active TB (sufficient distance to allow conversation), training in internal medicine & household TB contact.	726 (1172 HCWs invited.) HCWs median age 22 yrs (range 18-61) 71% BCG scars, 48% medical/ nursing students, 2% attending physicians. 68% reported direct contact. Exclusion: <18 yrs, Pregnant, allergy to tuberculin, past active TB	QFT-GIT. **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using 1 TU. **Positive result:** ≥10mm (5 & 15 mm used for comparison)	**TST & QFT-GIT:** 41% TST+ (10mm), 23% TST+ (15mm), 40% QFT-GIT+. **Concordance:** TST 5mm (71.4%, k=0.45, CI 0.39-0.51), 10mm (81.4%, k=0.61, CI 0.56-0.67), 15mm (77.9%, k=0.51, CI 0.44-0.57). **Discordance:** TST+/QFT- (5mm 24.6%, 10mm 10%, 15mm 2.6%) & TST-/QFT+ (5mm 4%, 10mm 8.6%, 15mm 19.5%). **Risk factors for discordance:** From multivariate analysis- 2 covariates important but not significantly associated with discordance-job category (attending physicians/faculty vs. med students OR 3.9, CI 0.9-15.6) & increasing yrs in healthcare 2-5 yrs (OR 1.3, CI 0.6-2.8), 6-10 yrs (OR 2.01, CI 0.8-5.4), ≥10 yrs (OR 2.1, CI 0.6-7.5) compared to those with ≤1 yr.	**Risk factors for TST+:** age & no of yrs in HCP (≤1 yr adj OR 1.00, 6-10yrs OR 2.78, CI 1.23-6.25, >10 yrs OR 3.20, CI 1.08-9.45) sig in multivariate regression. **Risk factors for QGT+:** age, no of yrs in HCP (≤1 yr adj OR 1.00, 6-10 yrs OR 4.15, CI 1.81-9.50, > 10 yrs OR 3.34, CI 1.13-9.81) and job category (med student adj OR 1.00, orderlies OR 2.71, CI 1.25-5.86).	Fogarty AIDS International Training and Research Program.	Limited definition of length of exposure. Symptomatic participants or those positive by either test investigated for active TB.

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Mirtskhulava, V., Kempker, R., Shields, K.L., Leonard, M.K., Tsertvadze, T., del, R.C., Salakaia, A., & Blumberg, H.M. 2008. Ref ID: 472	To assess LTBI using both TST and QFT-3G diagnostic tests. To assess concordance between the two diagnostic tests/ Cross-sectional/ Georgia	**High occupational exposure:** HCWs direct contact with infectious TB patients (e.g. on daily basis). **Limited exposure:** HCWs in administration building and had no routine patient contact and those working at research centers. Questionnaire also assessed **community exposure to TB**.	281 (1231 HCWs eligible). HCWs working at National Centre for TB and Lung Disease (NTP) & affiliated centers. Data for 265-mean age 42 yrs, 86% female, median length of employment 8 yrs, 81% frequent daily contact with TB patients, 77.7% positive BCG history.	QFT-GIT. **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using 5 TU. **Positive result:** ≥10mm.	**TST & QFT-GIT:** 66.8% TST+, 60% QFT-G+. **Concordance: 5mm:** (73.2%, k=0.39, CI 0.29-0.50), **10mm**: (73.6%, k=0.43, CI 0.33-0.55) & **15mm**: (70.3%, k=0.40, CI 0.29-0.51). **Discordance: TST+/QFT-** (5mm 23.4%, 10mm 16.6%, 15mm 11.3%). **TST-/QFT+** (5mm 3.4%, 10mm 9.8%, 15mm 18.5%)	From multivariate analysis- **Risk factors for TST+:** employment as HCW >5 yrs (OR 5.09, CI 2.77-9.33) sig associated with increased risk of TST+. **Risk factors for QFT-GIT+:** Age>30yrs (OR 2.91, CI 1.32-6.43) & employment as HCW >5yrs (OR 2.26, CI 1.27-4.01).	National Institutes of Health/ Fogarty International Center.	Unknown history of BCG classified as negative history of BCG. Didn't collect info on possible multiple BCG vaccinations.

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Casas, I., Latorre, I., Esteve, M., Ruiz-Manzano, J., Rodriguez, D., Prat, C., Garcia-Olive, I., Lacoma, A., Ausina, V., & Dominguez, J. 2009. Ref ID: 3428	To investigate the performance of QFT-GIT and T-SPOT.TB and TST for detecting LTBI in HCWs, specifically looking at concordance between both test results and association with known risk factors for LTBI/ cross sectional/ Spain	Questionnaire included degree of occupational exposure to TB. **High exposure**: HCWs from wards with ≥5 contagious patients per year, those from microbiology lab and autopsy wards and from ED. **Medium exposure:** HCWs from wards with 2-4 active cases/yr. **Low exposure:** HCWs from wards with max 1 active TB case.	147 participants. Median age 43.3 yrs, 76.9% female, 15.6% BCG vaccination, 2% unknown BCG, 10.9% high exposure, 42.8% medium exposure, 46.3% low exposure. 64.4% had previous positive TST and not re-tested.	T-SPOT.TB (spots counted by automated plate reader). QFT-GIT (ELISA). **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) in those without previous documented result. **Positive result:** ≥5mm (≥15mm in BCG vaccinated).	**TST, QFT-GIT & T-SPOT results:** 71.1% TST+, 38.8% T-SPOT+, 29.3% QFT-GIT+. **Concordance: TST vs. T-SPOT:** in all participants (62.9%, k=0.32, SE=0.06), no BCG (64.9%, k=0.35, SE=0.07) & in BCG vaccinated (47.8%, k=0.17, SE=0.09). **TST vs. QFT-GIT:** in all (58.7%, k=0.29, SE=0.05), in no BCG (63.2%, k=0.35, SE=0.06) & in BCG vaccinated (34.7%, k=0.09, SE=0.05). **T-SPOT vs. QFT-GIT:** in all (86.0%, k=0.69, SE=0.06), in no BCG (86.3%, k=0.70, SE=0.07) & in BCG vaccinated (86.9%, k=0.65, SE=0.18)	From univariate analysis of all participants- **Risk factors for TST+:** age & years in HCP (OR 1.12, CI 1.06-1.18, p=0.0001). From multivariate analysis- **Risk factors for T-SPOT+:** High occupational exposure (adj OR 3.67, CI 1.07-12.59). **Risk factors for QFT-GIT+:** none sig-occupational exposure important but n.s (OR 2.62, CI 0.81-8.42).	Sociedad Espanola de Neumologia y Cirugua Toracica, SOCAP & FUCAP.	Unable to confirm accuracy of previous TST performed in other institutions but didn't repeat TST in those with previous positive result. Unsure if active TB ruled out. Author's also reported concordance for participants with and without previous positive TST (not reported in evidence table).

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Kobashi, Y., Obase, Y., Fukuda, M., Yoshida, K., Miyashita, N., Fuji, M., & Oka, M. 2007. Ref ID: 658	To evaluate the usefulness of QFT-2G for detecting LTBI in contact investigation of HCWs/ Japan	Contact score =infectivity (of index) x time (hrs) of exposure. 3 groups based on 'contact score': **mild, moderate, severe**. This score qualifies duration of exposure to index case as well as degree of infectivity of index case.	190 Medical staff members who had recent contact history with 4 index cases of TB. 46 males, 144 females. Average age 30.6 yrs. 2 had clinical symptoms at time of investigation. 78% BCG. Past history of positive TST+ (≥10mm) 43%. No one had used mask during contact. Exclusion: history of TB or prior exposure to patient with TB.	QFT-2G (ESAT-6, CFP-10). **Positive result:** ≥0.35 IU/ml.	TST (Mantoux) using equivalent of 3TU. **Positive result:** ≥30mm.	**TST & QFT-2G:** TST+ (22% mild contact score, 31% moderate, 33% severe). QFT-2G+ (0% mild, 4% moderate, 33% severe). Significantly more participants in severe group had QFT-2G+ compared to mild and moderate contacts (both $p<0.05$). **Follow-up:** Those with QFT-2G+ given anti TB drugs-no active TB in these 5 cases. 2/4 converted from positive to negative at 6 & 9 months respectively after starting treatment.	N/A	Not reported	Used high TST cut off. Analyses not adjusted for BCG. **Author's conclusion:** The QFt-2G test showed significant relationship with the contact score when compared with the TST.

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Topic, R.Z., Dodig, S., & Zoricic-Letoja, I. 2009. Ref ID: 226	To assess the occupational risk of LTBI in HCWs at a children's hospital in country of intermediate prevalence of TB and to assess the association of LTBI with concentration of immunoglobulins, CRP & hematological changes/ Croatia	**Group A (high risk):** HCWs from TB ward & were exposed directly to TB patients during office hours over period of >5yrs. **Group B (low risk):** Controls from non TB ward without direct exposure to TB patients	54 Clinically healthy medical staff. Mean age 44 yrs, 27 group A (26 females) & 27 in group B (25 females). All BCG vaccinated x2. Exclusions: history of TB.	QFT-GIT. **Positive result:** ≥0.35 IU/ml.	TST (Mantoux).	**TST & QFT-GIT:** TST+ (5mm 83%, 10mm 63%, 15mm 35%). 31% QFT-GIT+ (high risk 20.4%, low risk 11.1%). **Calculated concordance:** TST 5mm 48%, 10mm 61%, 15mm 74%. Highest concordance when TST≥15mm (74%, k=0.418, CI=0.155-0.680). **Other results:** size of TST induration sig higher in those with positive IGRA (p=0.0006). Proportion of QFT-GIT+ participants differed between TB wards (64% school children & adolescents, 15% infants & children, p=0.028)	N/A	Not reported.	Calculated concordance for 5mm & 10mm (not clearly reported in results). Reported all participants 'healthy' but unsure what investigations used to exclude active TB.

