1 Appendix K: CG33 and CG117 referenced appendices

2 CG33

2.1 Appendix A: Clinical questions and search strategies 2006

Table

Question	Search Filters	Study Type	Database and Year
Section 5: Diagnosis			
DIAG1: What symptoms are suggestive of a diagnosis of respiratory TB disease?	These questions, which do not lead directly to recommendations, were not subject to a systematic literature search.		
DIAG2: What symptoms are suggestive of a diagnosis of non-respiratory TB?			
DIAG3: Whilst awaiting culture results in patients suspected of respiratory TB, what other tests (plain x ray and sputum smear microscopy and gastric washings in children) are predictive of a positive diagnosis? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive c) In children	Diagnosis		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 547 abstracts reviewed
DIAG4: In the presence of a negative culture, what other tests (plain x ray and sputum smear microscopy, tuberculin skin test) may support a positive diagnosis? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive	Diagnosis		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 81 abstracts reviewed
DIAG5: Whilst awaiting culture results in patients suspected of non-respiratory TB, is histology from biopsy predictive of a positive diagnosis? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive	Diagnosis		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 448 abstracts reviewed
DIAG6: In the presence of a negative culture, what other	Diagnosis		Medline 1966 – 2004 Embase

tests (histology from biopsy, tuberculin skin test) may support a positive diagnosis? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive			1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 62 abstracts reviewed
RAPD1: When should molecular methods for rapid diagnosis be used in patients with suspected TB disease?	These questions were answered by the NCCHTA met-analysis in the area, augmented by additional papers not found by the search but suggested by GDG members.		
RAPD2: When should liquid culture for rapid diagnosis be used in patients with suspected TB disease?			
Section 6: Management of Respiratory Tuberculosis			
MGTR1: In patients with respiratory TB on drug treatment, are regimens of less than six months duration as effective as regimens of six months or longer in eradicating TB infection? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive c) In children	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 780 abstracts reviewed
MGTR2: In patients with respiratory TB on drug treatment, are intermittent dosing regimens as effective as daily drug treatment regiments in eradicating TB infection? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive c) In children	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 490 abstracts reviewed
MGTR3: In patients with respiratory TB on drug treatment, are regimens of combination tablets as effective as single drug treatments in eradicating TB infection?	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 378 abstracts reviewed
MGTR4: What measures should be taken in terms of infection control in patients with smear positive disease not suspected to have MDR-TB? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) 499 abstracts reviewed
MGTR5: What measures should be taken in terms of infection control in patients with smear positive disease	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years)

suspected to have MDR-TB? Sub-questions from a single literature search: a) In people not known to be HIV-positive b) In people known to be HIV-positive			Cinahl 1982 – 2004 HMIC (all years) 136 abstracts reviewed
DOT1: In patients on drug treatment for TB disease or prophylactic drug treatment for TB infection, is directly observed therapy (DOT) effective in ensuring cure and/or treatment completion, compared to self-administered treatment?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 436 abstracts reviewed
DOT2: In which patients on drug treatment for TB disease or prophylactic drug treatment for TB infection, is DOT most effective in comparison with self-administered treatment in ensuring cure and/or treatment completion?	Removed Reviews, RCTs and letters.		Medline 1966 – 2004 Embase 1980 – 2004 Cinahl 1982 – 2004 271 abstracts reviewed
DOT3: In patients on drug treatment for TB disease or prophylactic drug treatment for TB infection administered by directly observed therapy (DOT), who is the most effective observer (health professional, lay health worker or family/community member) in ensuring cure and/or treatment completion?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 425 abstracts reviewed
CONC1a: Which concordance promoting strategies (e.g. patient reminder cards, patient education, an incentive for patients, help from peer group through community health workers or intensive staff supervision) are effective in ensuring cure and/or treatment completion, compared to self-administered treatment in patients on drug treatment for TB disease?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) PsycINFO 1887 – 2004 AMED 1987 – 2004 338 abstracts reviewed
CONC1b: Which concordance promoting strategies (e.g. patient reminder cards, patient education, an incentive for patients, help from peer group through community health workers or intensive staff supervision) are effective in ensuring cure and/or treatment completion, compared to self-administered treatment in patients on prophylactic drug treatment for TB infection?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) PsycINFO 1887 – 2004 AMED 1987 – 2004 80 abstracts reviewed

FUP1: In previously drug treated tuberculosis patients, is routine follow up effective in identifying relapse in comparison with no follow up?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 62 abstracts reviewed
Section 7: Management of Non-Respiratory TB			
MGTM1a: In adults with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve-month drug treatment regimen in eradicating TB infection?	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 478 abstracts reviewed
MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve-month drug treatment regimen in eradicating TB infection?	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) 100 abstracts reviewed
MGTM2: In patients of all ages with TB meningitis disease, do corticosteroids as an adjunct to an anti-tuberculosis drug treatment regimen, decrease morbidity and mortality compared to an anti-tuberculosis drug regimen alone?	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 485 abstracts reviewed
MGTO1: In patients with peripheral lymph node TB on drug treatment, are regimens of six months duration as effective as regimens of other durations in eradicating TB infection?	Systematic Review and RCT		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 128 abstracts reviewed
MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB infection?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 234 abstracts reviewed
MGTO3: In patients with TB of the spine, is surgery (anterior spinal fusion) with short course chemotherapy more effective than short course chemotherapy alone in eradicating TB infection?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 203 abstracts reviewed
MGTO4: In patients with TB pericarditis on drug treatment, are regimens of six months duration as effective as regimens of longer durations in reducing mortality and	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 108

morbidity?			abstracts reviewed
MGTO5: In patients with TB pericarditis, are corticosteroids in addition to drug treatment, effective in reducing mortality and morbidity compared to drug treatment alone?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 66 abstracts reviewed
MGTO6: In patients with disseminated TB (including miliary) on drug treatment, are regimens of six months duration as effective as regimens of longer durations in reducing mortality and morbidity?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 213 abstracts reviewed
MGTO7: In patients with genitourinary TB on drug treatment, are regimens of six months duration as effective as regimens of longer durations in reducing mortality and morbidity?	This question was not specifically searched on the decision of the GDG that all evidence was identified by searches for MGTO1-6.		
Section 8: Management of Latent TB			
LATD1: In patients with suspected TB infection are interferon gamma immunological tests more accurate tests of infection than the tuberculin skin test: Sub-questions from a single literature search: a) in people not known to be HIV-positive b) in people known to be HIV-positive c) in children	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 288 abstracts reviewed
LATM1: Which patients with TB infection or in close contact with smear positive pulmonary TB, according to their risk factors, should receive chemoprophylaxis?	Epidem. studies and Prognosis		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) 966 abstracts reviewed
LATM2: In patients with TB infection, is a prophylactic drug treatment regimen for six months effective in preventing the development of TB disease in comparison with treatment regimes of less than six months? Sub-questions from a single literature search: a) In adults b) In children	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) 234 abstracts reviewed
HIVM1: In HIV positive patients with TB infection, is a standard isoniazid containing prophylactic drug treatment regimen effective in preventing the development of TB	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 237

disease in comparison with other prophylactic drug treatment regimens?			abstracts reviewed
HIVM2: In HIV positive patients with TB infection, is a prophylactic drug treatment regimen effective in preventing the development of TB disease in comparison with placebo?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 79 abstracts reviewed
Section 9: Drug-resistant TB			
MDRD1: In patients with suspected TB disease, which relative risk factors are associated with a higher level of: Sub-questions from a single literature search: a) multi-drug resistant TB (MDR-TB)? b) any drug resistance?	Epidem. studies (cohorts/case-controls)		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 BNI 1982 – 2004 265 abstracts reviewed
MDRR1: To whom should patients with multi-drug resistant TB be referred once diagnosis is confirmed?	RCT/Prognosis/ Epidem. studies (cohorts/case-controls)		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (all years) 463 abstracts reviewed
Section 10: BCG vaccination			
BCG1: In newborns (up to 3 months old), is BCG vaccination effective in preventing the development of TB infection or disease in comparison with no vaccine?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 388 abstracts reviewed
BCG2: In school-aged children, is BCG vaccination effective in preventing the development of TB infection or disease in comparison with no vaccine?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC 1985 – 2004 BNI 1985 – 2004 166 abstracts reviewed
BCG3: In arrivals from high-risk countries, is BCG vaccination effective in preventing the development of TB infection or disease in comparison with no vaccine?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC 1985 – 2004 BNI 1985 – 2004 136 abstracts reviewed
BCG4: In health care workers, is BCG vaccination effective in preventing the development of TB infection or disease in	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years)

comparison with no vaccine?			Cinahl 1982 – 2004 HMIC 1985 – 2004 BNI 1985 – 2004 308 abstracts reviewed
BCG5: In contacts of those with TB disease, is BCG vaccination effective in preventing the development of TB infection or disease in comparison with no vaccine?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC 1985 – 2004 BNI 1985 – 2004 215 abstracts reviewed
BCG6: Is tuberculin testing cost-effective in selecting people for BCG vaccination?	This question was answered by health economic modelling rather than literature searches.		
Section 11: Active case finding			
CTS1: Are contact tracing procedures effective in identifying cases of tuberculosis disease or infection (excluding M Bovis)?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 360 abstracts reviewed
CTS2: Are contact tracing procedures effective in identifying cases in human contacts of *M Bovis* diseased cattle?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 29 abstracts reviewed
CTS3: Are contact tracing procedures which identify casual contacts in addition to close contacts effective in identifying cases of tuberculosis disease or infection?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 35 abstracts reviewed
OUTB1: Is contact tracing in suspected outbreaks of TB disease effective in identifying cases of tuberculosis disease or infection on aircraft?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004

			HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 28 abstracts reviewed
OUTB2: Is contact tracing in suspected outbreaks of TB disease effective in identifying cases of tuberculosis disease or infection in schools?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 89 abstracts reviewed
OUTB3: Is contact tracing in suspected outbreaks of TB disease effective in identifying cases of tuberculosis disease or infection in hospitals?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HealthPROMIS 1970 – 2004 Ingenta 1988 – 2004 99 abstracts reviewed
FACT1: In recent arrivals/returns from high prevalence areas, is a new entrant screening clinic effective in identifying cases of TB infection or disease, in comparison with other methods of service provision?	Comparative studies only in Medline and Embase.		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All years) BNI 1982 – 2004 151 abstracts reviewed
FACT2: What is the most effective screening method (Heaf test, gamma-immunological test, symptom questionnaire or chest x ray) to identify cases of TB infection or disease in recent arrivals/returns?	Comparative studies only in Medline and Embase.		
FACT3: What is the most effective screening method (Heaf test, gamma-immunological test, symptom questionnaire or chest x ray) to identify cases of TB infection or disease in street homeless people?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All years) 250 abstracts reviewed
Section 12: Preventing Infection in Specific Settings			
NHS1: What pre-and on-employment measures for new employees of NHS hospitals are effective in the prevention and control of TB?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All

NHS2: What measures are effective in staff in employment in NHS hospitals in terms of the prevention and control of TB?	None	All study designs	years) Health PROMIS (All years) 464 abstracts reviewed
NHS3: What measures are effective in staff with TB in employment in NHS hospitals in terms of prevention and control of TB?	This question was removed on the decision of the Project Executive that all issues had been addressed by NHS2.		
NHS4: What measures are effective in HIV infected health care workers in terms of pre-employment screening assessment for prevention and control of TB?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All years) Health PROMIS (All years) 331 abstracts reviewed
NHS5: What measures are effective in NHS workers known to be HIV-positive already in employment in terms of continuing assessment?	None	All study designs	
SETT1: Are there specific strategies that are more effective at preventing and controlling TB disease and infection in prisons?			Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All years) 362 abstracts reviewed
SETT2: Are there specific strategies that are more effective at preventing and controlling TB disease and infection in schools?	This question was removed on the decision of the Project Executive that all issues had been addressed by other clinical questions.		
SETT3: Are there specific management strategies that are more effective at preventing and controlling TB disease and infection in community childcare settings?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 HMIC (All years) 164 abstracts reviewed

2.2 Appendix G: Summary of Healthcare Needs Analysis - 2006

The epidemiology of tuberculosis in England and Wales (2004)

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Mrs Delphine Antoine - Tuberculosis surveillance co-ordinator, Health Protection Agency Centre for infections, London

Dr John Hayward - former Director of Public Health, Newham Primary Care Trust, London

Dr Jane Jones - Consultant Epidemiologist, Health Protection Agency Centre for infections, Communicable Disease Surveillance Centre, London

Dr Helen Maguire - Regional Epidemiologist, Health Protection Agency, London

Dr Jonathan Mant - Senior Lecturer, University of Birmingham

Professor Peter Ormerod - Consultant Physician, Blackburn Royal Infirmary, Blackburn

Ms Sally Taylor - Trainee Information Analyst, Patient Data Information Team, Health Solutions Wales

Dr John M Watson - Consultant Epidemiologist and Head of Respiratory Diseases, Health Protection Agency Centre for infections, London

Context
This summary overview of the epidemiology of TB disease in England and Wales was originally presented to the GDG in April 2004 both as background and as an aid to assist in the group's formulation of practical and relevant guideline recommendations. It is not therefore based on the most up to date epidemiological data available at the time of publication of this guideline, but is intended only as a record of what was considered by the GDG in the context of the guideline development process.

Introduction
Tuberculosis (TB) remains a major international public health concern, with the global incidence rate increasing at approximately 0.4% per year, but much faster in sub-Saharan Africa and in countries of the former Soviet Union. The 183 countries reporting to WHO in 2001 notified 3.8 million TB cases (62 per 100 000 population), of which 1.6 million (42%) were

sputum smear-positive. The African (21%), SouthEast Asian (37%), and Western Pacific Regions (22%) accounted for 80% of all notified cases and similar proportions of sputum smear-positive cases. ({WHO Global Tuberculosis Control Report, 2003})

In the context of the WHO European region, which includes 51 countries, 385 810 cases of TB were notified in 2000, with an overall incidence of 44 per 100 000 population ({Euro TB, 2003}). In the 14 Western European countries the incidence was 12 per 100 000, with the United Kingdom being only one of four countries in this region reporting an increase (less than 2% annually) in TB notification rates between 1995 and 2000 ({Euro TB, 2003}). Despite the relatively low incidence for the UK in 2000 of 11.4 per 100 000 population, the slight annual increase in TB notifications since 1995 is a cause for concern.

Tuberculosis disease and death rates in England and Wales

In England and Wales all forms of TB disease are compulsorily notifiable by the physician making or suspecting the diagnosis under the Public Health (Control of Disease) Act 1984. It first became a statutory requirement to notify suspected cases of TB in 1913, and the 1921 Public Health Tuberculosis Act expanded this legal requirement throughout England and Wales. This statutory notification of infectious diseases system (NOIDS) continues to play a role in the surveillance of TB. (Source: Health Protection Agency - CDSC - TB section).

However, Enhanced Tuberculosis Surveillance, a system established in 1999 for the collection of more detailed information on the occurrence of tuberculosis in England and Wales, recently reported higher case numbers of TB disease compared to NOIDS. Enhanced TB Surveillance provides an annual corrected analysis of TB case reports by age, sex, ethnic group, country of birth, site of disease and NHS region, and from 2002, treatment outcome. This system has reported a continued rise in TB disease cases from 1999 to 2002, and as it involves several measures to validate reports, it is likely better to reflect the true incidence of TB. For this reason caution is advised in interpreting recent NOIDS data. (CDR Weekly vol. 14 no. 30, 2004).