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Storla, D.G., Kristiansen, I., Oftung, F., Korsvold, G.E., Gaupset, M., Gran, G., Overby, A.K., Dyrhol-Riise, A.M., & Bjune, G.A. 2009. Ref ID: 154	To assess the risk for HCWs of acquiring M.tubercuolosis after exposure to patients with sputum smear positive pulmonary TB at 3 university hospitals/ Norway.	**Close contact:** stay in same room with smear positive TB patient in non-protected manner for min 1 hr**. Low exposure:** 1-8 cumulative hours of close contact. **High exposure:** >8 hours cumulative contact.	155 HCWs (48 controls). TB exposure HCWs from 3 university hospitals. Mean age 39 yrs, Controls had no known prior exposure & were non-clinical staff. Mean age 41 yrs. In total all but one had BCG scar. 10 participants from high endemic countries	T-SPOT.TB (spots counted manually using telescope).	TST (Mantoux) using 2TU. **Positive result:** an increase of ≥10mm or of ≥15mm if previous TST unknown	**TST & T-SPOT**: 27% TST+ (17% newly infected, 10% previous TST+). 3% T.SPOT+ (3 from newly infected & 2 from previous TST+: one was born in TB endemic country and one had previous treatment for TB). **Concordance:** TST+/T.SPOT+ (5/42, 12%) in both newly and previously infected participants. In only newly infected (3/42, 7%). **Exposure results:** High exposure (51), low exposure (104). No correlation between length of exposure and TST results, no correlation between T.SPOT+ and TST results. Only 1/3 infected had high exposure.	N/A	Financed by participating hospitals & Norwegian Institute of Public Health.	Not sure if those with previous TST+ were tested with TST again. No mention of X-ray results (how many normal vs. abnormal or indicative of active TB). No k values for concordance.

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Khana, P., Nikolayevskyy, V., Warburton, F., Dobson, E., & Drobniewski, F. 2009. Ref ID: 112.	To analyse the prevalence of LTBI in a new nursing entrant cohort at a large London hospital/ UK/	No specific active case as screening. Used **surrogate markers of TB exposure:** country of birth, employment history, BCG status, past TB diagnosis and past treatment for TB & previous direct contact with TB case.	171 nurses screened. 44.4% born in UK, 44.4% Africa, 2.3% India, 2.9% Caribbean. Median age 26 yrs, 82.5% BCG vaccinated, 11 reported direct contact with active case.	QFT-GIT	TST. **Positive result:** ≥15mm	**TST & QFT-GIT:** 16.2% (24/148) TST+ & 7.6% (13/171) QFT-GIT+. **Calculated concordance:** 87.8%. **Discordance:** 12.2% (3 TST-/QFT+, 15 TST+/QFT-). Those with TST-/QFT+ were all born in Africa & had BCG. 2 had direct contact with TB case & 1 received diagnosis of TB followed by treatment.	From univariate analysis-**Risk factors for TST+:** Birth in Africa (p=0.02), birth in high prevalence country (p=0.02) & >2 yrs in HCP (p=0.003). **Risk factors for QFT-GIT+:** Birth in Africa (p=0.02), birth in high prevalence country (p=0.009) & >2 yrs in HCP (p=0.003).	HPA Mycobacterium Reference Unit (UK).	Only 11 nurses reported direct contact with TB case. Multivariate data non-significant but data not shown in paper. Calculated concordance as not shown in paper-no k values reported.

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Vinton, P., Mihrshahi, S., Johnson, P., Jenkin, G.A., Jolley, D., & Biggs, B.A. 2009. Ref ID: 147.	To evaluate the QFT-GIT by comparing it with TST as a method for screening HCWs for LTBI in hospitals in Australia/ 66.5% born in Australia.	No specific active case. **Defined 5 groups with high risk for exposure to TB:** 1) born in high prevalence countries. 2) History of travel to high prevalence country for >12 months. 3) Occupation includes high likelihood of TB contact. 4) High risk occupational contact (>10hrs contact time with TB patient). 5) Household contacts of active TB case.	481 hospital staff members. Median age 42 yrs, 89.6% female, 78% BCG vaccinated. 12.7% high risk occupational exposure, 9% household contact.	QFT-GIT	TST (Mantoux). **Positive test:** ≥10mm	**TST & QFT-GIT:** TST+ (33% 10mm, 20% 15mm, 10.7% 20mm). 6.7% QFT-GIT+. **Concordance: Overall:** TST 10mm (71%, k=0.16) TST 15mm (82%, k=0.23) & TST 20mm (89%, k=0.25). **Non-BCG:** 10mm (92%, k=-0.03), 15mm (97%, k=-0.02. **BCG vaccinated:** 10mm (66%, k=0.15), 15mm (79%, k=0.22). From multivariate analysis- **Risk factors for discordance TST-/QFT+:** High risk occupational exposure (OR 31.1, CI 1.30-746, p=0.034). **Risk factors for TST+/QFT-:** BCG (OR 7.11, CI 2.04-24.7, p=0.002) & occupation with patient contact (OR 3.96, CI 1.74-9.02, p=0.001).	From multivariate analysis-**Risk factors for TST+:** receipt of BCG (OR 1.04, CI1.01-1.06, p=0.003), occupation involving patient contact (OR 2.58, CI 1.23-5.40, p=0.012) & greater no yrs lived in high prevalence country. **Risk factors for QFT-GIT+:** birth in high prevalence country, no yrs lived in high prevalence country & high risk occupational contact (OR 5.60, CI 1.42-22.0, p=0.014).	Department of Human Services Victoria, National Health and Medical Council, Edgar Tattnall Memorial Trust.	Small numbers of those with occupational risk and household contact.

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Girardi, E., Angeletti, C., Puro, V., Sorrentino, R., Magnavita, N., Vincenti, D., Carrara, S., Butera, O., Ciufoli, A.M., Squarcione, S., Ippolito, G., & Goletti, D. 2009. Ref ID: 3408.	To analyse data on HCWs in Italy who were tested by TST, in house ELISPOT, QFT-GIT & T-SPOT.TB and validate the use of these tests in this population by assessing association with occupational risk and to estimate their sensitivity and specificity by using latent class analysis/ cross sectional/ Italy	Wards routinely treated TB patients. **Ward or service of employment: High risk:** (>1 patient with TB cared for per year e.g. wards for infectious disease & respiratory disease) & **Low risk:** this not the case, e.g. pediatrics, internal medicine & epidemiology.	115 HCWs. Median age 41 yrs, BCG documented in 37.4%. 66.1% employed in wards with low risk of exposure to TB & 33.9% employed in wards with high risk of exposure to TB.	In-house ELISPOT (ESAT-6, CFP-10), T-SPOT.TB. QFT-GIT. **Positive result:** >0.35 IU/ml	TST (Mantoux). **Positive result:** ≥10mm.	**TST & IGRA:** 53% TST+, 36.5% T-SPOT+, 25.2% QFT-GIT+. Estimated sensitivity and specificity using latent class analysis. **Sensitivity:** TST (99.9%), T-SPOT (96.7%, CI 69.3-99.7), QFT-GIT (76.3%, CI 55.9-89.1). **Specificity:** TST (64.2%, CI 53.0-74.1), T-SPOT (85.6%, CI 75.3-92.0), QFT-GIT (93.6%, CI 85.4-97.3)	From multivariate analyses-**Risk factors for TST+:** BCG (OR 4.32, CI 1.56-11.95), age & physician lower risk of TST+ (OR 0.20, CI 0.04-0.92). **Risk factors for T-SPOT+:** worked in high risk TB services (OR 3.10, CI 1.28-7.48) & age. **Risk factors for QFT-GIT+:** age, physicians lower risk (OR 0.07, CI 0.01-0.70) compared to nurse assistants.	Not reported.	Active TB not excluded with investigations but there is some reference to the population as 'healthy' in discussion. Paper reports estimated sensitivity & specificity values for non-BCG group (not in evidence table). Latent class analysis used.

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Alvarez-Leon, E.E., Espinosa_Vega, E., Santana-Rodriguez, E., Molina-Cabrillana, J.M., Perez-Arellano, J.L., Caminero, J.A., & Serrano-Aguilar, P. 2009. Ref ID: 23	To compare how the TST and IGRA (QFT-G In-Tube) tests work in Spanish HCWs in order to improve procedures for the detection of LTBI/ Cross sectional/ Spain	Hospital departments classified as **high risk:** any HCW received diagnosis of TB in previous 10 yrs. **Intermediate risk:** >5 TB patients treated during previous yr. **Low risk:** 1-5 TB patients treated in previous yr. **Very low risk:** rest of departments. Also gained info on years working in direct patient contact, direct contact with TB cases, household contact with TB & high risk procedures in active TB cases.	134 HCWs working at Spanish hospital (50-60 TB patients admitted annually). 101 (75.4%) female, mean age=33.4 years. 57 (42.5%) HCWs had direct contact with TB patients and 28 (49.1%) of these reported respiratory protection not always used. 47 (35.1%) had BCG.	QFT-GIT.	TST **Positive result:** (≥5mm in non-BCG, ≥15mm with BCG).	**TST & QFT-GIT:** 8.96% TST+ & 5.97% QFT-GIT+. **Concordance: All HCWs:** (positive 59%, negative 97%, overall 94%, k=0.56, CI 0.27-0.85). **Non-BCG:** (positive 57%, negative 96%, overall 93%, k=0.53, CI 0.20-0.86). **BCG vaccinated:** (positive 67%, negative 99%, overall 98%, k=0.65, CI 0.03-1.00). **Discordance:** TST+/QFT- (3% all HCWs, 5% non-BCG, 0 BCG vaccinated). TST-/QFT+ (2% all HCWs, 2% non-BCG, 3% BCG vaccinated.)	From multivariate analysis **Risk factors for TST+:** working as an orderly (OR 21.5, CI 2-234, p<0.05). **Risk factors for QFT-GIT+:** age (OR 1.20 for every increased year of age p<.05).	Fondo de Investigaciones Sanitarias (FIS) & Evaluation of Sanitary Technologies (ETES).	2 step TST used.CXR to exclude active TB in HCWs with positive tests.

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Hesseling, A.C., Mandalakas, A.M., Kirchner, H.L., Chegou, N.N., Marais, B.J., Stanley, K., Zhu, X., Black, G., Beyers, N., & Walzl, G. 2009. Ref ID: 15	To assess the agreement of two commercially available IGRAs in relation to TST and to investigate the impact of exposure and age on TST and IGRA responses to detect infection/ Cross sectional/ South Africa	Modified M tuberculosis contact score. **Low exposure:** < 4. **High exposure:** ≥4.	82 (29 children, 53 adults) household contacts of Pulmonary TB index case. Overall Mean age 22.8, 75.6% BCG vaccination. Mean contact score 6.4 & 59.8% high exposure.	T-SPOT.TB & QFT-G	TST (Mantoux). **Positive result** ≥10mm	**TST, QFT-G & T-SPOT: All contacts** (69.2% TST+, 40.9% QFT+, 75% T-SPOT+). **Adults** (78% TST+, 39.6% QFT-G+, 66% T-SPOT +. **Concordance: All contacts:** TST vs. T-SPOT (65.8%, k=0.12, CI -0.11-0.36), TST vs. QFT-G (70.6%, k=0.45, CI 0.28-0.62), T-SPOT vs. QFT-G (31.9%, k=0.38, CI 0.21-0.55). **Adults:** TST vs. T-SPOT (76%, k=0.38, CI 0.10-0.66), TST vs. QFT-G (60%, k=0.34, CI 0.16-0.52), T-SPOT vs. QFT-G (74%, k=0.50, CI 0.31-0.70).	From logistic regression contact score ≥4 associated with positive TST (adj OR 3.83, CI 1.05-14.03), positive T-SPOT (adj OR 38.40, CI 7.59-616.11) & positive QFT-G (adj OR 14.94, CI 4.02-55.58).	South African National Research Foundation & Bill and Melinda Gates Foundation through Grand Challenges in Global Health grant & Norwegian Centre or Cooperation in Higher Education.	Information extracted for overall results & adults only. Discordant results not in evidence table. 2 children excluded based on abnormal CXR-infer CXR done for all participants. No details of normal CXR given.

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Pai, M., Joshi, R., Dogra, S., Zwerling, A.A., Gajalakshmi, D., Goswami, K., Reddy, M.V., Kalantri, A., Hill, P.C., Menzies, D., & Hopewell, P.c. 2009. Ref ID: 250	To determine the incidence of TST and QFT conversions and to assess whether different tests and variations in definitions are likely to produce different rates of conversion and estimated rates of QFT reversions/ India	No specific definitions given. Results include **sleeping proximity** to index case (same house, different house to index), **relationship to index** & **average amount of time spent with index** case per day (< 3hrs, 3-6hrs, >6hrs).	250 household contacts of smear positive index case (culture and HIV results not available for most patients as tests not routinely performed). 57% female, median age 25. 60% BCG scar present. At baseline 80% slept in same house as index, 20% in different house. 46% spent < 3hrs with index per day, 41% 3-6 hrs & 13% >6hrs. Participants followed up at 12 months.	QFT-GIT (ELISA) **positive result**: ≥0.35 IU/ml. Defined **uncertainty zone**: (0.20-0.50). <0.2 IU/ml= definitely negative, >0.5 IU/ml= definitely positive. **Conversion rates:** calculated for those TST-/QFT- or TST+/QFT- at baseline.	TST (Mantoux). **Positive result:** ≥10mm	**Baseline TST & QFT-GIT:** 46% TST+, 54% QFT-GIT+. **Baseline concordance:** 82%, k=0.63. **Follow-up conversion:** estimated rates of conversion using 4 definitions (range 11.8%-21.2%). **Concordance between TST & QFT-GIT conversions:** Range from 83%-93%. Highest concordance (93%, k=0.53, CI 0.20-0.86) with TST increase of 10mm & most stringent QFT definition. **QFT-GIT reversion:** 6.4% of participants QFT-GIT+ at baseline reverted to QGT-GIT-. No new cases of active TB at follow-up.	N/A	Canadian Institutes of Health Research	Unknown immunosupression. Active TB not excluded. Used 2 step TST 'Uncertainty zone' chosen arbitrarily (those in this range considered to have uncertain status). No separate analyses for adults and children. No analysis based on length of exposure.

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Adetifa, I.M., Lugos, M.D., Hammond, A., Jeffries, D., Donkor, S., Adegbola, R.A., & Hill, P.C. 2007. Ref ID: 577	To compare the diagnostic performance of an ex vivo ELISPOT and the QFT-GIT for the diagnosis of LTBI and active TB disease in The Gambia/ West Africa	Contacts categorised by **where they slept in relation to an active case:** in the same bedroom, a different bedroom in the same house or in a different house in the same compound.	320 (194 household contacts, 80 active TB cases). Data for 178 contacts. Same room (mean age 34.3 yrs, 51.2% female, 25% BCG scar & 8.3% uncertain BCG). Separate room (mean age 30 yrs, 66.9% female, 53.7% BCG scar &2.7% uncertain BCG, 2.6% HIV pos). Separate house (mean age 29.7 yrs, 52.6% female, 44.4% BCG scar).	QFT-GIT. **Positive test:** ≥0.35 IU/ml. Ex-vivo ELISPOT assay (ESAT-6, CFP-10)	PPD skin test.	**Concordance: Overall:** between TST & QFT-GIT (71.1%, k=0.43, CI 0.29-0.57) there was significant discordance (p=0.007) 18.8% TST+/QFT-GIT-, 36.2% TST-/QFT-GIT+. **Non-BCG:** (68.2%, k=0.37, CI 0.17-0.58, discordance p=0.02). **BCG vaccinated:** (76.5%, k=0.52, CI 0.31-0.73, discordance p=0.11).	**Risk factors for QFT-GIT+:** in those sleeping in same room (adj OR 3.8, CI 1.2-12.5). **Risk factors for TST+:** in those sleeping in same room (adj OR 4.8, CI 1.3-17.1)	Medical Research Council (UK).	Results for in house IGRA not reported in evidence table. CXR only given to those with positive TST. Those with symptoms underwent clinical assessment. 6/187 CXR had radiological abnormalities but were asymptomatic. One had previous TB treatment & 2 were diagnosed with active TB. 3 were HIV pos. Unsure if these were included in analysis.
Brodie, D., Lederer, D.J., Gallardo, J.S., Trivedi, S.H., Burzynski, J.N., & Schluger, N.W. 2008. Ref ID: 479	To compare the use of T-SPOT.TB test with TST in detecting LTBI in high risk individuals as well as discriminating LTBI from BCG vaccination/ USA	**Close contacts**: ≥8 hrs of contact with active TB patient per week. **Other than close contact:** contact <8 hrs per week. **Non-contacts:** not contacts of patients with active TB.	96 (123 enrolled but 27 excluded. 58% close contacts (mean age 33 yrs, 70% male, 68% BCG, 48% HIV status unknown). 42% controls-includes 3 'other than close contact' (mean age 34 yrs, 50% male, 75% BCG, 35% HIV status unknown). Close contacts: 73% foreign born. Controls: 80% foreign born.	T-SPOT.TB (spots counted manually & with automated plate reader).	TST (Mantoux) using 5 TU.	**TST & T-SPOT:** TST+ (63% close contacts, 78% control) T-SPOT+ (45% close contacts, 25% controls). **Concordance: Overall:** (64%, k=0.33, CI 0.19-0.48), **BCG vaccinated:** (56%, k=0.22, CI 0.06-0.37). **Non-BCG:** (82%, k=0.64, CI 0.38-0.91). **Sensitivity:** (all contacts) T-SPOT (45%, CI 31-59), TST (62%, CI 49-75). **Specificity:** (all contacts) T-SPOT (75%, CI 59-87), TST (23% (CI 11-38).	**Risk factors for TST+:** close contacts with BCG (adj OR 0.1, CI 0.001-0.5, p=0.01) & non-BCG (adj OR 9.1, CI 1.2-67, p=0.03). **Risk factors for T-SPOT+:** close contacts (adj OR 2.9, CI 1.1-7.4, p=0.03). **PPV:** (all contacts) T-SPOT (71%, CI 54-85), TST (53%, CI 40-65). **NPV:** (all contacts) T-SPOT (49%, CI 36-62), TST (30%, CI 15-49). **Diagnostic accuracy:** (all contacts) T-SPOT (57%, CI 47-67) & TST (46%, CI 36-56).	Stony Wold Herbert Fund Inc, NIH, National Heart, Lung & Blood Institute, Oxford Immunotec Ltd.	Included 3 'other than close contacts' with control group. May have included children. No mention of excluding active TB. Sensitivity, specificity, PPV & NPV values also reported for BCG and non-BCG groups but not reported in evidence table.

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O'Neal, S., Hedburg, K., Markum, A., & Schafer, S. 2009. Ref ID: 137	To report a worksite TB contact investigation in which TST and QFT-G were used in same people to compare the results of the two tests/ USA (Oregon).	No specific definition given for length of exposure-all contacts were co-workers of active case of cavitary pulmonary TB. Provide info on **work site**-index case worked in cutting area (adjacent to packaging/ boxing areas).	74 (127 employees invited). 61 employees of active case received both TST and QFT-G & 13 received TST alone. 46 males, 15 females, US born (25), Mexico (28), Asia (5), Other (3). 14 had BCG, 29 without BCG, 18 unknown BCG. 34 worked in cutting (same as index), packaging (6), boxing (4), Other (17).	QFT-G (ESAT-6, CFP-10). **Positive result:** ≥0.35 IU/ml.	TST. **Positive result**: ≥5mm.	**TST & QFT-G:** 57% TST+, 28% QGT-G+. **Discordance:** at TST ≥5mm discordance 30% (18), proportion agreement 69.5%, k= 41.9. TST+ (15mm)/ QFT-G- occurred in 11 (61%) discordant cases; one had QFT-G+/TST-. 40.7% with robust TST (≥15mm) had QFT-G-. **Risk factors of discordance:** not correlated with age, sex, BCG or worksite (logistic regression data not shown in paper).	Calc NPV of QFT-G at varying estimates of infection prevalence using pooled estimates of 78% sensitivity, 96% specificity. NPV decreases as prevalence increases (at 57% prevalence, NPV=77%).	Not reported.	No exclusion of active TB.
Porsa, E., Cheng, L., Seale, M.M., Delclos, G.L., Ma, X., Reich, R., Musser, J.M., & Graviss, E.A. 2006. Ref ID: 1070	To evaluate the performance of IGRA compared to TST for TB screening in a moderate-risk population in the US/ cross-sectional/ USA.	No specific active case or definition of length of contact. Info also gained relating to **known TB contact, prior incarceration, lived in shelter** & whether participants were **intravenous drug user.**	409 (533 invited) adult inmates in county jail. 72.1% male, mean age 31 yrs, 84.1% prior incarceration, 12.5% had prior TB contact, 20.3% lived in shelter, 13% intravenous drug user 90.5% US born. Exclusion: known history of LTBI (prior pos TST, current active TB, use of immunosuppressive drugs. All tested for HIV.	QFT-G (ELISA).	TST (5TU). **Positive result:** ≥10mm.	**Concordance:** 90% (CI 87.1-93.0), k=0.25 (CI 0.10-0.41). TST+/QFT+ (2.2%), TST-/QFT- (87.8%). **Discordance:** participants were more likely to be TST+/QFT-G- (6.8%) than TST-/QFT-G+ (3.2%). From multivariate regression- **Risk factors for concordance:** African-American ethnicity (adj OR 0.29, CI 0.11-0.77), foreign birth (OR 0.23, CI 0.07-0.80), prior incarceration (OR 0.06, CI 0.01-0.50). These factors more likely to be associated with discordance.	From multivariate analysis- **Risk factors for TST+:** older age (OR 1.04, CI 1.01-1.08), African-American ethnicity (OR 4.97, CI 1.58-15.68), foreign birth (OR 20.20, CI 4.21-97.02) & prior incarceration (OR 6.19, CI 1.48-25.95). **Risk factors for QFT-G+:** African-American ethnicity (OR 5.58, CI 1.16-26.74).	Health Resources and Services Administration Bureau of Health Professions & E.A.G & E.P have received research support from Oxford Immunotec Ltd.	Active TB not excluded.