It should be noted that neither the NOIDS nor Enhanced TB Surveillance systems collect information on persons with latent TB infection. The data in this document refer only to cases of active TB disease, and not to latent infection.

Between 1913 and 1987 the TB notification rate in England and Wales fell from over 320 per 100 000 to 10.1 cases per 100 000 population. However, the period 1987 to 2002 has seen a trend towards increasing rates (10.1 to 12.9 per 100 000).

The TB death rate declined overall from 1.14 to 0.73 per 100 000 population in the 20-year period 1982 to 2002. Most of this decline occurred in those aged 45–64 and 65 plus (reductions of 1.12 and 1.44 per 100 000 population respectively). However, over the same period there was a slight increase in the death rates for younger age groups (see Table i below).

Table i: Increase in TB death rates over the 20-year period 1982–2002

Age group	Increase in TB death rates per 100 000 population 1982–2002
15–24	0.03
25–34	0.9
35–44	0.1

Source: Health Protection Agency

TB cases by region

Enhanced TB Surveillance data on regional variation in TB disease prevalence indicate that London had the highest rates in England and Wales for the period 1999–2001, and experienced the sharpest increase in TB disease rates over this time from 32.8 to 37.8 per 100 000 (an increase of 5 per 100 000).

TB Notification data for 2002 show great cross-sectional variation in the TB disease rates in London boroughs varying from 89 per 100 000 in Newham to 3 per 100 000 in Bromley. Longitudinal trends have also varied between different London boroughs, for example in the 20-year period from 1982 to 2002, when rates in Hackney increased from 33 to 65 per 100 000, while in Hammersmith and Fulham they fell from 35 to 6 per 100 000. (Source: Health Protection Agency London, Notifications of Tuberculosis per London borough, 1982 – 2003)

Rising notification rates within boroughs may reflect changing demographic characteristics in populations, which increase the likelihood of TB disease occurring, rather than an inability of local health services to deal with a static public health problem.

Table ii below shows the regional variation in TB disease rates for England and Wales outside of London for 2001. While other cities in England and Wales apart from London may have high rates of TB disease relative to their surrounding suburban and rural areas, HPA data on TB rates in cities other than London were unavailable when the GDG considered these data in 2004, due to potential limitations in the datasets and calculation procedures used.

Table ii: TB disease rates by region in England and Wales 2001

Regions with relatively high TB disease rates	Cases per 100 000 population	Regions with relatively low TB disease rates	Cases per 100 000 population
East Midlands	13.7	North East	7.4
West Midlands	13.5	Wales	6.3

Yorkshire and Humberside	11.3	Eastern	6.1
North West	9.7	South East	5.9
		South West	4.4

Sources: Health Protection Agency, National Statistics

TB case rates and ethnic group

Enhanced TB Surveillance data for 2001 show that nationally, the Black African ethnic group had the highest TB disease rate followed by the Pakistani and Indian ethnic groups (see Table iii below).

Table iii: TB disease case rates by ethnicity, 2001

Ethnic group	TB case rate per 100 000 population
Black African	211
Pakistani	145
Indian	104
White	4

Source: Health Protection Agency, {Akhtar and Antoine (2003)}

It is possible that regions with larger populations of ethnic minorities may have higher overall numbers of TB cases in comparison to regions with smaller ethnic minority populations. The following two sections focus on data relevant to this issue.

TB cases by ethnicity and region

In 2001 Whites accounted for more than half of the TB disease caseload in Wales, the South West, North East, and East Midlands. In London, the West Midlands, the North West, South East, and Yorkshire and Humberside other ethnic minority groups contributed the major proportion of TB disease cases (Table iv).

Table iv: TB cases (proportion) reported by region and ethnic group, 2001

Region of reporting	White	Black African	Indian	Pakistani	Bangladeshi
East Midlands	52%	10%	15%	20%	0%
Eastern	42%	13%	14%	21%	3%
London	17%	30%	22%	8%	4%
North East	68%	8%	5%	10%	2%
North West	38%	6%	17%	29%	2%
South East	42%	10%	15%	18%	1%
South West	69%	7%	7%	5%	1%
Wales	73%	5%	7%	10%	2%
West Midlands	30%	6%	26%	25%	4%
Yorkshire & Humberside	33%	8%	9%	43%	1%
TOTAL	32%	17%	18%	17%	3%

Source: Health Protection Agency

TB cases by ethnicity and country of origin

It would be an oversimplification to attribute the high TB case rates in London (37.8 per 100 000) solely to the presence of greater concentrations of ethnic minority groups in the city. Data for the period 1998 to 2001 found that TB disease rates were substantially higher in people born abroad compared to those born in the UK (see table v below).

Table v: Trend in TB disease case rates in people born in the UK and abroad

Born in UK	TB case rate per 100 000 population	Born abroad	TB case rate per 100 000 population
1998	4.8	**1998**	72.7
2001	4.3	**2001**	78. 6

Source: Health Protection Agency

Foreign-born TB cases accounted for 63% of the national caseload and people born abroad were 15 times more likely to have TB disease compared to those born in the UK. (Source: Health Protection Agency)

In terms of ethnicity, TB disease rates for people born in the UK were much lower for all groups, compared to the rates for those born abroad (Table vi below).

Table vi: Trend in TB disease case rates by ethnicity in people born in the UK and abroad

Born in the UK	TB disease case rate per 100 000 population	Born abroad	TB disease case rate per 100 000 population
Black Africans	36	Black Africans	294
Indian Subcontinent	42	Indian Subcontinent	180
White	3.2	White	8.7

There was also considerable variation between the different ethnic groups for time from entry into the UK until development of TB disease (N=5589 cases; Table vii below), with the Black African ethnic group tending towards shorter time to active TB.

Table vii: Proportion of TB cases reported in the foreign born population by ethnic group, and by time since entry into the UK, 1998 – 2001

	< 1 year	1–4 years	5–9 years	10 years and over
White	16.4%	24.6%	11.9%	47.0%
Black African	11.9%	45.1%	34.2%	8.8%
Indian	6.3%	25.2%	16.4%	52.1%
Pakistani	9.0%	24.8%	16.4%	49.7%
Bangladeshi	7.6%	17.4%	17.4%	57.6%

Source: Health Protection Agency

Foreign-born people resident in the UK for less than one year contribute proportionally fewer cases of TB disease to the annual data than all foreign-born residents settled in the country for at least 10 years. However, this should not obscure the fact that the rates of TB disease in new immigrants are much higher than among foreign-born residents living in the UK for at least 10 years.

There is wide regional variation in the ratio of foreign-born TB cases to cases born in the UK. Table viii below shows the opposite ends of the spectrum in this regard for 2001.

Table viii: Foreign and local born TB cases in London and Wales, 2001

Region	Foreign-born TB cases	Local born TB cases	TB cases with no data on place of birth
London	1934 (71.2%)	455 (16.7%)	328 (12.1%)
Wales	29 (15.8%)	107 (58.5%)	47 (25.7%)

Source: Health Protection Agency

Wales, the South West and the North East had the highest proportions of local-born TB cases, while London, the South East, Eastern and North Western parts of England had the highest proportions of foreign-born TB cases. (Source: Health Protection Agency – CDSC - TB section-2001- Enhanced TB Surveillance).

Ethnicity, place of birth, and length of residence in the UK all appear to be important factors in accounting for regional variation in rates of TB disease in England and Wales. In the following section, the contribution of age and sex variables is explored.

TB cases by sex and age

The 1998 TB Survey and Enhanced TB Surveillance data from 1999 to 2001 provided national TB case rates broken down by sex and age. In 2001, men aged 25–34 had the highest TB disease rates (see Table ix). Women had somewhat lower TB disease rates, with those aged 25–34 having the highest.

Table ix: TB disease rates by sex and age group, 2001

Age group	Male TB disease case rate per 100 000 population	Female TB disease case rate per 100 000 population
15–24	16	14.9
25–34	23.7	17.5
65 +	19	12

Source: Health Protection Agency

Longitudinal data for the 1998–2001 period (Table x below) indicate that rates for younger males and females (15–24; 25–34) appear to be increasing, compared to older age groups.

Table x: TB disease case rates for males and females aged 15–34, 1998–2001

Year	Males aged	Males aged	Females aged	Females aged

	15–24, TB cases per 100 000	25–34, TB cases per 100 000	15–24, TB cases per 100 000	25–34, TB cases per 100 000
1998	11.9	17.6	13.1	13.3
1999	13.9	16.1	13.3	14.5
2000	15.1	22.1	14.0	17.0
2001	15.9	23.7	14.9	17.5

Source: Health Protection Agency

Regional variations in TB cases by age and sex

There is also regional variation in the distribution of TB disease cases according to age group. Enhanced Surveillance data for 2001 showed the highest proportions of TB cases outside of London and Eastern England occurred in those aged 45–64 and 65 plus (Table xi below). In Eastern England and London the highest proportions of TB cases occurred in those aged 25–34.

Table xi: Proportion of TB cases reported by age group and region, 2001

Region	0–14 yrs	15–24 yrs	25–34 yrs	35–44 yrs	45–64 yrs	65+yrs	Total pop
East Midlands	14.1%	14.9%	18.1%	14.1%	19.7%	19.2%	100.0%
Eastern	5.2%	13.7%	26.8%	11.9%	18.6%	23.8%	100.0%
London	6.0%	16.6%	28.6%	17.7%	19.8%	11.4%	100.0%
North East	7.0%	7.0%	15.7%	11.9%	28.6%	29.7%	100.0%
North West	4.6%	14.9%	19.8%	16.9%	21.8%	22.1%	100.0%
South East	3.6%	13.0%	20.9%	18.5%	22.3%	21.7%	100.0%
South West	1.9%	11.1%	13.9%	10.6%	22.7%	39.8%	100.0%
Wales	13.1%	9.8%	13.7%	7.7%	16.4%	39.3%	100.0%
West Midlands	7.9%	16.0%	20.2%	11.2%	22.9%	21.9%	100.0%
Yorkshire & Humberside	11.4%	13.0%	17.8%	11.5%	22.9%	23.4%	100.0%
TOTAL	7.1%	14.9%	23.1%	15.2%	20.9%	18.8%	100.0%

Source: Health Protection Agency

TB disease can either arise from recent exposure to and infection with Mycobacterium tuberculosis, or from the reactivation of dormant tubercule bacilli years or decades after initial infection ({Elender et al., 1998}, p.674). In England and Wales, older people who lived through a period of high TB incidence are more likely to have been infected, and reactivation of bacilli in this population may account for a large proportion of TB cases occurring in the age 45–64 and 65 plus age groups. In contrast, TB cases in younger age groups are more likely to be due to newly acquired external infection ({Elender et al, 1998}, p.674).

The 1998 TB survey and enhanced TB Surveillance data for 1999–2001 show that the median age of foreign-born UK TB cases is consistently younger (age 36 in 1998; 35 in 2001) compared to the median age of local-born UK TB cases (age 50 in 1998; 44 in 2001). (Source:

Health Protection Agency – CDSC - TB section - National TB Survey 1998, 1999, 2000 and 2001 Enhanced TB Surveillance).

This suggests that the higher proportion of foreign-born TB disease cases in London and Eastern England contributed to the high proportion of cases aged 25–34 in these areas. In other areas of England and Wales, TB disease in older age groups is more likely to be due to reactivation of prior long-term infection. It is also possible that different age groups have different risks for TB disease when analysed according to ethnicity. However, regional TB disease data broken down according to ethnicity and age was not available from the HPA at the time this document was written, since the denominator data used for ethnic groups is sourced from the Labour Force Survey, and this data is less reliable at the regional level.

TB cases and socio-economic deprivation

Aside from ethnicity, recent immigration, duration of residence in the UK, and age, other factors such as poor housing and overcrowded conditions may contribute to the increasing incidence of TB in the UK. A national survey of TB in the UK conducted by {Rose et al. (2001)} did not collect information on the socio-economic and housing status of the respondents, and so was unable to provide data on the effect of poverty on the occurrence of TB and its geographical variation in England and Wales. Enhanced TB surveillance surveys conducted from 1999 to 2001 by CDSC also did not collect information on the socio-economic status of TB disease cases.

One study ({Bhatti et al., 1995}) attempted to link TB notification data with socioeconomic deprivation on a national basis. The study used the Jarman Index to rank the 403 local authority districts in England and Wales in terms of socio-economic deprivation and compared local authority data with TB notifications. The study found that both overcrowding and ethnic minority status were strongly related to risk of TB disease (36% of cases occurred in the 10th of the population with the highest overcrowding index, while 33% of cases occurred in the 10th of the population with the highest number of ethnic minority residents).

However, the validity of the findings were undermined by the high correlation between the overcrowding and the ethnic minority factors (r=0.85). It is likely that ethnicity was an important confounder of the relation between TB and social deprivation ({Hayward et al., 1995}) in this study, and the real contribution of overcrowding to TB disease remains unclear. The Jarman index may have been inappropriate, since it included ethnicity as one of its other defining criteria, which was also strongly correlated with TB incidence. Use of the Townsend Deprivation Index would have avoided this problem since it only includes overcrowding and not ethnic minority status as one of its four criteria.

A study conducted in London by the London Tuberculosis Nurses' Network found that 235/2010 (12%) of TB disease cases in the capital were homeless, including 79 (4%) currently living in homeless hostels or on the street and 156 (8%) living in temporary insecure accommodation such as bed and breakfast rooms or squats. An additional 112 TB patients (5.7%) had a history of street or hostel homeless. No national dataset on the proportion of TB disease cases currently homeless was available at the time of writing.

TB cases and previous TB diagnosis

Enhanced TB Surveillance 2001 provides regional information on previous TB diagnosis. Nationally, for cases where information was reported on this issue (19.5 % of the total TB cases for 2001 had no or incomplete information), 91.4 % had no previous TB diagnosis compared to 8.6 % who did. There was variation in these case proportions by region, with the South West of England reporting the highest percentage of previous TB diagnoses (13.5%) and the West Midlands reporting the lowest percentage (6.8%). London reported a low percentage of cases with previous TB diagnosis (7.4%). (Source: Health Protection Agency – CDSC – TB section – 2001 - Enhanced TB Surveillance).

In London increasing age and poor adherence were independently associated with previous tuberculosis, while the relationships between previous TB and homelessness, imprisonment, alcohol and drugs were found not to be significant after controlling for poor adherence (The London Tuberculosis Nurses Network - A Hayward, personal correspondence). No national data on the risk factors associated with a previous TB diagnosis were available at the time this document was drafted.

TB cases by site of disease

Enhanced TB Surveillance 2001 data included information on the site of TB disease. TB cases were classified as:

Pulmonary with or without additional extra-pulmonary disease, and
Only extra-pulmonary TB disease.