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Kik, S.V., Franken, W.P., Arend, S.M., Mensen, M., Cobelens, F.G., Kamphorst, M., van Dissel, J.T., Borgdorff, M.W., & Verver, S. 2009. Ref ID: 60	To assess whether QFT-GIT, T-SPOT.TB and TST responses were influenced by remote exposure to TB among immigrants with recent contact with sputum smear case of TB/ Netherlands	**Close contacts:** frequent (min 3 times/week) and/or intensive contact (contact within small closed space or physically nearby) with index case. Recent contact also separated into **household contact, non-household contact, unknown contact** during analysis.	433 (715 eligible) immigrant close contacts of index case, aged ≥16 yrs, born in high TB endemic country. Also included second generation immigrants if BCG vaccinated & at least one of parents born in TB endemic country.	QFT-GIT. **Positive test:** ≥0.35 IU/ml. T-SPOT.TB (spots counted using magnifying glass).	TST (2TU). **Positive result:** ≥5mm. If TST negative repeated 3 months later.	**TST, QFT-GIT & T-SPOT:** (322/433, 74.4%) TST+, 53.9% (152/282) QFT-GIT+ & 59.6% T-SPOT+. **Concordance: QFT-GIT & TST:** 10mm (62.1%, k=0.198) & 15mm (71.3%, k=0.418). **T-SPOT.TB & TST:** 10mm (64.9%, k=0.190) & 15mm (69.9%, k=0.379). **QFT-GIT & T-SPOT:** 84.4%, k=0.683.	From multivariate analysis- **Risk factors for TST+:** TST results did not differ between household contacts and non-contacts (OR 0.96, CI 0.48-1.92, p=0.9). After adj: origins from sub-Saharan Africa (adj OR=6.00, CI=1.32-27.24, p=0.018). **Risk factors for QFT-GIT+ & T-SPOT+:** QFT-GIT (adj OR=2.97, CI=1.40-6.27, p=0.001) & T.SPOT.TB (adj OR=2.40, CI=1.13-5.10, p<0.001).	The Netherlands organisation for Health Research and Development.	IGRA only done with positive TST. Not sure if 2 step TST approach was used. Adjusted OR's for age, sex & degree of contact. **Author's conclusion:** When IGRAs are used to determine LTBI infection in foreign born individuals, positive findings not only relate to recent TB infection, but also reflect prior TB exposure in their country of origin.

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Zellweger, J.P., Zellweger, A., Ansermet, S., de, S.B., & Wrighton-Smith, P. 2005. Ref ID: 1101	To investigate how well T-SPOT.TB and TST results correlate with level of exposure to the index case and to examine whether prior BCG vaccination undermines the utility of either test in determining who should received treatment/ Switzerland/ 69.2% born in Switzerland.	**Duration of exposure to index case:** <3hrs, 3-8hrs, >8hrs. **Intensity of exposure:** Close exposure (>1hr face-to-face in the same room at <2m distance) or not close. Results classified into: **High exposure:** any participant with exposure of long duration (>8hrs) or close exposure. **Low exposure:** all combinations of exposure.	92 (143 invited) residents and staff at institution for alcoholic patients in Switzerland. 55% residents & 45% staff. 86% BCG vaccinated. Results of both tests available for 91 participants.	T-SPOT.TB	TST (Mantoux). **Positive result:** >10mm.	**TST & T-SPOT:** 44% TST+ & 15% T-SPOT+. **Concordance**: 65% concordance (59/91), level of agreement low (k=0.232, p=0.0021). 6/11 with positive concordance was initially TST+. 5 initially T-SPOT+/TST- but received 2nd TST month later. **Discordance:** TST+/T-SPOT.TB- (29/91, 31.9%), TST-/T-SPOT.TB+ (3/91, 3.3%) with non-sig results for T-SPOT.TB.	**Risk factors for TST+:** Age (OR 2.66, CI 1.02-6.92, p=0.04) & associated with BCG (p=0.0003). Being in high exposure group n.s (OR 1.85, CI 0.78-4.36, p=0.16). **Risk factors for T.SPOT+:** Being in high exposure group (OR 5.00, CI 1.05-23.86, p=0.03). **Risk of infection (defined by TST+):** 42.9% (< 3hrs exposure), 28.6% (3-8hrs), 64.3% (>8hrs). 50% (with close contact) & 37.2% (no close contact). **Risk of infection (T-SPOT+):** 7.1% (<3hrs), 8.6% (3-8hrs) & 32.1% (>8hrs). 20.8% (close contact), 9.3% (no close contact).	Vaud County Section of the Swiss Lung Association.	No mention of whether everyone with initial TST- given further TST. No mention of excluding active TB.

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Arend, S.M., Thijsen, S.F., Leyten, E.M., Bouwman, J.J., Franken, W.P., Koster, B.F., Cobelens, F.G., van Houte, A.J., & Bossink, A.W. 2007. Ref ID: 808	To compare TST, QFT-GIT & T-SPOT.TB in BCG unvaccinated contacts and correlate results with measures of recent exposure/ The Netherlands/	Participants visited the supermarket at least once monthly. Results include: **duration of exposure (months):** 0-3, 4-6, 7-9, ≥10. **Frequency of shopping:** ≤1x/mo, >1x/mo and <1x/wk, 1x/wk, >1x/wk. **Average shopping time (min):** 1-15, 16-30, 31-60, >60. **Cumulative exposure time (min):** 1-300, 301-600, 601-1200, 1201-2400, >2400.	785 from contact investigation of supermarket employee. All unvaccinated.	QFT-GIT & T-SPOT.TB	TST (Mantoux)	**TST, QFT-GIT & T-SPOT:** 10.3% QFT-GIT+, 18.7% T-SPOT+. **Concordance**: **TST & QFT-GIT** at 5mm (67.3%, k=0.26), at 10mm (75.4%, k=0.33) & 15mm (86.5%, k=0.49). **TST & T-SPOT** at 5mm (69.7%, k=0.34), 10mm (75%, k=0.37) & 15mm (81.8%, k=0.42). **QFT-GIT & T-SPOT** (89.6%, k=0.59). **Sensitivity: QFT-GIT** (5mm=23.8%, 10mm=28.5%, 15mm=42.2%). **T-SPOT** (5mm= 36.7%, 10mm= 40.6%, 15mm= 51.3%). **Specificity: QFT-GIT** (5mm=99.8%, 10mm=98.7%, 15mm=97.9%). **T-SPOT** (5mm= 95.1%, 10mm=92.3%, 15mm= 89.7%).	From multivariate analysis-**Risk factors for TST+:** Age is positive factor. Not associated with any measure of exposure. **Risk factors for IGRA+: QFT-GIT+** associated with cumulative shopping time (adj OR 1.48, CI 1.19-1.84, p<0.001). **T-SPOT+** also associated with cumulative shopping time (adj OR 1.30, CI 1.10-1.53, p=0.002).	Mr Willem Bakhuys Roozeboom Foundation, KNCV Tuberculosis Foundation, The Hague, Research Fund of Diakonesse nhuis	Contact tracing in supermarket. Active TB not excluded.

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Diel, R., Loddenkemper, R., Meywald-Walter, K., Gottschalk, R., & Nienhaus, A. 2009. Ref ID: 205	To assess the use of T-SPOT.TB head to head with QFT in prospective community based study of contacts with recent exposure to infectious TB/ Hamburg	**Close contacts:** people exposed to culture positive TB during their infectious stage. Results separated into **contact type**: household/intimate contact, coworkers, pupils/teachers, HCWs, non-intimate friends, co-patients in hospital, members of sports clubs. **Close contact to coughing index & contact time:** ≤8hrs, 8-40hrs, >40hrs.	1989 (no history of prior TST). 812 TST+ contacts had complete results available for QFT and T-SPOT.TB. 53.3% male, 55.8% with BCG, 51.7% foreign born. 39.5% household/intimate contact, 26.5% close contact to coughing index, mean cumulative exposure time 138.6 hrs.	QFT-GIT & T-SPOT.TB	TST (Mantoux). **Positive result:** >5mm.	**TST, QFT-GIT & T-SPOT:** 40.8% (812/1989) TST+, 30.2% QFT-GIT+ & 28.7% T-SPOT+. **Concordance: QFT-GIT & T-SPOT** (93.9%, k=0.852, CI 0.78-0.92). Assuming positivity to both IGRA's as true infection, **sensitivity** of TST at 10mm= 72% and at 15mm= 39.7%.	From multivariate analysis- **Risk factors for IGRA+:** increasing age, foreign origin, AFB smear positivity, source case coughing & exposure time 8-40hrs for QFT-GIT (OR 1.8, CI 1.0-3.2) & >40hrs for QFT-GIT+ (OR 5.7, CI 3.5-9.3, p<0.001) & for T-SPOT+ (OR 4.9, CI 3.0-8.0).	Not reported.	See online supplement for details of definition of contacts. Only those with TST+ had IGRA tests. No mention of excluding active TB. Sample includes some children but limited separate analyses based on age.