In England and Wales 55% of TB cases had pulmonary disease and 45% had only extra-pulmonary disease. Regionally there was some variation, with Wales having the highest (62%) and the West Midlands the lowest proportion of pulmonary cases (52.5%). The proportions for London were close to the national figures (56% pulmonary and 44% non-pulmonary). (Source: Health Protection Agency – CDSC – TB section – 2001 - Enhanced TB Surveillance)

TB cases and HIV co-infection

{Rose et al. (2002)} matched information from the 1993 and 1998 national TB survey databases with data from the HIV/AIDS database in order to identify cases of TB-HIV co-infection in England and Wales. In addition, the HPA collated data on 17 633 TB cases from the 1998 TB Survey and the 1999–2001 Enhanced TB Surveillance surveys and matched these with the HIV/AIDS patient database. TB disease and HIV co-infection was found in 479 (2.7%) TB cases. (Health Protection Agency – CDSC – TB section - Poster - Antoine, Delpech, Story, Forde, Mortimer, Evans, and Watson. Tuberculosis and HIV co-infection in England and Wales, 1998 to 2000.) Relevant data from these two sources is reported under the sub-headings below.

Age

In co-infected HIV/TB cases, 99.6% were aged between 15 and 64 years. No cases were found below the age of 15 and just two were over 64 years of age. The groups with the highest proportions of co-infection were aged 35–39 (7.3%), 30–34 (6.4%), and 40–44 (4.7%). (Sources: Health Protection Agency – CDSC – TB section, National TB Survey 1998, 1999, 2000 and 2001 Enhanced TB Surveillance; HIV/AIDS patients dataset).

Sex

Sixty-four percent of HIV-TB co-infected cases were males. (Health Protection Agency – CDSC – TB section - Poster - Antoine, Delpech, Story, Forde, Mortimer, Evans, and Watson. Tuberculosis and HIV co-infection in England and Wales, 1998 to 2000.)

Region

Sixty-five percent of all HIV/TB co-infected cases between 1998 and 2000 were found in London (Health Protection Agency – CDSC – TB section - Poster - Antoine, Delpech, Story, Forde, Mortimer, Evans, and Watson. Tuberculosis and HIV co-infection in England and Wales, 1998 to 2000.). {Rose et al (2002)} found that in 1993, 64% of all HIV/TB co-infected patients aged 16–54 were in London, and in 1998 this had increased to 77%. The London Tuberculosis Nurses Network study found that 188/2010 (9.6%) TB cases in London had confirmed HIV co-infection (although one third of patients were not tested).

Ethnicity

In London the proportion of HIV/TB co-infected patients of White ethnic origin increased from 5.2% to 9.8% between 1993 and 1998, while the proportion of Black African HIV/TB cases increased from 7.4 to 10% during the same five-year period ({Rose et al. 2002}, p.443).

Outside London between 1993 and 1998 there was an 18% rise in the number of HIV/TB co-infections, mostly in the White ethnic group, but by 1998 the proportion of co-infection cases in

the White ethnic group was still only 2% versus 10% in Black African patients (Rose et al., 1998, p.443).

Place of birth

HPA 1998–2001 data indicate that the overall proportion of HIV/TB co-infection cases was higher in persons born abroad than in those born in the UK (3.9% vs. 2.8%). However, the contribution varied considerably between regions of the world (Table xii).

Table xii: HIV/TB cases in England and Wales born abroad

Origin of HIV/TB cases	Proportion (%) co-infected
Africa	9.6
Europe (excluding UK)	7.9
Americas and Oceania	4.1
Asia	0.8

Source: Health Protection Agency

Site of disease

Sixty-seven percent of all HIV/TB co-infected cases had pulmonary TB disease. (Health Protection Agency – CDSC – TB section - Poster - Antoine, Delpech, Story, Forde, Mortimer, Evans, and Watson. Tuberculosis and HIV co-infection in England and Wales, 1998 to 2000.)

Risk factors for HIV-TB co-infection

On univariate analysis, HIV/TB co-infected cases were significantly more likely to be:

male
aged 30 to 49 years
born in Africa or Europe (except in the UK)
living in London
ill with pulmonary TB.

The results represent a minimum estimate of HIV/TB co-infection due to limitation in the matching process and probable under reporting of tuberculosis cases among people with HIV. (Sources: Health Protection Agency – CDSC – TB section - Poster - Antoine, Delpech, Story, Forde, Mortimer, Evans, and Watson. Tuberculosis and HIV co-infection in England and Wales, 1998 to 2000.).

TB cases and treatment outcomes

Information on treatment outcome of all TB cases reported in 2001 was collected from January 2002 in England, Wales, and Northern Ireland. The analysis of the first national results was performed on 5139 TB cases, representing 79% of all cases reported in 2001. The key socio-demographic variables of TB cases with and without outcome data were similar when compared (CDR Weekly 14 (1), 2004).

Almost 80% of TB cases with outcome data completed treatment at 12 months.
The treatment completion rate was significantly lower in pulmonary cases than in extra pulmonary cases (77% versus 84%, p<0.001).
Overall 8.3% of patients died, representing 39% of the 1106 cases failing to complete treatment at one year.
The proportion with treatment completion decreased in the older age groups (>80% in those aged under 60 years, and <70% in those aged 70 years and over, p<0.001) reflecting the contribution of death in older age.
Four percent of all cases were lost to follow-up and 4% were still on treatment.
The proportion of cases lost to follow-up in the 10 – 34 years age group was 6.3% versus 1.3% in those aged 0–9 years versus 2.5% in those aged 35 plus, p< 0.001.

Cure and completion rates were defined by recording death (from any cause) as non-completion, so these rates cannot be expected to reach 100%. (Source: Health Protection Agency – CDSC - TB section – 2001- Enhanced TB Surveillance). The data should be interpreted with caution, as outcome information was unavailable for 21% of TB cases reported in 2001 (CDR Weekly 14 (1), 2004).

In London, a multivariate analysis revealed that a history of homelessness, imprisonment, problem drug use, problem alcohol use, mental health problems, living alone and previous tuberculosis were independently associated with poor treatment adherence amongst TB patients (The London Tuberculosis Nurses Network).

TB cases and drug resistance
The proportion of drug resistant cases reported through Enhanced TB Surveillance for 2001 was derived from MycobNet information on initial isolates at the start of treatment. The proportion of TB isolates (N=4043) with some form of drug resistance was as follows:

Isoniazid resistance 7.84%,
Rifampicin resistance 1.7%
Multiple Drug Resistance (MDR) 1.24%

(Sources: Health Protection Agency – CDSC - TB section – 2001 - Enhanced TB Surveillance and MycobNet).

In England and Wales in the period between 1994 and 2001, isoniazid resistance increased by 2.04%, rifampicin resistance decreased slightly by 0.2%, and MDR-TB decreased by 0.26%. (Source: Health Protection Agency – CDSC – TB section – 2001 - Enhanced TB Surveillance and MycobNet).

Risk factors for drug-resistant TB

{Djuretic et al. (2002)} reported an analysis of MycobNet data that included 24,876 initial isolates of *Mycobacterium Tuberculosis* collected between 1993 and 1999.

The highest proportions of isoniazid resistance and MDR-TB were reported in the following groups (isoniazid-resistant %, MDR TB %):

Those aged 15–44 (7.6%, 1.5%)
Males (5.9%, 1.4%) compared to females (5.4%, 0.9%; MDR p<0.001).
Black African cases (10.1%; 2%) compared to Indian subcontinent (7.2%; 1.4%) versus White ethnic group cases (4.1%; 1.4%)
TB cases born abroad (9.1%, 2%) compared to UK born (4.2%, 1%; isoniazid p<0.001, MDR p<0.001)
London (7.6%, 1.7%) compared to rest of the UK (4.6%, 0.9%)
England (6%; 1.3%) compared to Wales (4.4%; 0.6%)
Pulmonary TB (MDR 1.5%) compared to non-pulmonary TB (MDR 0.8%; p<0.001).
Previous TB diagnosis (15.5%, 9.4%) compared to TB cases without previous diagnosis (5.7%, 0.8%) compared to cases with no available data (4.9%, 0.7%; isoniazid p<0.001, MDR p<0.001)
TB/HIV co-infection confirmed in 3.6% of all isolates collected between 1993 and 1999 (11.6%, 4.6%) compared to s cases with unknown and negative HIV status (5.5%, 1.1%; isoniazid resistance p<0.001, MDR p<0.001) ({Djuretic et al., 2002}, p.480).

In the context of London, a multivariate analysis found that history of imprisonment and previous tuberculosis were independently associated with drug resistance (isoniazid or MDR-TB; both p<0.001) in TB cases (The London Tuberculosis Nurses Network).

TB and NHS hospital resources

According to Hospital Episode Statistics (HES) data for England, TB disease accounted for 5666 finished hospital episodes for the year 2002 – 2003. This represented 0.04 % of all finished NHS hospital episodes for all diagnostic categories that year.

TB of the lungs and respiratory system accounted for 3779 hospital episodes (67% of all completed TB hospital episodes), and 38 833 hospital bed days (61% of all bed days for TB admissions).
Sixty-nine percent of TB patients were aged 15–59, with 10% aged 75 plus.
Male patients accounted for 57% of all finished TB episodes.
Mean length of stay in hospital was 18.1 days for TB compared to 7.9 days for all diagnostic categories.

Just 8% of all completed TB episodes were day cases (admitted and discharged on the same day) compared to 29% for all diagnostic categories.
The total number of bed days occupied by all TB patients was 63 347, or 0.12 % of all bed days for all primary diagnostic categories for that year.

(Source: Hospital Episode Statistics, England, 2002–03
http://www.doh.gov.uk/hes/tables/tb00202a.pdf)

In Wales, TB accounted for 153 finished episodes of hospital treatment in 2001–02, representing 0.02% of all completed hospital episodes during this period (Patient Episode Data Wales).

Lung and respiratory forms of TB accounted for 107 completed hospital episodes and 1199 bed days (57% of all TB bed days in Wales).
Sixty-six percent of TB admissions were male, with 57% of TB episodes completed by patients aged 15–59 and 20% by those aged 75 plus.
Six percent of all TB admissions were day cases with the remaining 94% requiring a stay of at least one night. For all diagnostic categories, the proportion of day cases was 18%.
Completed TB episodes amounted to 2120 bed days, or 0.05% of all hospital bed days for all diagnostic categories.

(Source: Health Solutions Wales - Patient Episode Data Wales (PEDW) 2001–2002 via personal communication).

BCG vaccination
Prior to intended immunisation with BCG, a tuberculin skin test is administered and only those who are found negative are immunized, although infants can be immunized without a skin test. In England in 2002–03, just over 413 000 persons were skin-tested of whom 33 000 (8%) were TST positive, including some due to previous immunisation. Just over 449 000 BCG vaccinations were administered, with Table xiii providing a breakdown of the data by relevant age group.

Table xiii: BCG vaccinations by age group in England, 2002–03

Age group	Number and proportion (%) of total vaccinations
Under 1	53 000 (11.8)
10–13	204 000 (45.4)
14–15	168 800 (38)
16 plus	17 000 (3.8)

Source: NHS Immunisation Statistics for England 2002–03
http://www.doh.gov.uk/public/sb0316.pdf

In Wales, 33 536 BCG vaccinations took place in 2002–2003, with Table 14 providing a breakdown of the data by relevant age group.

Table xiv: BCG vaccinations by age group in Wales, 2002–03

Age group	Number and proportion (%) of total vaccinations
Under 1	638 (1.9)
10–15	26 000 (77.5)
16 plus	6792 (20.3)

Source: National Statistics

There was some evidence that BCG vaccination coverage varied in different regions of England and Wales. A survey conducted by {Joseph et al. (1992)} found that 15/169 health districts in England and Wales had discontinued routine school BCG vaccination by 1992, and 31/169 districts did not offer a neonatal BCG program. A total of 148 health districts (80%), including 14 of the 15 districts without a school BCG program, offered BCG to babies from ethnic minority groups, and 120 districts offered BCG vaccine to neonates of recent immigrants from high incidence countries ({Joseph et al., 1992}, p.496). There was no national dataset available at the time of drafting this document on regional variation of BCG vaccination coverage defined as that proportion of the local population of eligible candidates who receive BCG.

Conclusion

The rising incidence of TB in England and Wales since 1987 may be linked to a number of different socio-demographic factors. The major contributor on a regional level to this rising incidence is London, and yet within the capital there is a great degree of variation in TB rates within boroughs. Some boroughs have incidence rates below the national average of 12.9 per 100 000, while others have rates in excess of 80 per 100 000. Other cities in England and Wales may also be contributing to this rise in TB incidence, but at the time this document was written, the TB case rate data that existed for other specific cities was not considered reliable.

The concentration of ethnic groups, some of which include large numbers of people born abroad, may explain some of the local variation in TB rates both within London, and also between different regions in England and Wales. However, both country of birth, and length of residency in England and Wales appear to be important risk factors for TB disease. Unfortunately, there is an absence of robust national data on the impact of socio-economic deprivation on TB disease rates.

The HPA Centre for infections intends to begin collecting socio-economic data on TB cases in future, and this may facilitate a clearer understanding of the relative contributions of ethnicity,

country of birth, length of residency and socio-economic deprivation to TB disease rates in England and Wales.

Age and sex are also important variables, since males have higher rates of TB disease than females, and TB rates are increasing more rapidly for those aged 15–24 and 25–34, particularly in London and the Eastern NHS region. Those aged 45–64 and 65 plus still have the highest proportions of TB cases in the other regions of England and Wales.

The median age of TB cases who were born abroad is younger than those born in the UK, suggesting that young people born outside the UK are at increased risk for TB disease. It is possible that age and sex differences in TB disease case rates are also influenced by ethnicity, but the national data that stratifies TB cases by sex, age, and ethnicity was not considered reliable at the time this document was written.

Although data on TB/HIV co-infection is limited by the matching methodology used, it appears that TB/HIV co-infection is most commonly found in those aged between 35–44, living in London, who were born abroad.

The 2001 treatment completion rate was significantly lower in pulmonary cases than in non-pulmonary cases. Multiple Drug Resistance (MDR) detected in isolates at the start of treatment decreased overall between 1994 and 2001, although isoniazid resistance increased during the same time period.

TB disease appears to require a longer period of hospital inpatient treatment than the average for all diagnostic categories. Pulmonary forms of TB account for the majority of completed TB hospital episodes and bed days in both England and Wales.

There may be some regional variation in BCG vaccination coverage of infants and children aged 10–15.

Finally, it is worth noting that national data on other groups at high risk for TB disease such as homeless people, drug and alcohol abusers, and those in prisons were not routinely collected in England and Wales at the time of writing.