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Diel, R., Loddenkemper, R., Meywald-Walter, K., Niemann, S., 7 Nienhaus, A. 2008. Ref ID: none	To compare the QFT-GIT with TST in recently exposed close contacts of active TB cases with respect to their development of TB disease within 2 years/ Germany	Only close contacts included. **Close contact:** aggregate exposure time, before diagnosis of respective active case of min of 40 hrs in closed rooms. **Exposure time:** 40-<60 hrs, 60-<100 hrs, 100-<200 hrs & 200+ hrs. **Excluded:** contacts with unclear/occasional and contact <40 hrs during period of infectiousness.	601 contacts included with complete results for TST & QFT. 50.7% female, 46% BCG vaccinated, 28% foreign born. Mean age 27.7 yrs, 216 household/ intimate contacts, 165 colleagues of source, 155 pupils/ teachers, 50 HCWs & 21 sports club members. 53 children <15 yrs (18 preschool age).	QFT-GIT	TST (Mantoux). **Positive result:** ≥5mm.	**TST & QFT-GIT:** 40.4% TST+ & 11% QFT-GIT+. **Concordance: All participants** (69.2%, k=0.276, CI 0.22-0.33), **BCG vaccinated** (44.2%, k=0.119,) & **non-BCG** (90.7%, k=0.616). **Follow-up:** Those with QFT+ offered prevention treatment. 6 active cases found. 6/41 (14.6%) of QFT-GIT+ participants who refused treatment developed active TB by 09/2007. 5/219 (2.3%) participants with TST >5mm without treatment developed active TB. Significantly lower rate than that found for QFT-GIT (p<0.003). Only one case had BCG (relative risk reduction 76.4% p=0.15, n.s).	From multiple regression- **Risk factors for TST+:** At 10mm BCG (adj OR 4.6, CI 2.8-7.6), age, origin outside Germany (OR 5.2, CI 3.2-8.4) & exposure time (OR 1.001, CI 1.00-1.003, p=0.03) all sig associated. **Risk factors for QFT-GIT+:** Age (OR 1.04, CI 1.016-1.064), origin (OR 2.28, CI 1.3-3.9) & cumulative exposure time (OR 1.002, CI 1.001-1.003).	Not reported.	Follow-up at 2 years. Adults and children included. No mention of excluding active TB at start of study.

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Machado, a., Jr., Emodi, K., Takenami, I., Finkmoore, B.C., Barbosa, T., Carvalho, J., Cavalcanti, L., Santos, G., Tavares, M., Mota, M., Barreto, F., Reis, M.G., Arruda, S., & Riley, L.W. 2009. Ref ID: 161	To analyse factors associated with discordance between TST and IGRA results among household contacts of patients with Pulmonary TB/ Cross sectional/ Brazil	**Household contact**: resided in same household & spent min 100 hours with index case during symptomatic period. Also collected data on if contact **sleeps in same room** as index case & **length of exposure** as ≤1 month & >1 month.	301 household contacts of index case in public chest disease hospital. BCG scar in 228/301 (76%)- median age for these 22.0 years. Median age for those without BCG scar =33.5 years. Female 181 (60%).	QFT-GIT **Positive result:** ≥0.35 international units	TST. **Positive result:** ≥10mm.	**TST & QFT-GIT:** 145/261 (55.6%) TST+ & 27/298 (43.1%) QFT-GIT+. **Concordance:** TST+/QFT+ (39.2%), TST-/QFT- (36.8%). Agreement =76%, k= 0.53, CI 0.43-0.63. **Discordance:** 72% TST+/IGRA- & 28% TST-/IGRA+.	From multiple regression- **Risk factors for discordance:** Compared to negative concordant group, CXR showing old scar (adj OR 6.8, CI 1.3-35, p=0.02) was significantly associated with TST+/QFT- discordance. Also less likely for TST-/QFT+ to be associated with index case with CXR of cavitary disease (OR 0.2, CI 0.05-0.9, p=0.04) and reported length of exposure >1 month (OR 7.2, CI 1.7-29.3, p<0.01).	Fogarty International Center, National Institutes of Health	CXR used to exclude active TB.

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Kik et al 2009	To determine the positive predictive value for progression to TB of two IGRA in immigrant contacts/ Longitudinal study/ Netherlands	**Incident cases:** contacts diagnosed with TB at least 3 months after diagnosis of index case. **Co-prevalent case:** contacts diagnosed within first 3 months-these were excluded from analysis. No specific distinctions between levels of exposure.	339 close contacts of active TB who were ≥16 years old and were born in TB endemic country. Diagnosis of active disease based on CXR, symptoms, smear and/or culture results. Contacts with TST ≥5mm (or positive past TST) followed up at 6, 12, 18 and 24 months- when contacts did not show up for follow-up after several initiations, they were interviewed by phone where possible.	QFT-GIT **Positive result:** ≥0.35 IU/ml & T-SPOT (as defined by manufacturers criteria)	TST. **Positive result:** ≥5mm	Sensitivity and specificity values calculated using progression to active TB. Follow-up until 1st August 2008 **Sensitivity:** 100% for TST ≥10mm, 88% for TST ≥15mm, 63% for QFT-GIT & 75% for T-SPOT. **Specificity:** 15%, 44%, 46% & 40% respectively. Secondary analysis for progression to disease within first 12 months before August 1st 2008. **Sensitivity:** 100%, 86%, 50% & 67% respectively. **Specificity:** 15%, 43%, 45% & 39% respectively.	339 contacts followed up for median follow-up of 1.83 year. Follow-up until 1st August 2008. **PPV for progression to active TB:** 3.1% for TST ≥10mm, 3.8% for TST ≥15mm, 2.8% for QFT-GIT & 3.3% for T-SPOT. **NPV:** 100%, 99.3%, 98% & 98.3% respectively. Secondary analysis for progression to disease within first 12 months before August 1st 2008. **PPV:** 2.5%, 3.3%, 1.7% & 2.2% respectively. **NPV:** 100%, 99.3%, 98% & 98.3% respectively.	Netherlands organization for health research and development (ZonMw).	All contacts had CXR to exclude active TB.

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Evidence Tables: Immunocompromised

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<tr><td>Balcells, M.E., Perez, C.M., Chanqueo, L., Lasso, M., Villanueva, M., Espinoza, M., Villarroel, L., & Garcia, P. 2008 (294)</td><td>Observational study of individuals from Chile.HIV Positive patients Mean CD4 Count 393/µl (range 100-977) 116 mean age 38.8years (Range 21-71). Older age, history of previous tb disease, previous known exposure to a case of active pulmonary tb, healthcare workers or individuals working with homeless people, residence in prison,</td><td>TST (Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA(QFT)</td><td>Correlation between TST and IGRA results in HIV positive individuals
<table>
<tr><td></td><td>IGRA+</td><td>IGRA-</td><td>TOT</td></tr>
<tr><td>TST+</td><td>9</td><td>2</td><td>11</td></tr>
<tr><td>TST-</td><td>8</td><td>90</td><td>98</td></tr>
<tr><td></td><td>17</td><td>92</td><td>109</td></tr>
</table>
They also performed univariate analysis for a positive LTBI test depending on several factors TB risk factors.</td><td>Not determined</td><td>Supported by a grant from the Department of the Pontificia University of Chile. IGRA were supplied at reduced price by Cellestis</td><td>Authors observed that, multivariate analysis confirmed that past TB was independently associated with a positive TST (p=0.016) as well as a higher CD4 count (p=0.044). For IGRA past tb was the only factors significantly associated with a positive result. (p=0.041)</td></tr>
</table>

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<tr><td>Luetkemeyer, A.F., Charlebois, E.D., Flores, L.L., Bangsberg, D.R., Deeks, S.G., Martin, J.N., & Havlir, D.V. 2007 (797)</td><td>294 HIV infected patients sampled from two cohorts based in the United States. 55% of participants had lived or worked in homeless shelter, prison, hospital, or a drug rehab unit or were born in a country with high TB incidence, or had had contact with an active tb case.</td><td>TST (5TU PPD)</td><td>IGRA (QFT)</td><td>196 participants with both TST and IGRA results valid had the following overall result.
<table>
<tr><td></td><td colspan="4">TST</td></tr>
<tr><td>IG</td><td></td><td>+</td><td>-</td><td>TOT</td></tr>
<tr><td></td><td>+</td><td>8</td><td>11</td><td>19</td></tr>
<tr><td></td><td>-</td><td>10</td><td>167</td><td>177</td></tr>
<tr><td></td><td>TOT</td><td>18</td><td>178</td><td>196</td></tr>
</table>

Results were also stratified by CD4 count.
<table>
<tr><td colspan="5">CD4+ STRATA (cells/mm3)</td></tr>
<tr><td></td><td><100</td><td>100-350</td><td>>350</td><td>tot</td></tr>
<tr><td>IG+</td><td>0</td><td>6</td><td>19</td><td>25</td></tr>
<tr><td>IG-</td><td>26</td><td>101</td><td>127</td><td>254</td></tr>
<tr><td>IG(I)</td><td>5</td><td>4</td><td>6</td><td>15</td></tr>
<tr><td>TOT</td><td>31</td><td>111</td><td>152</td><td>294</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>TST+</td><td>0</td><td>7</td><td>12</td><td>19</td></tr>
</table></td><td>Not determined</td><td>Not recorded</td><td>Authors noted that until further data are available on the implication of discordant TST and IGRA results, a strategy of simultaneous TST and QFT testing where feasible would maximize potential LTBI diagnoses in HIV infected patients</td></tr>
</table>

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Talati, N.J., Seybold, U., Humphrey, B., Aina, A., Tapia, J., Weinfurter, P., Albalak, R., & Blumberg, H.M. 2009 (253)	336 HIV positive patients of mean age of 42 years. Patients had a past med history of LTBI, diabetes mellitus, chronic renal insufficiency, history of malignancy, anytime smoker and Intravenous drug use. Study done in the US.	TST 0.1ml (5TU) of Siebert PPD	IGRA (TSPOT.TB AND QFT)	Reported a CD4 count of < 200 as associated with an indeterminate result for both IGRAs OR= 3.6(1.9,6.8)	Not determined	Partly supported by Centers for Disease Control and Prevention (CDC)	Authors commented that given the results of the study and the limited data currently available it was unclear if IGRAs can be used alone for the diagnosis of LTBI in HIV infected individuals

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<tr><td>Jones, S., de, G.D., Wallach, F.R., Gurtman, A.C., Shi, Q., & Sacks, H. 2007 (621)</td><td>207 HIV infected individuals with a mean age of 47 years. 52% were male. They were also stratified according to CD4 count <100, 19; 101-199, 24; 200-499, 88; >500, 70. Study conducted in Mount Sinai medical centre in New York. United States</td><td>TST 0.1ml (5TU PPD)</td><td>IGRA (QFT)</td><td>Overall concordance between IGRA and TST results
<table><tr><td></td><td colspan="4">IGRA</td></tr><tr><td></td><td>Ind</td><td>-</td><td>+</td><td>Tot</td></tr><tr><td>TST-</td><td>10</td><td>172</td><td>6</td><td>188</td></tr><tr><td>TST+</td><td>0</td><td>8</td><td>5</td><td>13</td></tr><tr><td></td><td>10</td><td>180</td><td>11</td><td>201</td></tr></table>
Ind = Indeterminate</td><td>Not determined</td><td>QuantiFERON kits donated by Cellestis</td><td>IGRA is able to distinguish between indeterminate tests and those that are truly negative. In contrast, a negative TST does not differentiate between individuals who are anergic and those who might have a truly negative TST.</td></tr>
</table>

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<tr><td>Mandalakas, A.M., Hesseling, A.C., Chegou, N.N., Kirchner, H.L., Zhu, X., Marais, B.J., Black, G.F., Beyers, N., & Walzl, G. 2008 (486)</td><td>43 HIV infected participants were enrolled in this study. 23 children and 20 adults. The mean age of adults was 18.7 years where as the mean for children was 4.4years. Study was conducted in South Africa</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA (QFT & T.SPOT))</td><td>Discordant results for TST and IGRAs
<table>
<tr><td></td><td>TSPOT +</td><td>TSPOT -</td></tr>
<tr><td></td><td>TST -</td><td>TST +</td></tr>
<tr><td>All</td><td>29.7</td><td>10.8</td></tr>
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<tr><td>Adults</td><td>14.3</td><td>7.1</td></tr>
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<table>
<tr><td></td><td>QFT+</td><td>QFT-</td></tr>
<tr><td></td><td>TST -</td><td>TST+</td></tr>
<tr><td>All</td><td>0</td><td>26.9</td></tr>
<tr><td>Children</td><td>0</td><td>25.0</td></tr>
<tr><td>Adults</td><td>0</td><td>28.6</td></tr>
</table></td><td>Not determined</td><td>Funded by Bill and Melinda Gates Foundation</td><td>Authors commented that no indeterminate results were observed in children with a CD4 count higher than adults. Adults with indeterminate results tended to have low CD4 counts and negative TST results.</td></tr>
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<tr><td>Vassilopoulos, D., Stamoulis, N., Hadziyannis, E., & Archimandritis, A.J. 2008 (347)</td><td>Observational study Some were on DMARD and various other immunosuppressive medicines such as steroids.

70 participants with various rheumatic diseases with a mean age 60years. The study was conducted in an Outpatients rheumatology clinic in Athens Greece</td><td>TST (Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (T.SPOT.TB</td><td>Overall results showing discordant and concordant results between tests<table><tr><td></td><td colspan="4">TST</td></tr><tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr><tr><td>+</td><td>12</td><td>4</td><td>16</td></tr><tr><td>-</td><td>15</td><td>39</td><td>54</td></tr><tr><td></td><td>27</td><td>43</td><td>70</td></tr></table></td><td>Not determined</td><td>Not recorded</td><td>Authors concluded that at this point based on the available data, replacement of the TST by the TSPOT cannot definitely be recommended. More data examining the tests cost, feasibility and reproducibility as well as the outcome of anti TNF treated rheumatic patients with discordant TST/TSPOT results are needed before recommendations can be made.</td></tr>
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<tr><td>Ponce de, L.D., Acevedo-Vasquez, E., Alvizuri, S., Gutierrez, C., Cucho, M., Alfaro, J., Perich, R., Sanchez-Torres, A., Pastor, C., Sanchez-Schwartz, C., Medina, M., Gamboa, R., & Ugarte, M. 2008 (450)</td><td>Cross sectional study conducted in Peru. 106 Rheumatoid arthritis patients, of whom 73% were receiving methotrexate and 91%, were receiving prednisolone at a dose of less than 10mg daily. They also recruited 97 controls</td><td>TST(Mantoux method. 2TU dose of PPD RT23)</td><td>IGRA (QFT)</td><td>Overall results showing TST and IGRA results of immunosuppressed patients and controls

RA patients
<table>
<tr><td></td><td colspan="4">TST</td></tr>
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<tr><td>-</td><td>6</td><td>50</td><td>56</td></tr>
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Control
<table>
<tr><td></td><td colspan="4">TST</td></tr>
<tr><td rowspan="4">IG</td><td></td><td>+</td><td>-</td><td>tot</td></tr>
<tr><td>+</td><td>50</td><td>5</td><td>55</td></tr>
<tr><td>-</td><td>11</td><td>27</td><td>38</td></tr>
<tr><td></td><td>61</td><td>32</td><td>93</td></tr>
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RA= Rheumatoid arthritis</td><td>Not determined</td><td>Not recorded</td><td>Authors concede that a limitation of the study was the lack of a gold standard method for diagnosing LTBI. They attempted to compensate for this by evaluating both diagnostic tests in RA patients and matched controls. Data indicate that IGRA more accurate than the TST in RA patients but cannot determine absolute sensitivity of both tests</td></tr>
</table>

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<th>Positive and Negative predictive values</th>
<th>Source of Funding</th>
<th>Comments</th>
</tr>
<tr>
<td>Bartalesi, F., Vicidomini, S., Goletti, D., Fiorelli, C., Fiori, G., Melchiorre, D., Tortoli, E., Mantella, A., Benucci, M., Girardi, E., Cerinic, M.M., & Bartoloni, A. 2009 (82)</td>
<td>398 participants with rheumatic diseases requiring the use of biological drugs in Italy. Participants were treated with systemic corticosteroids, conventional DMARDs, and TNF alpha inhibitors. Risk factors associated with LTBI included birth or residence in high prevalence area, close contact with to patients with sputum positive TB.</td>
<td>TST(5units PPD)</td>
<td>IGRA(QFT)</td>
<td>Overall results
<table>
<tr><td></td><td>IGRA</td><td></td><td></td></tr>
<tr><td></td><td>+</td><td>-</td><td>Tot</td></tr>
<tr><td>TST+</td><td>39</td><td>35</td><td>74</td></tr>
<tr><td>TST-</td><td>13</td><td>306</td><td>319</td></tr>
<tr><td>Tot</td><td>52</td><td>341</td><td>393</td></tr>
</table>
Also presented Odds ratios adjusting for the association of risk factors for Tb infection and IGRA and TST positivity
<table>
<tr><td>No of Risks</td><td>IGRA +</td><td>p-val</td><td>TST +</td><td>P-val</td></tr>
<tr><td></td><td>OR</td><td></td><td>OR</td><td></td></tr>
<tr><td>0</td><td>1</td><td></td><td>1</td><td></td></tr>
<tr><td>1</td><td>3.3</td><td><0.05</td><td>2.57</td><td><0.05</td></tr>
<tr><td>>2</td><td>5.71</td><td><0.05</td><td>5.35</td><td><0.05</td></tr>
</table>
</td>
<td>Not determined</td>
<td>Not recorded</td>
<td>Until further data are available on the implication of discordant TST/IGRA results, a strategy of simultaneous TST and IGRA testing in populations with low prevalence of BCG vaccination should maximise the sensitivity of LTBI diagnosis</td>
</tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Cobanoglu, N., Ozcelik, U., Kalyoncu, U., Ozen, S., Kiraz, S., Gurcan, N., Kaplan, M., Dogru, D., Yalcin, E., Pekcan, S., Kose, M., Topaloglu, R., Besbas, N., Bakkaloglu, A., & Kiper, N. 2007 (623)	106 divided into groups 1 and 2. Group 1 (38 healthy individuals), Group 2 (68 patients with chronic inflammatory diseases) 87% of these patients were on immunosuppressive medications such as methotrexate, methylprednisolone , prednisolone. The study was conducted in the University Faculty of Medicine in Ankara Turkey	TST 0.1ml (5TU) of PPD	IGRA(QFT)	Results stratified by age to adjust for supposed BCG effect. < 25years (57 participants) Group 1 9/25 Discordant results All TST+ IGRA – Group 2 17/32 Discordant results 16 (TST+ IGRA -) 1 (TST- IGRA +) >25years (40 participants) Group1 4/11 Discordant results 3(TST+ IGRA -) 1(TST- IGRA+) Group 2 13/29 Discordant results All 13 (TST+ IGRA-) 9 had IGRA indeterminate results of whom 7 were immunocompromised	Not determined	Not recorded	Authors say study should be accepted as a basis for the design of future studies that will be helpful for physicians to decide whether the IGRA is more sensitive than TST to detect LTBI before the use of TNF α blockers.

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised
Condition/Medicines.
Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Piana, F., Ruffo, C.L., Baldan, R., Miotto, P., Ferrarese, M., & Cirillo, D.M. 2007 (975)</td><td>138 immunosuppressed haematology patients in Italy. All patients were identified as nosocomial contacts of a case of smear positive TB. No information on graded exposure. Study was conducted in a Chemotherapy unit in Italy.</td><td>TST 0.1ml
(5TU) of Siebert PPD</td><td>IGRA (T.SPOT.TB)</td><td>Overall result
<table>
<tr><td></td><td colspan="5">IGRA</td></tr>
<tr><td></td><td>+</td><td>-</td><td>Ind</td><td>Ins
T cell</td><td>Tot</td></tr>
<tr><td>TST+</td><td>21</td><td>3</td><td>0</td><td>0</td><td>24</td></tr>
<tr><td>TST-</td><td>34</td><td>57</td><td>5</td><td>2</td><td>98</td></tr>
<tr><td>No res</td><td>6</td><td>8</td><td>1</td><td>1</td><td>16</td></tr>
</table></td><td>Not determined</td><td>T-SPOT.TB kits provided by Oxford Immunotech</td><td>It was important to determine whether the higher apparent prevalence of infection found with IGRA was due to the TST being falsely negative due to anergy, or to the IGRA being falsely positive in a number of patients.</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table><tr><td>Tot</td><td>61</td><td>68</td><td>6</td><td>3</td><td>138</td></tr></table>

Ind =Indeterminate

Ins= Insufficient

No res= No result

Results also stratified by pathological WBC count.