2.3 Appendix I: Papers excluded due to methodological limitations - 2006

Table

Guideline section	Reference	Rationale for exclusion
Diagnosis	{10}	No reference standard (some studies use degree of exposure as a reference standard) or blinding and only fourteen HIV positive participants had both TST and ESAT-6/CFP-10-based ELISPOT results available.
	{40}	Evaluated the sensitivity of sputum smear in a small group of AIDS/ARC patients (N=38) however it was unclear whether any of the control group were HIV positive and there may have been confounding (for example, 74% of the AIDS/ARC group were intravenous drug users whilst none of the control group were).
	{41}	Lack of clarity concerning the calculation of sensitivity values and small numbers in sub-group analyses.
Management of drug resistant TB	{257}	Very select group included in the study (only those with drug susceptibility and HIV test results even though these tests were not routinely undertaken).
	{265}	It was unclear how study participants were selected, in how many cases drug sensitivity testing was performed and several of the risk factors considered were ill defined.
	{271}	Differences within the baseline characteristic s of the two groups and possible confounding. In terms of the latter, it was difficult to assess whether better treatment completion rates in the specialist TB hospital were attributable to being an inpatient rather than an outpatient (the median duration of hospitalisation was 270 days), or receiving specialist TB care versus no specialist TB care.
Management	{214}	No details of randomization

of latent TB		were given, the study was not blinded, details were not given as to how a diagnosis of active TB was established and no details were given of treatment completion rates or adverse events.
Non-respiratory TB	{159}	The baseline characteristics of the two groups were not reported separately so it was not possible to assess group comparability, patients in the long course chemotherapy group received a variety of different combinations of treatment, the proportion of patients receiving corticosteroid treatments probably differed between the groups and finally, statistics were merely descriptive with no performance of statistical significance tests.
	{160}	Prednisolone was given to differing proportions of patients in each group (38% in group I and 55% in group II), the two chemotherapy regimens were slightly different for the treatment groups, study numbers were small and the two groups were not similar at baseline. Statistics were descriptive and tests of statistical significance were not performed.
	{161}	The study was performed in a small number of patients in Thailand. They were diagnosed on the basis of characteristic clinical features and cerebrospinal fluid findings (lymphocytic meningitis with low glucose level and elevation of protein content) only. A number of patients were lost to the study (14%), prednisolone was given in some but not all of the patients, patients were in various clinical stages on admission and it was unclear how underlying cause of death and neurological deficits were assessed.
	{162}	Study performed in Ecuador in a small number of patients who were mostly male and in variable clinical stages of the condition. Additionally, steroid therapy was used in only some

		of the patients and there was no indication of how neurological deficits were assessed.
	{163}	The number of patients in the relevant study arm was small (N=20) and baseline characteristics for this arm were not reported separately. The number of deaths and relapses were not reported. Study outcomes were cytological response in weeks, clinical response in weeks and time to occurrence of neurological sequelae, however it was unclear how these outcomes were calculated.
	{164}	Large numbers of patients excluded from the analysis due to insufficient information, dissimilar groups at baseline, no quality appraisal of studies and only presentation of descriptive statistics.
	{168}	A substantial proportion of these relapsing patients (57%) took treatment for less than 6 months, which has never been advocated as an adequate treatment duration for TB meningitis. A large number of patients who were not available for regular follow- up and are thus not included in this analysis, had unknown outcomes in terms of relapse and duration of treatment. Limited diagnostic assessments were reported.
	{165}	The method of assessment of neurological sequelae was not specified, types of sequelae for the surviving patients on this treatment regimen were not reported and an upper age limit for children in the study is not given so it is unclear how "child" was defined.
	{166}	It is not explicit how "major motor deficits" were assessed or what these were considered to be and 16% of the children who completed treatment were subsequently lost to follow-up, so the occurrence of relapse in this group was not known.
	{170}	The nutritional status of these children was found to be very

		poor with 97% having either mild to moderate or severe malnutrition, thus it is difficult to generalise any results found from this population.
	{179}	Some elements of study quality were considered, but not systematically and studies in the review were not excluded on the basis of quality. Of the 7 trials included only two were RCTs so for the others in particular, potential confounding factors had not been considered.
	{186}	Inadequate search strategy, no assessment of study quality or heterogeneity.
	{184}	No details of randomisation, blinding or intention to treat analysis and the treatment regimen included streptomycin during an intensive four month treatment period, which would not be a regimen generally used in the UK.
	{190}	Follow-up being terminated before all patients had reached five years, so 58% of patients were not included in the analysis.
	{197}	Small numbers in each group and no power analysis. In addition, chemotherapy duration was 18 months using isoniazid, sodium PAS and in only some cases, streptomycin.
Management of respiratory TB	{83}	No blinding or details of randomisation or concealment. No intention to treat analysis, no power analysis and no table of baseline characteristics. Unclear how many centres took part.
	{87}	Insufficient details supplied about methods used. Unclear how patients are allocated to each group, no baseline characteristics supplied, no blinding. Small study and no differences found between the groups so possibly underpowered.
	{86}	No blinding or details of randomisation or concealment. No intention to treat analysis and no power analysis.
	{88}	A small retrospective chart

		review with ill-defined outcomes and confounded by those in the intermittent group also receiving DOT.
	{89}	Only 4% of the study population had a confirmed TB diagnosis and outcomes were based on an amalgamated scoring system (rather than cure or relapse rates), which seemed subjective and open to bias in an unblinded study.
	{93}	Lack of blinding, no intention to treat analysis, no details of randomisation procedures and no reporting of baseline characteristics
	{94}	Lack of blinding, no intention to treat analysis, no details of randomisation procedures. Small study with no power analysis and less than half of the patients recruited were included in the analysis at two years.
	{90}	Lack of blinding, randomisation detail and intention to treat analysis, plus it was not clear how many patients in each group had received supervised treatment.
	{91}	No intention to treat analysis, no blinding, no randomisation methodology reported and no reporting of the baseline statistics of all patients recruited. Additionally this study used combination tablets on an intermittent rather than daily basis and included streptomycin in the regimen (not used in standard UK treatment).
	{105}	Included >25 mainly observational studies frequently with comparisons with uncontrolled or historical data, however study quality was not assessed prior to study inclusion
	{106}	Included >25 mainly observational studies frequently with comparisons with uncontrolled or historical data, however study quality was not assessed prior to study inclusion
	{110}	Lack of detail in reporting methodology, no reporting of

		statistical measures of uncertainty and no power or intention to treat analysis.
	{131}	Inadequate randomisation and concealment, dissimilarity of treatment and control groups and uncertainty about the equal treatment of the groups.
	{134}	No baseline characteristics given for the groups, unclear whether patient groups were treated equally apart from the intervention and treatment outcomes not defined.
	{136}	Those who were lost to follow-up or who were uncooperative were not included in the analysis. It is unclear how many participants were initially recruited to the study and thus how many were excluded. It is unclear whether all those who were eligible for inclusion in the incentive programme were asked to participate or whether only particular patients were referred. There was no reference to blinding and no power analysis. There is no reference to how patients were diagnosed or the treatment regimen used in the study.
	{137}	The study does not report or discuss confounding factors, statistical power, exclusion or inclusion criteria, how patients were selected, how many patients refused to participate or differences between participants and non-participants.
	{130}	No details concerning randomisation and concealment. Additionally it seems that a confounding factor could be that the increased attention and motivation from health care professionals rather than the health education itself could improve concordance.
	{138}	Small in size with no power analysis or true randomisation. Additionally it was unclear what the health education and counselling interventions assessed in the study entailed.
	{127}	Lack of detail in terms of exactly what the intervention

		"intensive supervision of staff" entailed. True randomisation was not used and the details of randomisation procedures were not been reported.
	{151}	Only 58% of the patients with active TB had restriction fragment-length polymorphism results available which could be evaluated to assess possible transmission.
Contact tracing and DNA fingerprint analysis	{381}{382}; {383}; {384}; {385}; {386}	Contact tracing interview procedures were not described Contact tracing clinical screening procedures were not described Length of follow-up and level of intimacy of contact tracing were not described Different contact tracing investigations within a study were not described in terms of similarities and differences Those undertaking the DNA fingerprint analysis of tuberculosis isolates were not blinded to the retrospective results of the contact tracing Retrospective data collection procedures were not described DNA fingerprint cluster was not defined
Contact tracing versus self-referral/routine screening	[387]	Contamination effects for cases and controls No performance of significance tests for the outcome of interest.
Comparison of two different contact tracing methods	[388]	Only interim findings based on follow-up of contacts that varied between 27 and 60 months were reported, with 90% of contacts having incomplete follow-up periods. Data collectors were unblinded to the group to which study participants were allocated.
Contact tracing versus new entrant screening	[389]	Study groups were not equivalent as new entrants selected were foreign-born immigrants or asylum seekers from countries with a high incidence of tuberculosis, whereas contacts may have included these populations in addition to UK-born persons. Baseline characteristics on key demographic variables of

		participants were not reported, and it was unclear how these would have affected the tuberculosis screening outcomes for the compared screening methods.
Patient and staff perspectives on the effectiveness of contact tracing interviews	[390]	The study was limited by the lack of an audit trail explaining how themes and categories had been generated from the data collected.
Comparison of contact tracing, targeted routine screening and symptom reports	[391]	This cross-sectional questionnaire survey, only reported the number of completed questionnaires, but the extent of non-response bias, and how this affected the results is unknown. No adequate definition of contact tracing provided in terms of case detection, methods, procedures, and staff used. No adequate definition of targeted routine TST screening. No definition of evaluation of clinical symptom reports. Clinicians were used to check and collate patient data together with test results, and it is possible that data entry errors occurred or were present in the original patient case reports.
Contact tracing and transmission of M.Bovis in humans	{329}	To be confident of TST conversion rates between different groups of contacts, it was estimated that 101 M.bovis contacts and 605 M.tuberculosis contacts would be required. However, only 77 M.bovis and 469 M.tuberculosis contacts were included. The actual size of the possible error in statistical estimates was 0.36, rather than the projected 0.20, indicating that the study was underpowered, i.e. 64% rather than 80% power. Data was unavailable on differences in duration, proximity and environment of exposure to source cases between the M.bovis and

		M.tuberculosis contacts, which could have affected TST rates. Different strains of TB (both M.bovis and M. tuberculosis) may be more or less virulent, so transmission of infection with some strains occurs more easily with less exposure time in comparison to other strains. Data on consumption of unpasteurised dairy products by M.bovis contacts was unavailable, and transmission via ingestion of the same contaminated milk or cheese that produced infection in the putative human source case would have the effect of overestimating the extent of direct human-to-human transmission of M.bovis infection. As the proportion of contacts who did not receive a second TST was higher in the M.tuberculosis compared to the M.bovis group, it is possible that a proportion of LTBI cases went undetected, resulting in an underestimate of the proportion of TST converters in the M.tuberculosis group. No data was given on the BCG status of contacts, although figures for 2000 and 2001 indicate that 62% of M.bovis contacts and 50% of M.tuberculosis contacts (not all eligible for the study) were foreign-born, and many of these may have had prior BCG vaccination. Therefore BCG vaccination could have accounted for a substantial number of first and second TST+'s and may have led to an overestimation in the number of contacts in both groups identified with LTBI. It was not reported whether investigators independently determined the number of TST conversions for each contact group without knowledge of whether they were contacts of M.bovis or M. tuberculosis cases.
Contact tracing	{313}; {314}; {315}; {316};	Missing values for tuberculin

of close versus casual contacts	{317}; {312}	skin tests for some contacts could have affected latent tuberculosis infection case yields for close and casual contacts. Information on duration of exposure of contacts to the index case was missing. Specification of criteria for allocation of contacts to close and casual categories were inadequate. Baseline characteristics of close and casual contacts were not described. No explanation was provided why some contacts were not screened or did not complete screening. Interpretations of tuberculin skin test results administered by different providers in the same study were potentially inconsistent. Contact tracing data collection methods across different sites in the same study were potentially inconsistent.
Outbreaks in schools	{11}{336}	Participation and completion rates not reported No baseline characteristics reported Number of participants in the comparison groups not reported Non-school contacts included with school pupils in the low-exposure group, so a meaningful comparison between school pupils with low exposure and those with moderate and high exposure to the index case could not be made.
Outbreaks in hospitals	{348}{349}, {72}	Over 50% of eligible contacts lost to the analysis were at high risk to exposure, suggesting that many cases of latent TB infection and active TB disease were missed. Tuberculin skin test method was not specified, nor was a value defined for classification of a TST positive reaction. Demographic information was not reported for contacts, including possible prior risk

		factors for tuberculosis infection. Some sub-group populations were very small and this may detract from the generalisability of statistically significant results reported for these sub-groups. Proximity to the index case was based on an arbitrary score of spatial separation, and it was reported that the index case was known to move about the ward. It was not reported whether individuals unaware of infection status undertook the assessment of risk factors. No information was reported on the numbers in each group who agreed to screening, those who failed to complete screening, and number in each group that completed screening. Definitions of TST positivity/negativity, abnormal chest X-ray or reported symptoms suggestive of TB disease were not reported.
TB screening models for new immigrants	{292}{353}[392]	The service models compared used different screening procedures and resulted in statistically significant differences in non- completion rates, suggesting that different screening procedures confounded the impact of the different service provider models. Non-completion of screening was not reported, so the proportion of dropouts for the two service models cannot be compared. The cut-off point for defining newly arrived immigrants was five years, and it was unclear whether this duration of stay would be applicable to new entrants eligible for screening in the UK care setting. No duration of residence in the country was reported as a participant characteristic for new immigrants. No comparison of key baseline demographic variables such as ethnicity, country of origin, duration of stay, age and sex

		were reported. Definitions of new immigrants, and of the different service models investigated were not provided. It was not reported whether screening procedures used in both service models were identical or differed in key aspects. In the UK, screening of new immigrants is done only on entry into the country, whereas the reported results were for only one half (entry screening) of a two-level screening pathway that included pre-entry screening. By definition, all active TB cases identified among potential immigrants at pre-entry screening would not have gained entry into the destination country, and so are excluded from entry screening. In the UK, entry screening includes identification of more advanced TB cases filtered out by pre-entry screening, so the results cannot be generalised to UK settings. It was not stated how many foreign-born subjects screened by routine surveillance did not have active TB. It is not clear whether routine surveillance refers to some form of routine targeted active case finding, or passive case finding via evaluation of patient symptom reports. Without a clear definition of routine surveillance it cannot be ascertained exactly what alternative model of case detection is being used in comparison to new immigrant screening.
Comparing different TB screening methods for new immigrants	{356}	Baseline characteristics apart from age were not reported. The number of participants lost to follow-up over the five-year follow-up period was not reported. Criteria for establishing a normal and abnormal chest X-ray were not reported. Administration of TST and

		chest X-ray screening and by whom was not reported. It was not reported when TST reactions where read and whether those taking the readings had the necessary professional training. No information on data collection or data collectors was reported. Data was retrospectively collated from patient charts, but how this was organised in a standard way, and how missing values were dealt with in terms of data analysis was not addressed. Only 46% of the active TB cases identified were confirmed as culture-positive for *M.Tuberculosis*, and it was not reported how the remaining 54% were diagnosed.
TB prevention and control measures for NHS hospital employees	{367}{368}{369}{370}{273}	Four studies did not report baseline characteristics for either the total number of hospital employees screened or tuberculin skin test converters, so details of BCG history, foreign-birth status, or possible household/family/community exposure to TB among study participants were missing, and the contribution of these factors to observed TST conversion rates could not be determined. A lack of complete data on study participants obliged the authors to use number of tuberculin skin tests completed as the unit of analysis rather than number of participants, so the sample attrition rate could not be determined. In two studies, descriptions of the administration of tuberculin skin testing were inadequate. Tuberculin skin test conversion data did not include reporting of time interval since previous screening or increase in reaction size. A heightened concern about TB transmission could have contributed to an improvement in screening adherence in the pre-intervention period, which may have inflated the tuberculin

		skin test conversion rate at this time relative to the decrease in the rate observed in the post-intervention period. It was not reported how implementation of new patient isolation procedures were evaluated, and whether the effectiveness of negative-pressure rooms were tested to ensure they were operating as per the new policy specifications. There were screening records for only 76% of the target population, which meant that 24% of potentially eligible participants were eliminated from the analysis. The authors concede that sample attrition could have affected the data analysis and results.
BCG vaccination in newborns	{287}	It was not reported whether some potentially eligible cases and controls chose not to participate in the study, and whether they differed significantly from participating cases and controls. TB cases were randomly selected for the study, but the randomisation procedure used and the total number of cases from which selection took place was not reported. It was not reported why a random sample of TB cases was taken instead of selecting all eligible cases, and since the sampling procedure used was not described, it is possible that TB cases not selected differed significantly from those that were. It was not reported whether selection of cases and controls was done blind to BCG vaccination status. Confidence intervals reported for many of the results were wide, with some crossing the line of no effect. The study reported local findings and may have limited generalisability to neonatal BCG vaccination in England and Wales.