Pathological ($<4.3x10^3$ or$>10.8X10^3$ WBC.mm^{-3})

IGRA 44.3% +VE TST 14.5% +VE

Non Pathological

IGRA 44.6% +VE TST 25.9+VE</td><td></td><td></td><td></td></tr>
</table>

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Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Richeldi, L., Losi, M., D'Amico, R., Luppi, M., Ferrari, A., Mussini, C., Codeluppi, M., Cocchi, S., Prati, F., Paci, V., Meacci, M., Meccugni, B., Rumpianesi, F., Roversi, P., Cerri, S., Luppi, F., Ferrara, G., Latorre, I., Gerunda, G.E., Torelli, G., Esposito, R., & Fabbri, L.M. 2009 (107)	369 participants who were prospectively enrolled into the following immunosuppressed groups. Liver transplantation candidates, Chronically HIV infected patients and patients with hematologic malignancies. Study participants were evaluated in a referral centre in Italy. Only about 3.6% patients were BCG vaccinated.	TST(5iu PPD)	IGRA (T-SPOT.TB) & (QFT)	Overall results <table><tr><td></td><td>LTC</td><td>HIV</td><td>HM</td></tr><tr><td></td><td>120</td><td>116</td><td>95</td></tr><tr><td>TST +</td><td>20</td><td>6</td><td>10</td></tr><tr><td>TST -</td><td>100</td><td>110</td><td>85</td></tr><tr><td>TSP+</td><td>32</td><td>4</td><td>25</td></tr><tr><td>TSP-</td><td>87</td><td>112</td><td>69</td></tr><tr><td>TSP.I</td><td>1</td><td>0</td><td>1</td></tr><tr><td>QFT+</td><td>28</td><td>5</td><td>17</td></tr><tr><td>QFT-</td><td>80</td><td>104</td><td>73</td></tr><tr><td>QFT.I</td><td>12</td><td>7</td><td>5</td></tr></table> LTC Liver Transplantation Candidates HM Hematologic Malignancies HIV Human Immunodeficiency Virus	Not determined	Not recorded	Study shows that the performance of IGRA, both in terms of rates of positive results and in diagnostic agreement varies greatly across different categories of patients who are at increased risk of TB reactivation. Because of the importance of targeting such high-risk groups, for effective TB control, we advise caution when interpreting the results of IGRA among immunosuppressed patients.

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
				TSP T.SPOT.TB TSP.I Indeterminate result QFT.I Indeterminate result			

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Soborg, B., Ruhwald, M., Hetland, M.L., Jacobsen, S., Andersen, A.B., Milman, N., Thomsen, V.O., Jensen, D.V., Koch, A., Wohlfahrt, J., & Ravn, P. 2009 (6)</td><td>302 patients with inflammatory disease were included. 153 had rheumatoid arthritis, 40 spondyloarthropathies 51 sarcoidosis, and 58 participants presenting with other conditions such as psoriatic arthritis. Patients either received DMARDS or corticosteroid treatment. The study was conducted in Rheumatology department of the Heart centre in Copenhagen Denmark</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Results presented as risk ratios which determined the associations between factors relevant to TB infection and test reactivity to either IGRA or TST.

<u>CORTICOSTEROID TREATMENT (YES, NO)</u>

RR IGRA = 0.5(0.1-1.6)

RR TST = 0.4(0.1-1.0)

<u>DMARDS TREATMENT (YES, NO)</u>

RR IGRA= 0.7(0.3-1.7)

RR TST = 1.3(0.7-2.3)

<u>CD4 COUNT (<500 >500)</u>

RR IGRA = 1 (0.2-3.2)

RR TST = 1.5(0.7-3.3)

Danish Guideline
<table><tr><th></th><th>TST -</th><th>TST+</th></tr><tr><td>IGRA-</td><td>180</td><td>36</td></tr></table></td><td>Not recorded</td><td>Not recorded</td><td>Interesting that authors stated that study was not designed to address the question of disease progression, as protocol recommended prophylactic treatment to test-positive patients.</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table><tr><td>IGRA +</td><td>9</td><td>9</td></tr></table>US Guideline<table><tr><td></td><td>TST-</td><td>TST+</td></tr><tr><td>IGRA-</td><td>159</td><td>57</td></tr><tr><td>IGRA+</td><td>9</td><td>9</td></tr></table></td><td></td><td></td><td></td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Matulis, G., Juni, P., Villiger, P.M., & Gadola, S.D. 2008 (565)</td><td>142 participants of which 126 received immunosuppressive therapy. 50% were female. Anti TNF, DMARDS and corticosteroids were the medicines they received. The mean age was 48years. Study was conducted in a University Hospital in Berne Switzerland.</td><td>TST (2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results

<table><tr><th></th><th>TST+</th><th>TST-</th><th>Un</th><th>tot</th></tr><tr><td>IG+</td><td>10</td><td>5</td><td>2</td><td>17</td></tr><tr><td>IG-</td><td>34</td><td>60</td><td>23</td><td>117</td></tr><tr><td>Ind</td><td>2</td><td>4</td><td>2</td><td>8</td></tr><tr><td>Tot</td><td>46</td><td>69</td><td>27</td><td>142</td></tr></table>

Multivariate analysis were presented as Odds ratios

CORTICOSTEROID TREATMENT (YES, NO)

OR IGRA = 1.11(0.30-4.14)

OR TST = 0.74(0.32-1.72)

DMARDS TREATMENT (YES, NO)</td><td>Not determined</td><td>Study funded by Swiss commission for Rheumatic Disease and the Swiss National Science Foundation</td><td>They did a multivariate analysis which did not include analysis for the participants which had two or more immunosuppressant medications</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
				OR IGRA= 2.34(0.52-10.6) OR TST = 0.75(0.32-1.77) **TNFα INHIBITORS** OR IGRA = 0.19 (0.05-0.76)			

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Bibliography (Ref id)	Number of participants. Type of study/Country of origin. Immunocompromised Condition/Medicines. Risk factors. Characteristics	Reference Test	Index Test	Specificity & Sensitivity or Modified Measure of effect/Measures of agreement	Positive and Negative predictive values	Source of Funding	Comments
Schoepfer, A.M., Flogerzi, B., Fallegger, S., Schaffer, T., Mueller, S., Nicod, L., & Seibold, F. 2008 (310)	212 participants consisting of 114 crohns disease, 44 ulcerative colitis 10 indeterminate colitis and 44 controls. Study was conducted in Switzerland	TST(2TU 0.1ml PPD RT23)	IGRA(QFT)	Overall results (see table below) IBD= Inflammatory Bowel Disease	Not determined	Not recorded	Authors concluded that the application of TST for detecting LTBI is limited in RA patients by the frequent presence of anergy. Combined IGRA assay and TST can aid in detecting LTBI in RA patients receiving adalimumab therapy

Diag	N	BCG	Igra+	Tst+
IBD	168	+ve	12/ 118	27/ 118
		-ve	2/50	3/50
Cont	44	+ve	3/33	17/ 33
		-ve	1/11	2/11

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Manuel, O., Humar, A., Preiksaitis, J., Doucette, K., Shokoples, S., Peleg, A.Y., Cobos, I., & Kumar, D. 2007 (615)</td><td>153 patients with chronic liver disease who were candidates for liver transplant. Patients had various risk factors such as contact with active tb patient, born or stay in country with high prevalence tb. Study was conducted in a preliver transplant clinic in Canada</td><td>TST</td><td>IGRA (QFT)</td><td>Overall results

5mm cut off
<table>
<tr><th></th><th>TST+</th><th>TST-</th><th>Total</th></tr>
<tr><td>IGRA+</td><td>25</td><td>9</td><td>34</td></tr>
<tr><td>IGRA-</td><td>12</td><td>95</td><td>107</td></tr>
<tr><td>Total</td><td>37</td><td>104</td><td>141</td></tr>
</table>

10mm cut off
<table>
<tr><th></th><th>TST+</th><th>TST-</th><th>Total</th></tr>
<tr><td>IGRA+</td><td>18</td><td>16</td><td>34</td></tr>
<tr><td>IGRA-</td><td>9</td><td>98</td><td>107</td></tr>
<tr><td>Total</td><td>27</td><td>114</td><td>141</td></tr>
</table>

Indeterminate IGRA result 12/153= 7.8%</td><td>Not determined</td><td>Test kits provided by Cellestis Ltd</td><td>Authors conclude that study demonstrates that IGRA and TST performed similarly for the diagnosis of LTBI in a population with end stage liver disease.</td></tr>
</table>

Key: CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

<table>
<tr><th>Bibliography (Ref id)</th><th>Number of participants. Type of study/Country of origin. Immunocompromised

Condition/Medicines.

Risk factors. Characteristics</th><th>Reference Test</th><th>Index Test</th><th>Specificity & Sensitivity or Modified Measure of effect/Measures of agreement</th><th>Positive and Negative predictive values</th><th>Source of Funding</th><th>Comments</th></tr>
<tr><td>Shovman, O., Anouk, M., Vinnitsky, N., Arad, U., Paran, D., Litinsky, I., Caspi, D., & Elkayam, O. 2009 (3413)</td><td>Study performed in Israel. 35 rheumatoid arthritis patients and 15 controls</td><td>TST(2TU 0.1ml PPD RT23)</td><td>IGRA(QFT)</td><td>Overall results

<table>
<tr><td></td><td colspan="3">TST results as percentage</td></tr>
<tr><td></td><td>+ve</td><td>-ve</td><td>Anergy</td></tr>
<tr><td>RA</td><td>45</td><td>17</td><td>37</td></tr>
<tr><td>Control</td><td>15</td><td>7</td><td>78</td></tr>
</table>

<table>
<tr><td></td><td colspan="3">IGRA results by percentage</td></tr>
<tr><td></td><td>+ve</td><td>-ve</td><td>ind</td></tr>
<tr><td>RA</td><td>11.4</td><td>60</td><td>28.6</td></tr>
<tr><td>Control</td><td>13</td><td>87</td><td>0</td></tr>
</table>
RA = Rheumatoid Arthritis</td><td>Not determined</td><td>Not recorded</td><td>The authors commented that the high rate of indeterminate results reduces the clinical utility of IGRA and questions its use in the diagnosis of LTBI in rheumatoid arthritis patients.</td></tr>
</table>

<u>**Key:**</u> CXR=Chest X-Ray, Adj=adjusted, OR=Odds Ratio, HR=Hazard Ratio, TST=Tuberculin Skin Test, QFT-G/QFT-GIT=Quantiferon TB Gold/Quantiferon TB Gold In-Tube, CI=Confidence Interval, QFT+=positive QFT test result, TST+=positive TST result, IGRA+=positive IGRA result, T-SPOT+=positive T-SPOT result, n.s=non-significant, NPV=Negative predictive value, PPV=positive predictive value, HCW=Health Care Worker, LTBI=Latent TB Infection, OPD=Outpatient Department, ED=Emergency Department, HCP=Health Care Profession

Evidence Tables: Screening

Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
Harada, N., Nakajima, Y., Higuchi, K., Sekiya, Y., Rothel, J., & Mori, T. 2006 (Ref ID 1009)	332 Japanese Healthcare workers of mean age 41.4 years. 15 participants were BCG naive while 14 had unknown BCG status. 95% of participants had been vaccinated. Some of the participants were employed on a tuberculosis ward while the others were employed on the outpatients' tuberculosis clinic. These participants were not newly employed.	TST	IGRA (QFT)	The authors conducted univariate and multivariate analysis. They found that age relative to persons aged over 30 years, for each decade of increased age, history of working in a tuberculosis ward, and history of working in the outpatient department of the hospitals tuberculosis clinic were significantly associated with a positive IGRA result. The measure of effect was the odds ratio.	Japanese Ministry of health, labour and welfare	Authors comment that for a small number of HCW who had TST reactions of 30mm and above, the rate of QFT positivity was significantly higher, suggesting that such strong tuberculin reactions may more likely represent tuberculosis. However there was no significant correlation between QFT positivity and tuberculin reaction size for HCW with a diameter less than 30mm.
Alvarez-Leon E et al 2009 (Ref ID 23)	Cross sectional study of 134 Healthcare workers of mean age 33.4 years in Spain in an 800-	TST	IGRA (QFT)	Multivariate analysis confirmed that the only significant risk factor for a positive TST result was working as an orderly, whereas only age (yearly increase in age) remained as a significant risk factor associated with	Evaluation of Sanitary Technologies	Authors note that a positive IGRA results with high interferon gamma levels should be taken into

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	bed university hospital to which 50 to 60 tuberculosis patients are admitted annually.35% of participants had been BCG vaccinated.			a positive QFT result. Variables such as age, sex, employment category, and number of years in healthcare profession were adjusted for.		account. They note however that in the absence of long term follow up data, it could be too early to replace the TST with IGRA in HCW for LTBI screening.
Storla, D.G., Kristiansen, I., Oftung, F., Korsvold, G.E., Gaupset, M., Gran, G., Overby, A.K., Dyrhol-Riise, A.M., & Bjune, G.A. 2009 (Ref ID 60)	155 **exposed** HCWs and 48 healthy controls. All but one of them had a visible scar from BCG vaccination.	TST	IGRA (T.SPOT.TB)	Measured concordance between IGRA and TST.	Study financed by participating hospitals and Norwegian Institute of Public Health	The authors found that the risk of a positive TST result was associated with prior BCG vaccination.

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Hotta, K., Ogura, T., Nishii, K., Kodani, T., Onishi, M., Shimizu, Y., Kanehiro, A., Kiura, K., Tanimoto, M., & Tobe, K. 2007(Ref ID 3967)	Prospective study of participants enrolled at the **beginning of their clinical training**. The participants consisted of medical, nursing and dental students. The study was conducted in Japan. Most students had been BCG vaccinated	TST	IGRA	Measured concordant results stratified by cut off point of TST.	Not recorded	The authors conclude that IGRA and TST results were quite discordant in a medical university setting, probably because of the influence of BCG vaccination on the TST results.

Result	>5	>10	>15
Tst+/igra+	1.4%	1.4%	1.4%
Tst-/igra-	17.4%	39.6%	71.0%
Tst+/igra-	78.7%	56.5%	25.1%
Tst-/igra+	0	0	0

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<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type and Population Screened</th><th>Reference Test</th><th>Index Test</th><th>Measure of effect</th><th>Source of funding</th><th>Authors Comments</th></tr>
<tr><td>Zhao, X., Mazlagic, D., Flynn, E.A., Hernandez, H., & Abbott, C.L. 2009 (Ref ID 3)</td><td>Cross sectional study. Pilot of 40 HCWs 20 of whom had tested positive to TST and 20 negative. Study was based in a hospital in United States.</td><td>TST</td><td>IGRA (QFT)</td><td>Measured discordance between TST and IGRA
<table>
<tr><th></th><th>Igra+</th><th>Igra-</th><th>Tot</th></tr>
<tr><td>TST+</td><td>10</td><td>10</td><td>20</td></tr>
<tr><td>TST-</td><td>0</td><td>20</td><td>20</td></tr>
<tr><td>Tot</td><td>10</td><td>30</td><td>40</td></tr>
</table></td><td>Not recorded</td><td>Paper mentions that participants were interviewed about confounding factors. However the proportion of BCG vaccinated individuals is not stated.</td></tr>
</table>

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Bibliographic Reference (Ref ID)	Study type and Population Screened	Reference Test	Index Test	Measure of effect	Source of funding	Authors Comments
Cummings, K.J., Smith, T.S., Shogren, E.S., Khakoo, R., Nanda, S., Bunner, L., Smithmyer, A., Soccorsi, D., Kashon, M.L., Mazurek, G.H., Friedman, L.N., & Weissman, D.N. 2009(Ref ID 3420)	Observational study looking at **newly** hired HCWs in a hospital in the United States. 96% were born in the US and had a median age of 28years. 93% did not report having a risk factor for TB or BCG vaccination.	TST	IGRA (QFT)	Discordance and concordance between the tests were measured. The overall agreement between the TST result and the 1st IGRA results was 96% but the agreement on positive results was 0%.	The work was financially supported by the National Institute of Environmental Health Services.	Paper was very inclusive about the advantages of IGRA over TST. The authors also said that in low risk populations where the pre test probability of a negative result is high, reanalysis of positive results may improve the test's diagnostic efficiency.

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Appendix P-Data for meta-analysis for children

Study ID	Study	High and low risk as defined by exposure	Test	ROR	Log ROR	SE
1434	Brock et al 2004	Paper was already separated into high and low exposure. High=individuals with close contact to index case through household, school class or the local choir. Low=other classes at the high school that had no connection with index case.	QFT-RD1	1.930159	0.657602	0.712432
276	Chun et al 2008	High exposure=children with history of close contact with index case, low=children with casual contact-the index cases for these children were relatives living in different households or school teachers.	QFTG	0.935829	-0.06632	0.614417
3427	Hansted et al 2009	Study was already separated into high and low exposure. High=those living with a family member with infectious TB or having contact in school classes, low=no identifiable risk factor for TB.	T-SPOT	2.559359	0.939757	0.541671
164	Higuchi et al 2009	High=close contact group who were students in the class where the index case was the teacher in charge. These students had aggregate of at least 90 hours, low=casual contacts consisting of other students attending the same school.	QFT	4.475623	1.498646	0.600847
282	Lighter et al 2009	Study already separated into high, low/moderate and minimal exposure. High=known direct contact with index case, low=no known risk factors for TB or low moderate risk including birth in or travel to disease endemic region and/or living with a household member with specific risks (HIV, emigration from high endemic region, history of imprisonment etc)	QFT	9.580645	2.259745	0.603062
393	Okada et al 2008	Used smear positivity of index case to separate into high and low exposure. High=smear positive grade 1+, low=smear negative.	QFT	2.089849	0.737092	0.555979

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Appendix Q- Data for meta-analysis for contacts

Study ID	Study	BCG Vaccination	High and low risk as defined by exposure	Test	ROR	Log ROR	SE
60	Kik 2009	83%	High=household contact, low=non-household contact or unknown. No other definitions given.	QFTG	1.345167	0.296518	0.312163
				T-SPOT	1.325594	0.281861	0.313462
479	Brodie 2008	68% contacts 75% controls	High=Close contact, low=control subjects. Controls defined as having no or ≤8 hours of contact with active case per week. Close contact defined as having ≥8 hours of contact per week.	T-SPOT	5	1.609438	0.461184
23	Alvarez-Leon 2009	35.1%	Used exposure based on direct contact with TB. High=direct contact, low=no direct contact. Exposure based on whether HCW had direct contact with TB patient (yes/no response).	QFTG	0.832	-0.18392	0.693304
112	Khana 2009	82.5%	Used previous direct contact with TB High=previous contact, low=no contact. Defined as contact at a conversational distance with a person who had sputum smear positive for TB.	QFTG	0.89798	-0.10761	0.99908
1199	Kang 2005	Close contacts 67% Low risk 93%, casual contacts 90%	High exposure=close contacts (gp3), low exposure=low risk infection & casual contacts (gp 1 & 2). Close contacts defined as household contact or worked in same room as active case for ≥8 hours/day. Low risk of infection defined as healthy students without risk for exposure. Casual contacts defined as healthy hospital staff with history of casual contact with active TB patients.	QFTG	4.409511	1.483764	0.453007
226	Topic 2009	All BCG vaccination	High =group A (TB wards), low=group B (non-TB ward). High risk (group A) defined as HCWs from TB ward & were exposed directly to TB patients during office hours over period of >5 years. Low risk (group b) defined as those from non-TB wards without direct exposure to TB patients.	QFTG (10mm)	0.906971	-0.09764	0.595566
				QFTG (15mm)	1.052734	0.051391	0.596232
3408	Girardi	37.4%	High=high TB risk, low=low TB risk (this is based on ward/service). High risk ward	QFT	0.485704	-0.72216	0.4170

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Study ID	Study	BCG Vaccination	High and low risk as defined by exposure	Test	ROR	Log ROR	SE
	2009		defined as one with >1 patient with TB cared for per year. Low risk wards do not have >1 patient with TB-e.g. pediatrics, internal medicine & epidemiology.				46
				T-SPOT	1.150462	0.140164	0.4001 34
137	O'Neal 2009	23%	By work site (high=cutting, packaging & boxing & low= other). Index case worked in cutting area (adjacent to packaging and boxing areas).	QFTG	0.624383	-0.47099	1.3175 91
455	Diel 2008	46%	High=100-<200hrs & 200+ hrs. Low=40-<60hrs & 60-<100hrs. Hours of exposure are during the presumed period of infectiousness (before diagnosis of his or her respective index case)	QFTG	1.079863	0.076834	0.2413 87
1101	Zellweger 2005	86%	Already in high and low exposure groups based on length or type of exposure. High exposure defined as exposure of long duration (>8 hours) or close exposure (>1 hr face to face in same room at <2 m distance). Other participants defined as low exposure.	T-SPOT	2.708333	0.996333	0.6916 7
3428	Casas 2009	15.6%	By occupational TB degree exposure high=HCWs from wards with ≥5 contagious patients per year, low=wards with 1-4 contagious patient per year (medium + high categories from paper).	QFT	1.940625	0.66301	0.3696 02
				T-SPOT	3.01875	1.104843	0.3666 4

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