BCG vaccination in new immigrants	{295}	The study compared local data on incidence of active TB disease in tuberculin skin test negative (TST-) BCG vaccinated South Asian new immigrants, with national TB incidence data for this population, matched on age and duration of stay. As the national dataset was not stratified by vaccination or tuberculin skin test status, it was not possible to compare the local TB disease incidence rate for TST- BCG vaccinated new immigrants with the rate for TST- unvaccinated new immigrants within the national cohort. Since the guideline area was concerned with evaluating the protective efficacy of BCG vaccination against TB disease in the new immigrant population, an unvaccinated cohort was required as a comparator.
BCG vaccination in contacts	[393]	No demographic baseline characteristics were reported. Local policy was to provide neonatal BCG vaccination, but many children in the study were born outside the area or were the children of returned emigrants and had not received BCG vaccination. Since children of returned emigrants may have been born in foreign countries with a higher prevalence of TB than Ireland, this could have increased their vulnerability to TB infection in comparison to pupils born in Ireland, who were more likely to have received BCG vaccination. BCG vaccinated and unvaccinated groups were not stratified according to locality of birth, age, sex, or socio-economic status. BCG vaccinated and unvaccinated groups may not have been equivalent, apart from the intervention of interest.
TB prevention and control in	[394]{379}{380}	It was not reported how many of the inmates who received the

prison settings		education intervention were released from jail before completing prophylaxis and could therefore be classified as study participants. The observed decline in TST conversion rates and TB cases over the study period may have been due to changing TB control practices in the community rather than to interventions implemented in the prison system. It was unclear which of the new prison TB control measures actually contributed to the observed decline in TST conversion rates and TB disease cases. Two studies did not report baseline demographic characteristics for the study groups focused on. A full description of the administration of the TST and the reading of these tests was not reported, and items on the symptom questionnaire were not described. Chest X-ray, sputum AFB and culture methods were not fully described with regard to how the tests were done, who did them, and how the test results were interpreted and by whom. Directly observed preventative therapy and DOT for treatment of TB disease were reported as being mandatory, but how these methods were carried out, by whom, and how the therapeutic completion outcome was assessed was not reported. No results were reported for the number of cases that completed DOT TB treatment during the study period, from 1991 to 1997. It was not reported whether data collectors were trained to collect data according to a standardised procedure, and whether they used a data input co-validation system to counteract any errors in input or interpretation.

Economic analysis of school-based BCG

INTRODUCTION

This paper presents the final version of the economic analysis of the school BCG programme in England and Wales. The model has been revised in line with discussion at the SG11 preventive sub-group meeting.

For this analysis, we define a '*high-risk*' group consisting of children who should have already been offered BCG before the school programme. This might include: 1) children eligible for selective neonatal BCG programmes (from high-incidence ethnic groups); 2) children eligible under new entrant schemes before the age of 10 (from high-incidence countries); and 3) other children covered by universal neonatal programmes in high-incidence areas. We also define a '*low-risk*' group as the remainder of the 10–14 year old cohort: those not eligible for any prior vaccination programme. The school BCG programme is potentially beneficial for low-risk children, but also as a catch-up for high-risk children who for whatever reason have not been previously vaccinated. The model described below allows us to estimate the costs and effects of school BCG for both of these groups. It does not provide any information about the cost-effectiveness of neonatal BCG, or about the value of BCG for arrivals from high-risk countries.

The model is a simple decision tree that estimates the number of primary cases for a cohort of 10–14 year olds, the consequent number of secondary cases in the population, and the associated costs and health outcomes, with and without a school BCG programme. Estimates of the impact of school BCG for white 10–14 year old children have been provided by Saeed et al (2002), updating the work of Sutherland and Springett (1989). These estimates are used in our model to estimate the benefits of vaccination for the low-risk group. The benefits for unvaccinated high-risk children are then estimated by varying the proportion of high-risk children in the cohort, the proportion of high-risk children previously vaccinated, and the relative risks for the high-risk group.

It is also important to note that this methodology can only give approximate results for an infectious disease such as TB. A population dynamic model would be expected to provide more reliable results. However, we do not have the resources or time required to build such a model for the NICE guideline. The present analysis will, however, provide a broad indication of the range of cost-effectiveness for different areas. It will also suggest how sensitive the results are to various parameters, which should help to focus further work.

METHODS

Structure of the model

The decision tree is shown below (Figure 3). A cohort of 10 to 14 year old children enters the tree from the left. Some of the high-risk group will have already been vaccinated. It is assumed that these children are easily identified and incur no extra costs (or benefits) for the schools programme. Some proportion of the low-risk and unvaccinated high-risk children participate in the school programme - attending for the initial tuberculin skin test (TST) and then returning to have the result read and BCG if indicated. Those with a negative TST reaction are given the BCG vaccination, and consequently have a somewhat lower chance of contracting TB in future years than if they had not been vaccinated. Children with an intermediate TST reaction are assumed to be immune, and have a lower chance of subsequently contracting TB. Finally, those with a strongly positive skin reaction are referred to an outpatient clinic for evaluation, and may be treated for active TB, given treatment for latent TB infection, or discharged with no further action. The incidence of TB for unvaccinated TST- high-risk children is estimated by multiplying the incidence for the low-risk group (*rL*) by a relative risk (*rrHigh*).

The model is evaluated by attaching probabilities to each branch of the tree and values to the end nodes on the right. In Figure 1, the outcomes shown (0 or 1) indicate presence or absence of a primary case of active disease. The tree can thus be used to estimate the expected (mean) number of primary cases with the school BCG programme. Similarly, the model is adapted to estimate the total number of TB cases (primary and secondary), the resultant health outcomes (loss of quality adjusted life years, QALYs), and health care

costs (for both the BCG programme and future health care). The formulae for the QALY and calculations are shown in Appendix 1 and those for the cost outcomes in Appendix 2.

Input parameters

The probability, QALY and cost parameters used in the model are summarised in Table 1, Table 2 and Table 3 respectively. These parameters have been estimated from a variety of sources. Where possible, the estimates are based on recent, UK-relevant data. However, where no such information could be found, the values and ranges are based on subjective estimates by the guideline economist and members of the GDG. See Appendices 3–5, for a full list of sources and assumptions.

Methods of economic evaluation

The evaluation followed the methods of the NICE 'reference case'. Amongst other things, this means that an NHS perspective has been adopted. Costs are estimated for the organisation and delivery of the vaccination programme, as well as savings from reduced treatment of TB disease. However costs or savings to individuals or other organisations are not included.

The time horizon for the analysis has been chosen to reflect the expected duration of benefit from BCG vaccination in the school programme. Analysis of the MRC trial suggests a maximum protection of fifteen years, whereas meta-analysis of all trial data only supports a more limited estimate of ten years. The economic analysis has been conducted for both ten year and fifteen year protection (with estimated of cases prevented and associated costs and QALYs from age 15 to 24, and from age 15 to 29).

Both costs and non-monetary health effects were discounted at an annual rate of 3.5%, which reflects the current UK Treasury recommendations.

There is considerable uncertainty over the values of some of the input parameters. Sensitivity analysis was used to estimate the impact of this uncertainty. Firstly, a simple one-way sensitivity analysis was performed for each parameter – varying its value from the lower to the upper limit shown in

Tables 1–3. Secondly, a probabilistic sensitivity analysis was performed, using distributions listed in these tables.

Figure 3 Decision tree

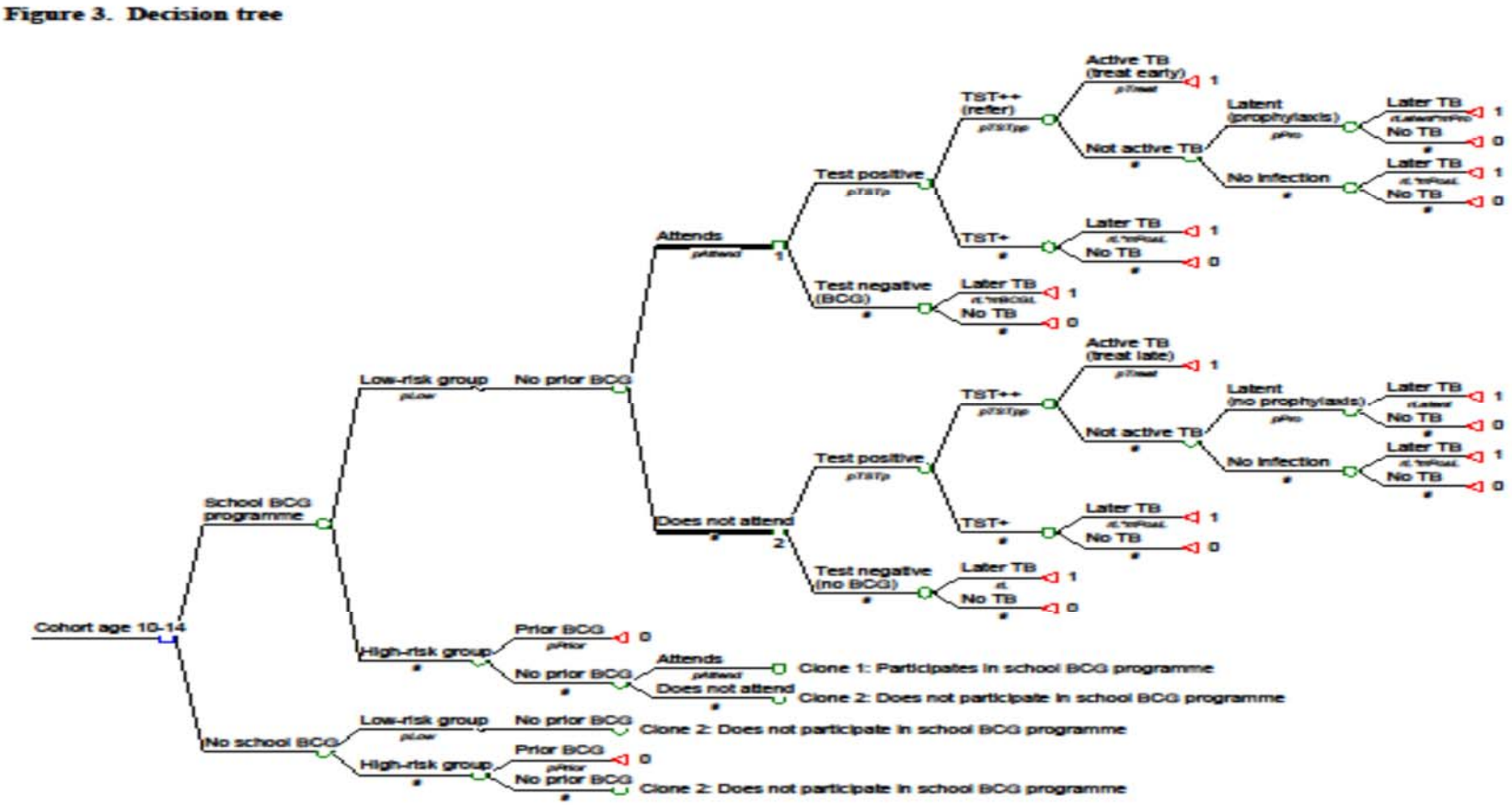


Table 6: Programme effectiveness and epidemiology parameters used in the model

• Parameter	• ame	• ase case	• Range for simple sensitivity analysis		• Distribution for probabilistic sensitivity analysis			
					• istribution	• E	• Paramet ers	
			• ower	• pper			• 1	• 2
Proportion of cohort in low-risk group	*pLow*	*85%*	*80%*	*100%*	beta	*7.65%*	18.50	3.27
Proportion who are TST+ at school BCG	*pTSTp*	*7.70%*	*7.61%*	*7.78%*	beta	*0.04%*	30,032	360,082
Proportion of TST+ at school BCG who are referred	*pTSTp p*	*0.5%*	*0.0%*	*1.0%*	beta	*0.26%*	3.82	760.66
Proportion of referred children treated	*pTreat*	*10%*	*5%*	*20%*	beta	*5.10%*	3.46	31.12
Proportion of non-treated children given prophylaxis	*pPro*	*20%*	*5%*	*30%*	beta	*5.10%*	12.29	49.17
Proportion of eligible population attending school programme	*pAttend*	*64%*	*60%*	*80%*	beta	*8.39%*	20.93	12.00
Proportion of 'high-risk' population previously given BCG	*pPrior*	*64%*	*60%*	*80%*	beta	*7.95%*	23.35	12.90
Baseline risk of TB (age 15–24) in TST- low-risk group	*r10*	*0.03%*	*0.018%*	*0.045%*	beta	*0.01%*	20.05	64,083
Baseline risk of TB (age 15–29) in TST- low-risk group	*r15*	*0.05%*	*0.028%*	*0.072%*	beta	*0.01%*	20.06	39,977

Risk of TB with latent infection (untreated)	*rLatent*	*1.7%*	*1.5%*	*1.8%*	beta	*0.07%*	557.00	32,556
Relative risk of TB for high-risk group	*rrHigh*	*40*	*10*	*70*	gamma	*15.3*	104.53	2.61
Relative risk of TB for TST- with BCG (10 year protection)	*rrBCG10*	*0.24291*	*0.24288*	*0.24295*	gamma	*0.000017*	3,397	13,984
Relative risk of TB for TST- with BCG (15 year protection)	*rrBCG15*	*0.18157*	*0.18156*	*0.18158*	gamma	*0.000004*	8,347	45,969
Relative risk of TB (age 15–24) if TST+	*rrPos10*	*0.24291*	*0.24288*	*0.24295*	gamma	*0.000017*	3,397	13,984
Relative risk of TB (age 15–29) if TST+	*rrPos15*	*0.18157*	*0.18156*	*0.18158*	gamma	*0.000004*	8,347	45,969
Relative risk of TB for latent cases with prophylaxis	*rrPro*	*0.40*	*0.31*	*0.52*	gamma	*0.061*	2.61	6.53
Relative risk of transmission if index case detected early	*rrEarly*	*0.5*	*0.2*	*1*	gamma	*0.255*	0.98	1.96
Mean secondary cases per primary case	*nSec*	*0.75*	*0.37*	*1.12*	gamma	*0.19*	2.94	3.92
Mean latent infections treated per primary case	*nPro*	*0.06*	*0.04*	*0.08*	gamma	*0.01*	0.42	6.62

Table 7: QALY estimates used in the model

Parameter	**Name**	**Base case**	**Range for simple sensitivity analysis**		**Distribution for probabilistic sensitivity analysis**			
					Distribution	**SE**	**Parameters**	
			Lower	**Upper**			**P1**	**• 2**

QALY loss due to BCG adverse reactions	*qBCG*	*0.00005*	*0.00000*	*0.00046*	gamma	*0.0002*	0.000013	0.248451
QALY loss for LI detected at school BCG	*qPro*	*0.05000*	*0.00000*	*0.10000*	gamma	*0.0255*	0.0980	1.9600
QALY loss for LI detected from index cases (age 15–24)	*qPro10*	*0.04028*	*0.00000*	*0.08056*	gamma	*0.0206*	0.0789	1.9600
QALY loss for LI detected from index cases (age 15–29)	*qPro15*	*0.03647*	*0.00000*	*0.07295*	gamma	*0.0186*	0.0715	1.9600
QALY loss for TB (diagnosed early at school BCG)	*qTBearly*	*0.14032*	*0.03087*	*0.30239*	gamma	*0.0827*	0.2381	1.6970
QALY loss for TB (age 10–14)	*qTB*	*0.15699*	*0.03454*	*0.33830*	gamma	*0.0925*	0.2664	1.6970
QALY loss for primary case (age 15–24)	*qTB10*	*0.16648*	*0.03662*	*0.35876*	gamma	*0.0981*	0.2825	1.6970
QALY loss for primary case (age 15–29)	*qTB15*	*0.16344*	*0.03596*	*0.35220*	gamma	*0.0963*	0.2774	1.6970
QALY loss for secondary case (index age 10–14)	*qSec*	*0.67589*	*0.14869*	*1.45652*	gamma	*0.3983*	1.1470	1.6970
QALY loss for secondary case (index age 15–24)	*qSec10*	*0.54450*	*0.11979*	*1.17338*	gamma	*0.3209*	0.9240	1.6970
QALY loss for secondary case (index age 15–29)	*qSec15*	*0.49305*	*0.10847*	*1.06250*	gamma	*0.2905*	0.8367	1.6970

Table 8: Cost estimates used in the model

Parameter	Name	Base case	Range for simple sensitivity analysis		Distribution for probabilistic sensitivity analysis			
					Distribution	SE	Parameters	
			Lower	Upper			P1	P2

Cost of school BCG programme (£ per child attending)	*cTST*	*£8*	*£5*	*£32*	gamma	*12.68*	4.522	0.597
Cost of vaccination (£ per child vaccinated)	*cBCG*	*£4*	*£1*	*£11*	gamma	*3.40*	5.027	1.215
Cost of referral for strongly positive cases (£ per referral)	*cRefer*	*£252*	*£214*	*£289*	gamma	*19.13*	3,306	13.145
Cost per primary case: age 10–14 (£ per case)	*cTB*	*£5,157*	*£1,928*	*£11,598*	gamma	*3286.65*	8,090	1.569
Cost per primary case: age 15–24 (£ per case)	*cTB10*	*£4,298*	*£1,607*	*£9,667*	gamma	*2739.23*	6,743	1.569
Cost per primary case: age 15–29 (£ per case)	*cTB15*	*£3,891*	*£1,455*	*£8,751*	gamma	*2479.92*	6,105	1.569
Cost per secondary case (index age 10–14)	*cSec*	*£5,098*	*£1,906*	*£11,466*	gamma	*3249.08*	7,998	1.569
Cost per secondary case (index age 15–24)	*cSec 10*	*£4,107*	*£1,535*	*£9,237*	gamma	*2617.48*	6,443	1.569
Cost per secondary case (index age 15–29)	*cSec 15*	*£3,719*	*£1,390*	*£8,364*	gamma	*2370.13*	5,834	1.569
Cost per latent case detected through school BCG	*cPro*	*£494*	*£251*	*£857*	gamma	*185.37*	1,315	2.664
Cost per treated latent case (index age 15–24)	*cPro 10*	*£398*	*£202*	*£690*	gamma	*149.34*	1,059	2.664
Cost per treated latent case (index age 15–29)	*cPro 15*	*£360*	*£148*	*£504*	gamma	*73.22*	1,772	4.919

QALY estimates

A previous version of the model suggested that the results were sensitive to the QALY estimates. Hence, a rather more accurate method has now been used to estimate the QALY loss from cases of TB at different ages. QALY loss due to TB-related mortality was estimated from information about the distribution of incidence by age (Figure 4), the estimated case fatality rate by age (Figure 5), and life expectation by age (Figure 6).

Figure 4 Estimated incidence by age
(HPA data, mean cases 1999–2003, curve fitted by cubic interpolation)

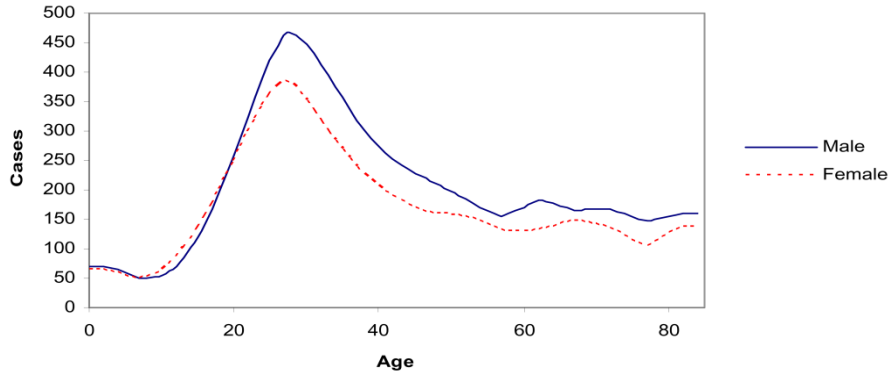


Figure 5 Estimated case fatality rate by age
(HPA data, mean TB deaths and cases 1999–2003, curve fitted by cubic interpolation)

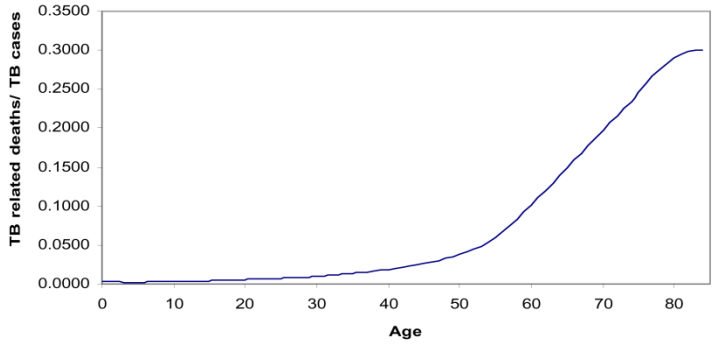
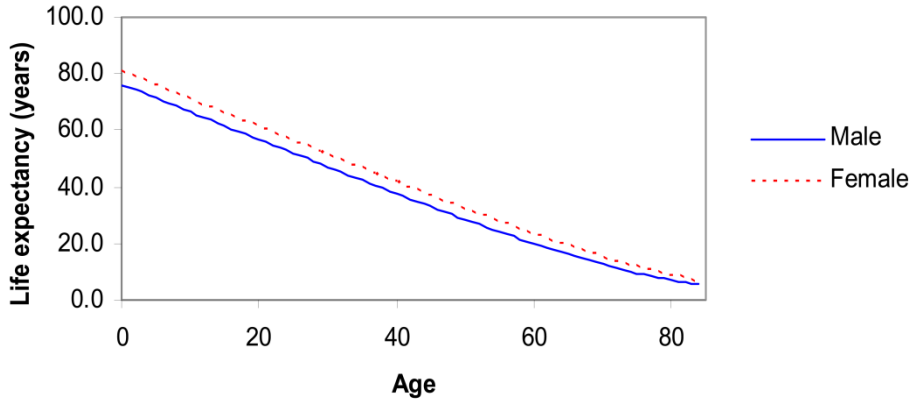


Figure 6 Life expectancy by age (GAD life tables, based on 2000–2 data)



The resulting estimates of QALY loss per fatality and per active case of disease are shown below. It can be seen that at younger ages (under 20) the impact of TB-related mortality is less than that of morbidity, whereas for older cases the reverse is true (Figure 7).

Figure 7 Estimated QALY loss per fatality (discounted to age of death)

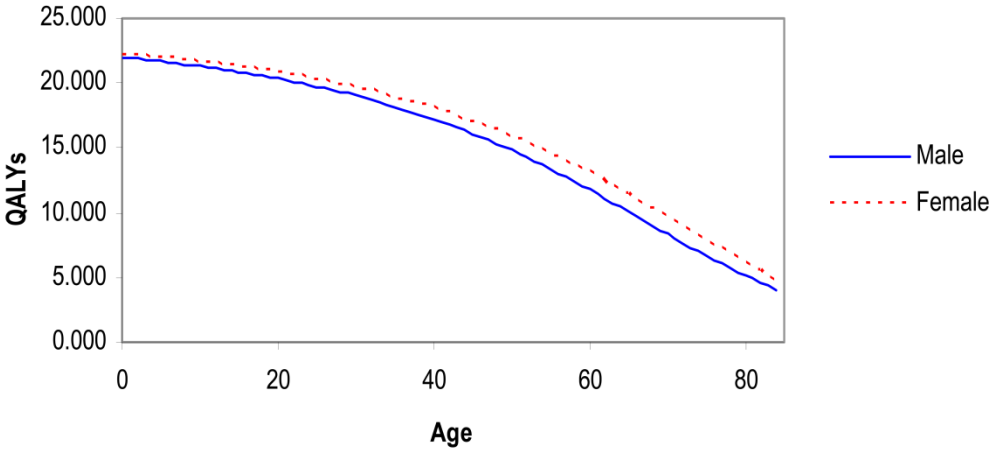


Figure 8 Estimated QALY loss due to mortality per case (discounted to age of death)

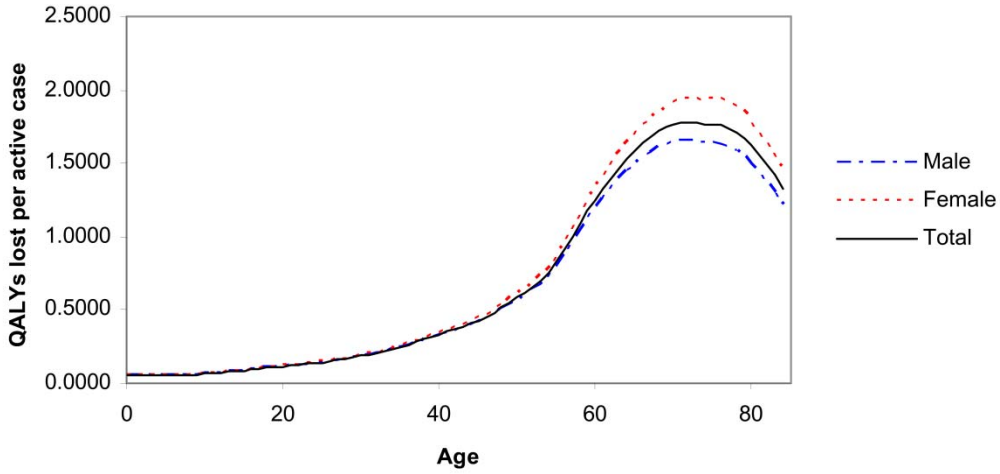
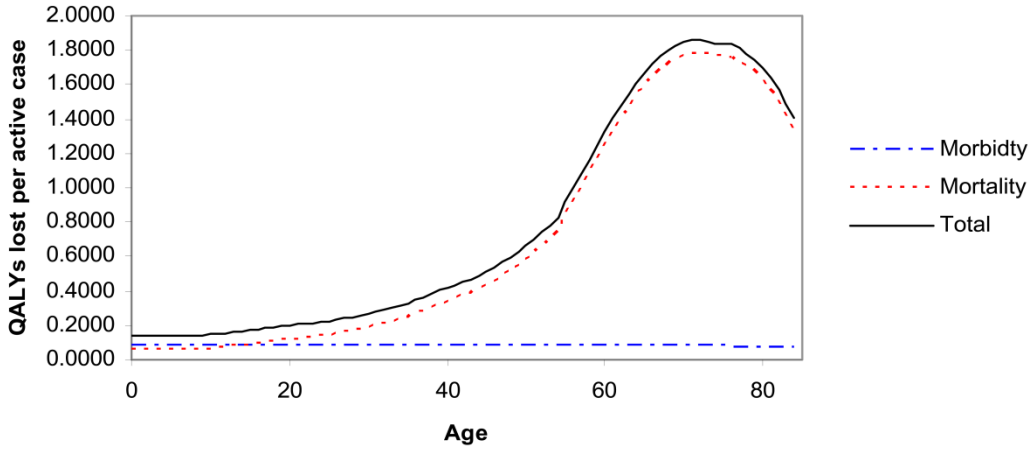


Figure 9 Estimated QALY loss for morbidity and mortality per case (discounted to age of incidence)



- ***Other modelling assumptions***

The model assumes that current levels of BCG coverage and baseline TB risk (for TST negative children who are not vaccinated) continue in those areas where a School BCG programme is retained, regardless of whether the programme is withdrawn from neighbouring areas. In reality, there would be some spill-over of effects.

Patients who survive active TB are assumed not have a recurrence within the time horizon of the analysis.

Once referred to hospital, identification of active TB and latent infection is assumed to be 100% accurate (there are no false positives or false

negatives). After effective prophylaxis, the risk of TB is assumed to be the same as for patients with a positive skin reaction.

RESULTS

Basecase analysis

The results of the basecase analysis are shown in Table 4. The schools programme does not appear to be cost-effective for the low-risk group alone – with 0% in the high-risk group, the incremental cost per QALY gained (ICER) is considerably higher than the conventional threshold of around £20,000–£30,000. However, this may change for some areas if we take account of the catch-up benefit for previously unvaccinated high-risk children. Assuming ten-year BCG protection, the schools programme appears to be cost-effective for areas with around 10–14% or more of children in the high-risk group. If we assume fifteen-year BCG protection, school BCG appears cost-effective with around 4–6% or more in the high-risk group. These results are based on the assumption that 64% of high-risk children have been previously vaccinated, and that they have a relative risk of 40 (compared with the low-risk group).

Table 9: Cost-effectiveness of School BCG by % of cohort in high-risk group

'High-risk' as % of cohort	10 year protection			15 year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0%	£651	5	£123,557	£588	10	£56,200
2%	£614	7	£83,327	£535	14	£38,312
4%	£578	9	£60,983	£482	17	£27,595
6%	£542	12	£46,767	£429	21	£20,458
8%	£506	14	£36,926	£376	24	£15,364
10%	£469	16	£29,710	£323	28	£11,544
12%	£433	18	£24,192	£270	31	£8,575
14%	£397	20	£19,836	£217	35	£6,200
16%	£361	22	£16,309	£164	38	£4,258
18%	£325	24	£13,396	£111	42	£2,639
20%	£288	26	£10,950	£58	45	£1,270

School BCG appears to be cost-effective for the low-risk population only if their baseline level of risk (from 15–24 or 15–29 years of age) is approximately 0.08-0.1% (Table 5). This compares with current estimates of 0.03% (age 15–24) or 0.05% (age 15–29).

Table 10: Cost-effectiveness of School BCG for low-risk group only by baseline risk of TB

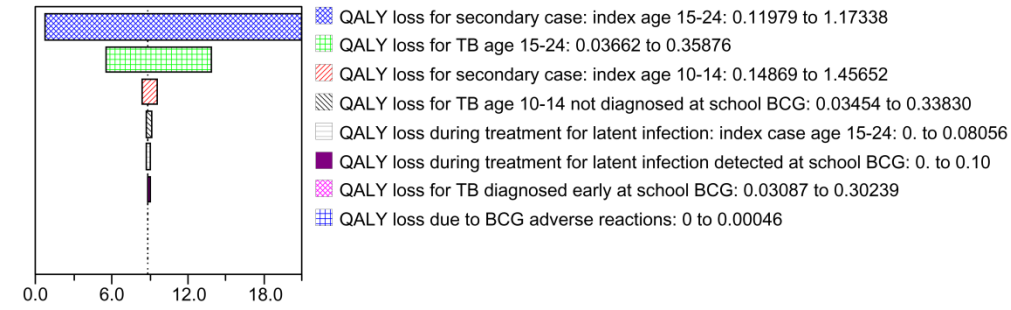
Risk of TB over period of protection	10 year protection			15 year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QAL
0.03%	£651	5	£123,600	-	-	
0.04%	£617	8	£78,700	-	-	
0.05%	£584	10	£56,000	£588	10	£56,2
0.06%	£551	13	£42,400	£555	13	£42,6
0.07%	£518	16	£33,200	£523	16	£33,5
0.08%	£485	18	£26,700	£491	18	£26,9
0.09%	£452	21	£21,800	£458	21	£22,0
0.10%	£419	23	£18,000	£426	23	£18,2

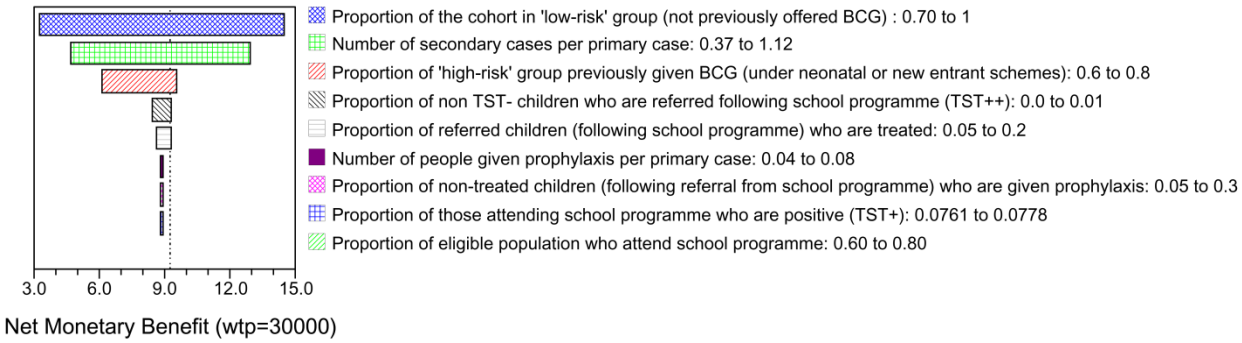
One-way Simple Sensitivity Analysis

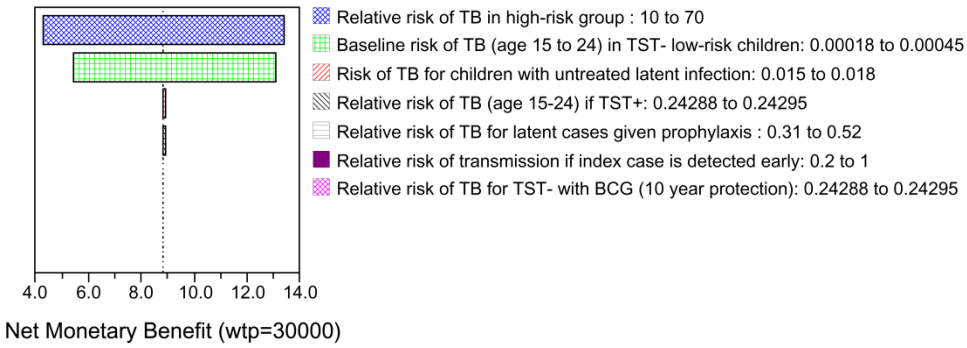
The results of the one-way sensitivity analysis are shown in the 'tornado diagrams' in Figures 10 and 11. These indicate that the cost-effectiveness of the schools' programme is most sensitive to:

The estimated QALY loss per case of active TB age 15–24 or 29, and for secondary cases resulting from these index cases.
The proportion of the population in 'high-risk' groups, and the proportion of these who have previously been vaccinated.
The mean number of secondary cases per primary case.
The baseline level of risk in the low-risk group (TST- unvaccinated), and the relative risk for those in the high-risk group (TST- vaccinated).
The mean cost of treating a case of TB age 15–24/29, or secondary cases resulting from such cases.

Figure 10 Tornado diagrams (10 year protection)







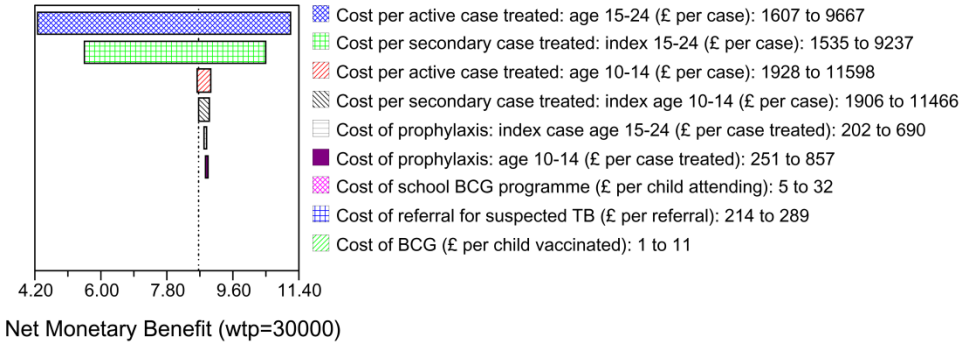
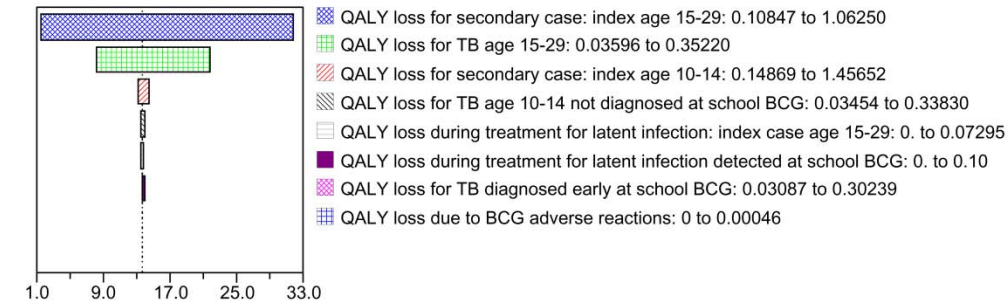
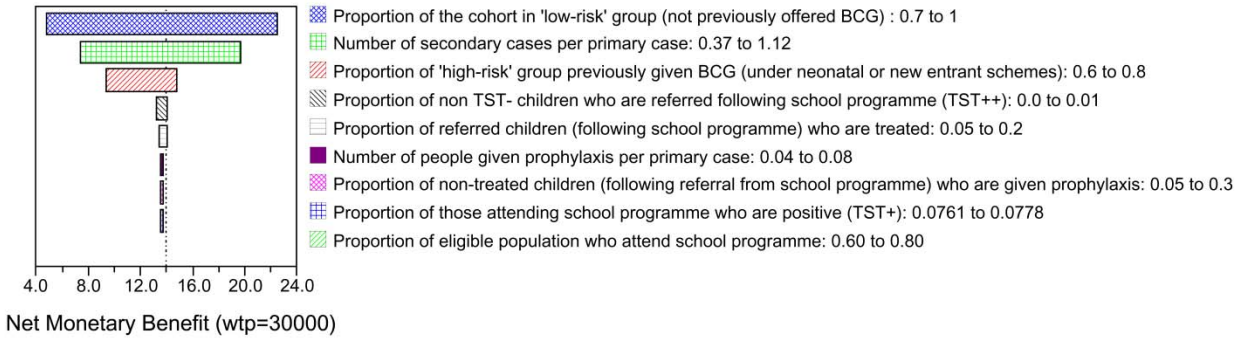
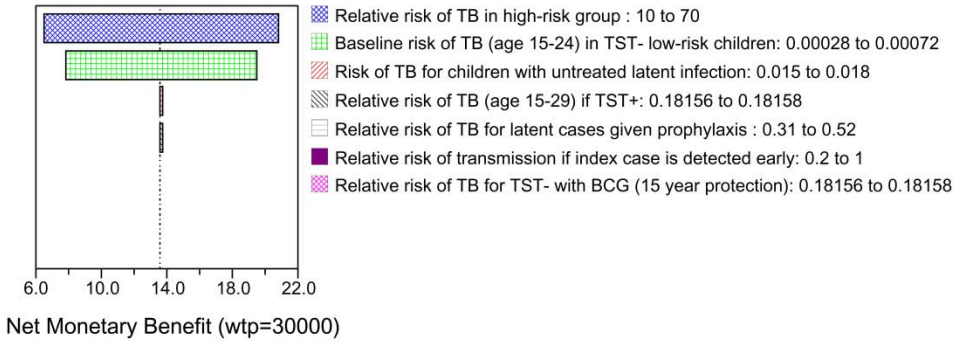
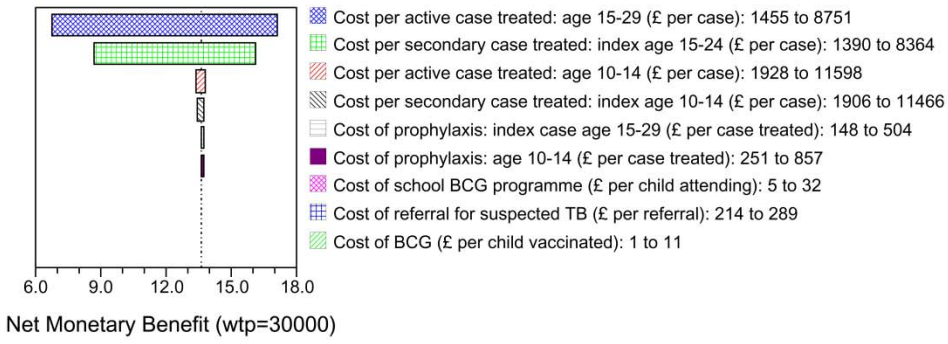


Figure 11 Tornado diagrams (15 year protection)







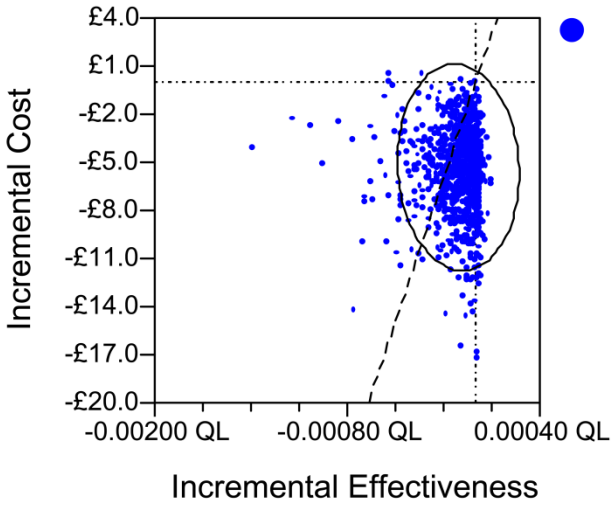


Probabilistic Sensitivity Analysis

The extent of uncertainty over the mean costs and effects of the school BCG programme is illustrated in Figure 10 for a population with 5% high-risk and assuming only 10 year protection from BCG. In this diagram the dotted line represents the £30,000 per QALY cost-effectiveness threshold

– all points to the northwest of this line indicate that the schools programme is cost-effective. The ellipse shows the region of 95% confidence, based on underlying uncertainty about the input parameters for the model. It can be seen that there is a high degree of uncertainty about the cost-effectiveness of the school programme.

Figure 12 Results of probabilistic sensitivity analysis (5% high-risk, 10 year protection)



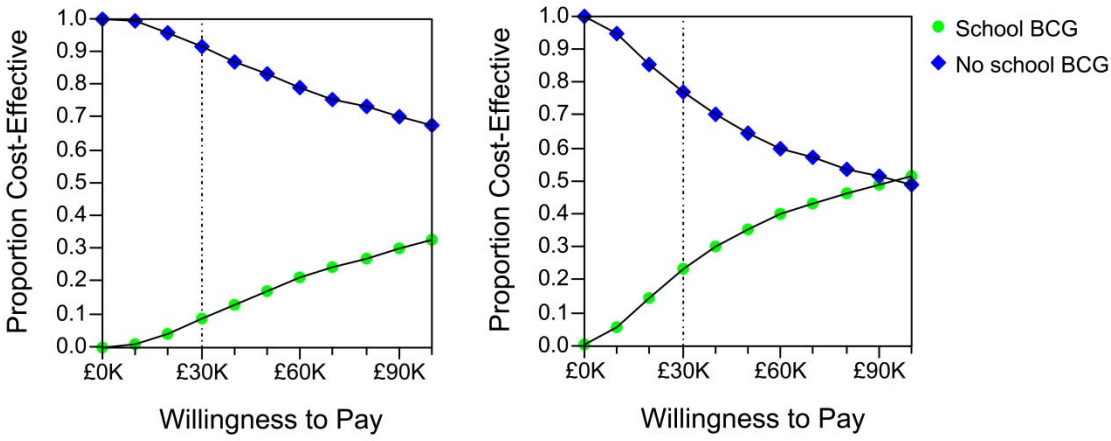
This uncertainty is further illustrated by the cost-effectiveness acceptability curves (CEACs) shown below. With no high-risk children in the cohort, there is a high estimated probability that withdrawing the schools programme would be cost-effective: 90% assuming 10 year BCG protection, and 80% with 15 year protection (Figure 11).

With a 5% proportion of high-risk children in the cohort, there is roughly a 75% chance that withdrawing the schools programme would be cost-effective assuming only 10 year protection and a 55% chance assuming 15 year protection (Figure 12)).

However, with 10% high-risk children, the estimated probability that withdrawing the school programme would be cost-effective is lower:

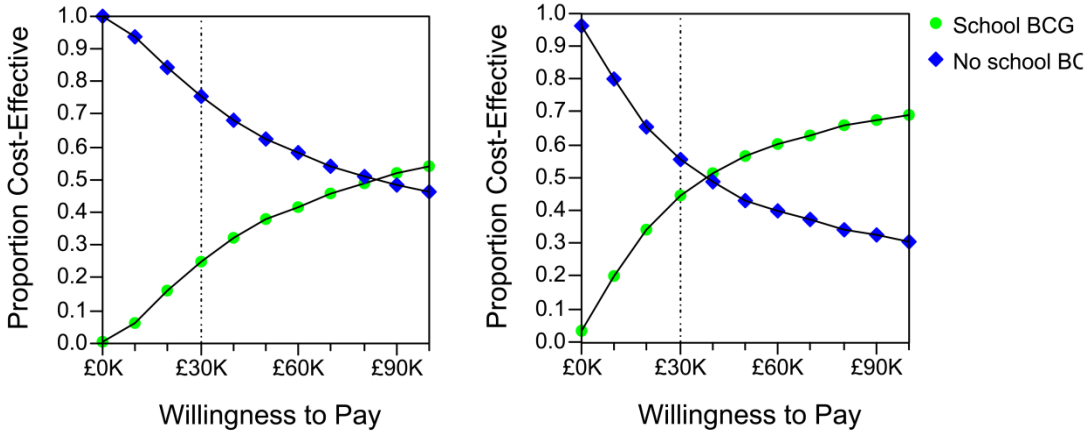
approximately 60% with 10 year protection, and only 40% with 15 year protection (Figure 13).

Figure 13 Cost-effectiveness acceptability curve (0% high-risk)



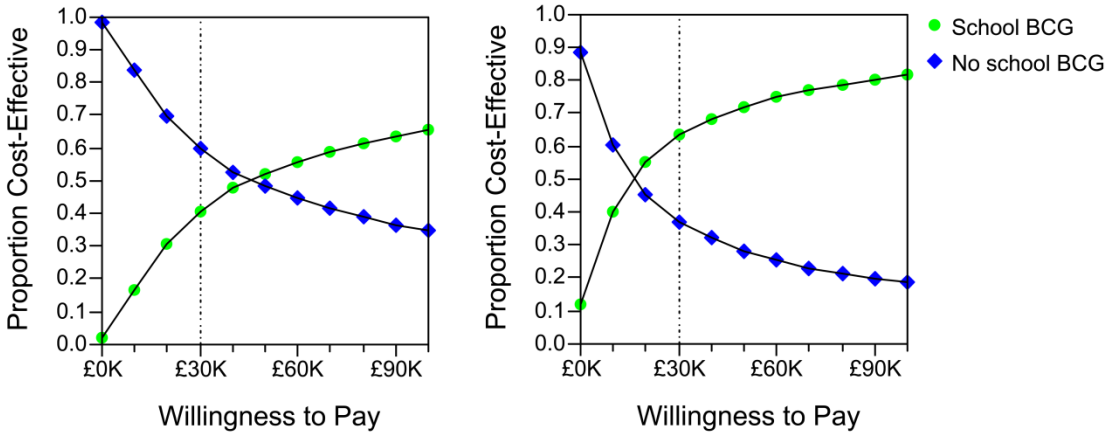
10 year BCG protection *15 year BCG protection*

Figure 14 Cost-effectiveness acceptability curve (5% high-risk)



10 year BCG protection *15 year BCG protection*

Figure 15 Cost-effectiveness acceptability curve (10% high-risk)



10 year BCG protection *15 year BCG protection*

CONCLUSIONS

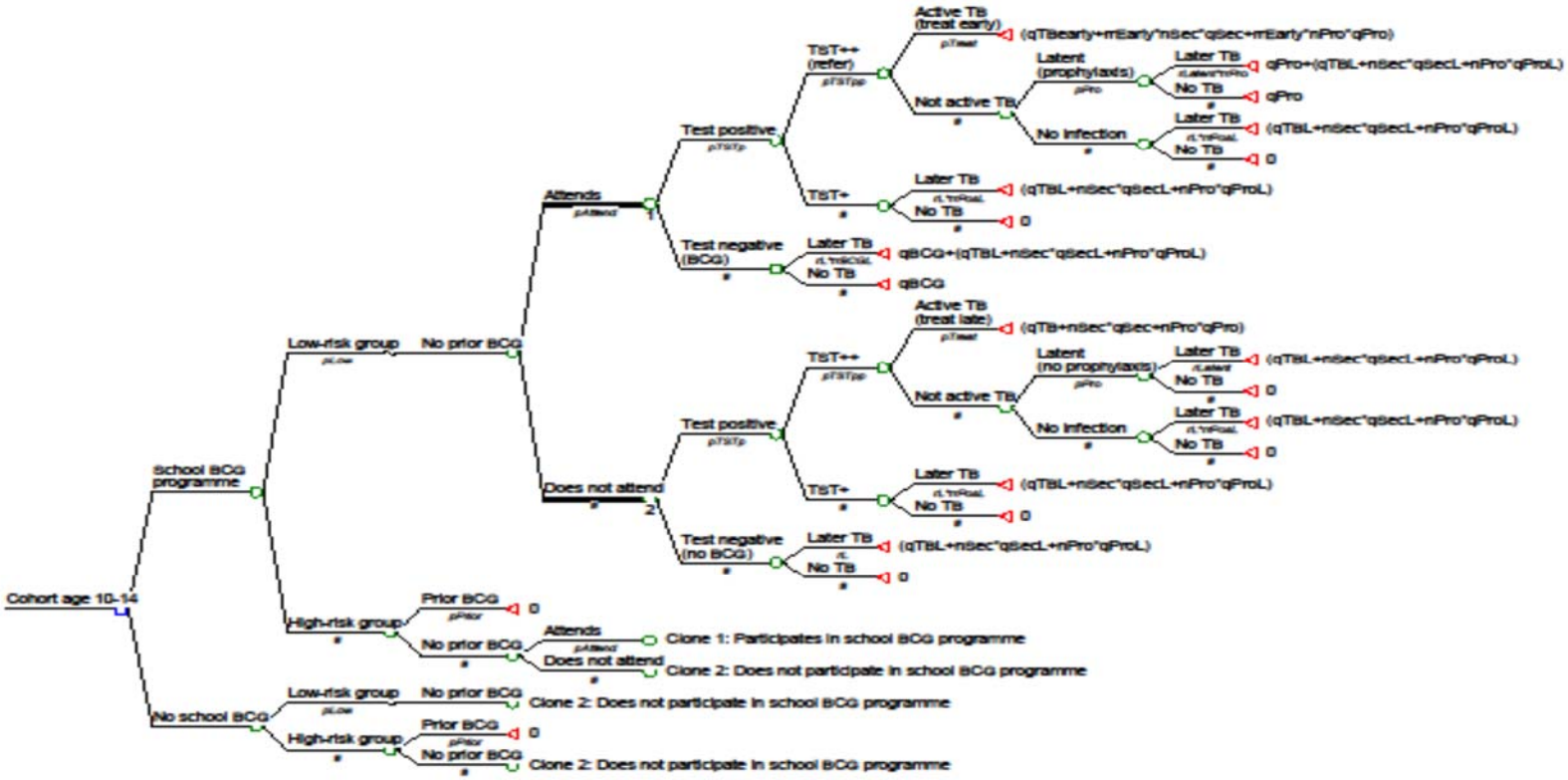
This analysis suggests that the current schools' BCG programme is only likely to be cost-effective in areas of the country with relatively high proportions of unvaccinated 10–14 year olds in 'high risk' groups: approximately 10% or more, assuming that high-risk children have forty times the incidence of low-risk children and that only 64% of high-risk children are vaccinated prior to school BCG. This is most likely to apply to areas such as London and the West Midlands, with relatively large numbers of children from high-incidence ethnic groups or born in high-incidence countries.

This analysis has only considered the costs and consequences of the schools programme. It is therefore unclear whether even in high-incidence areas, the resources used for the schools programme could be better directed towards improving the uptake of neonatal or new entrant schemes, or by introducing universal neonatal programmes.

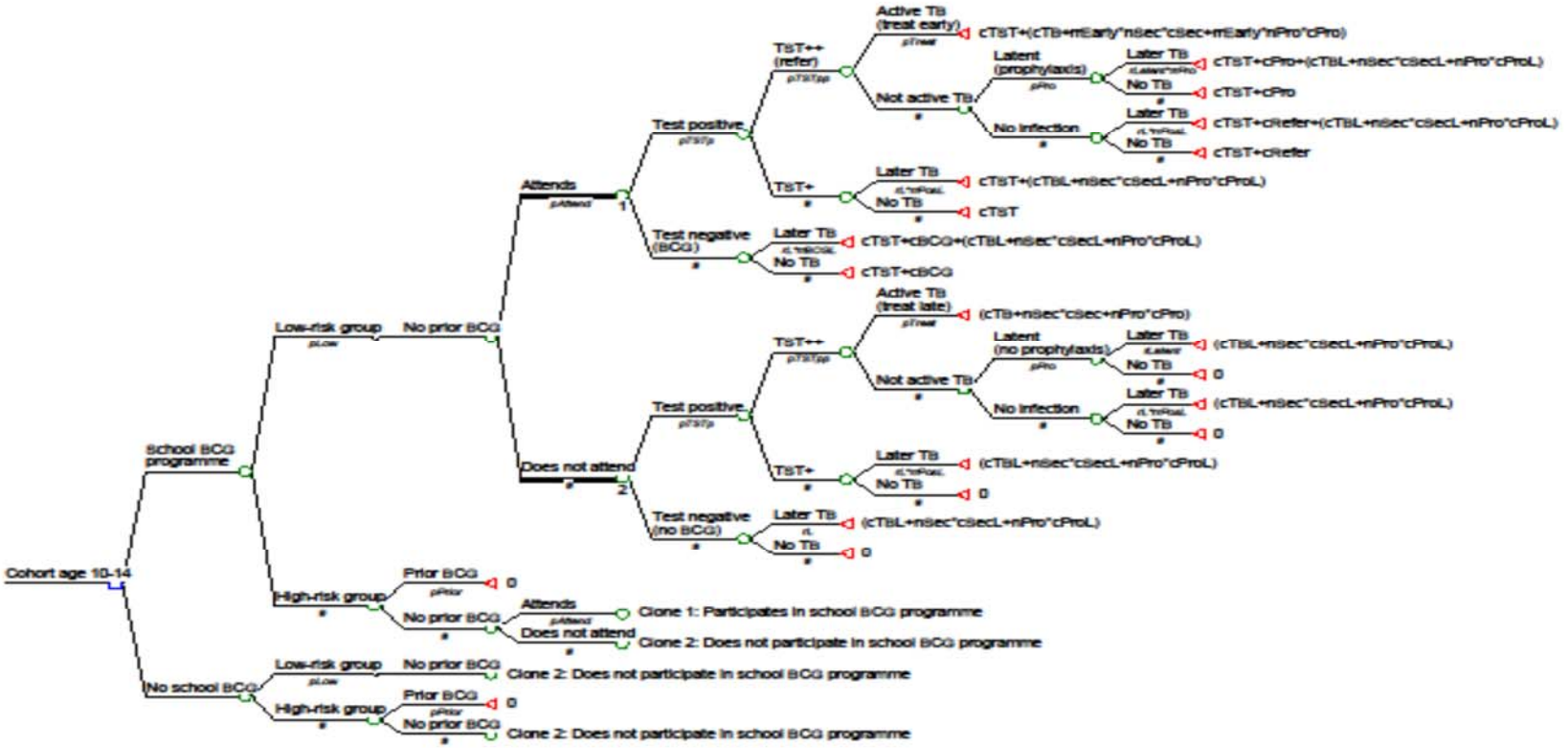
There is considerable uncertainty over the results of the model due to uncertainty over some of the input parameters for the analysis. In particular, the results are sensitive to the proportion of 10–14 year olds in 'high-risk' groups, the proportion of these high-risk children previously vaccinated, the baseline level of risk in the cohort, and the relative risk for the high-risk group. The results are also sensitive to the estimated QALY loss due to TB, and the estimated cost of treating a case of TB. Finally, the

results were sensitive to the mean number of secondary cases per primary case. This suggests that more reliable results might be obtained from a population model, reflecting the dynamics of transmission of the disease.

ANNEX 1 - Decision tree with QALY outcomes



ANNEX 2 – Decision tree with cost outcomes



ANNEX 3: Input data and assumptions: programme effectiveness and epidemiology

		Base case	Lower limit	Upper limit	Source	Comments
Population and baseline risks						
Proportion of cohort in low-risk group	*pLow*	85%	70%	100%	Assumption	Range to reflect possible variation between areas.
Baseline risk of TB (age 15–24) in TST-low-risk group	*r10*	0.031%	0.018%	0.045%	Saeed et al 2002 (table 2a)	1 in 3197 - assuming 10 year protection, 2003 cohort. Lower limit shows estimate for 2033 cohort (1:5685)
Baseline risk of TB (age 15–29) in TST-low-risk group	*r15*	0.050%	0.028%	0.072%	Saeed et al 2002 (table 2b)	1 in 1994 - assuming 15 year protection, 2003 cohort. Lower limit shows estimate for 2033 cohort (1:3545)
Relative risk of TB for high-risk group	*rrHigh*	40	10	70	Assumption	Current recommendation for neonatal screening for groups/populations with 40/100,000 (compared with baseline risk for white UK born of around 1 in 100,000). Range to examine variation between areas.
Mean secondary cases per primary case	*nSec*	0.75	0.37	1.12	Saeed et al 2002 (table 4b)	Inferred from estimated numbers of secondary/primary notifications between 2003 to 2023 from stopping BCG at end of 2002 (assuming 10

						year BCG protection)
Mean latent infections treated per primary case	*nPro*	0.06	0.04	0.08	Underwood et al 2003)	41 contacts given prophylaxis out of 646 traced.
Coverage of BCG programmes						
Proportion of eligible population attending school programme	*pAttend*	64%	60%	80%	DH & NAW 2002–3	Estimated from number of skin tests divided by estimated white population in one year cohort (age 10–14)
Proportion of 'high-risk' population previously given BCG	*pPrior*	64%	60%	80%	DH & NAW 2002–3	Estimated from annual number of vaccinations (age 0–9) divided by estimated high-risk population in one year cohort (assuming (1-pLow) proportion of year group is high risk).
Effectiveness of BCG programmes						
Relative risk of TB for TST- with BCG (10 year protection)	*rrBCG10*	0.24291	0.24288	0.24295	Saeed et al 2002 (table 2a)	1 in 13161/1 in 3197 - assuming 10 year protection, 2003 cohort. Upper limit shows estimate for 2033 cohort.
Relative risk of TB for TST- with BCG (15 year protection)	*rrBCG15*	0.18157	0.18156	0.18158	Saeed et al 2002 (table 2b)	1 in 10,982/1 in 1994 - assuming 15 year protection, 2003 cohort. Lower limit shows estimate for 2033 cohort.
Relative risk of TB (age 15–24) if TST+	*rrPos10*	0.24291	0.24288	0.24295	Assumption	Assumed same as for TST-with BCG: 10 year protection
Relative risk of TB	*rrPos15*	0.18157	0.18156	0.18158	Assumption	Assumed same as for TST-

(age 15–29) if TST+						with BCG: 15 year protection
Proportion who are TST+ at school BCG	*pTSTp*	7.7%	7.6%	7.8%	DH & NAW 2002–3	Positive rate for 10–15 age group 2002/3. Range 95% CI.
Proportion of TST+ at school BCG who are referred	*pTSTpp*	0.5%	0.0%	1.0%	Assumption	
Proportion of referred children treated	*pTreat*	10%	5%	20%	Assumption	
Proportion of non-treated children given prophylaxis	*pPro*	20%	5%	30%	Assumption	
Relative risk of transmission if index case detected early	*rrEarly*	0.5	0.2	1.0	Assumption	
Risk of TB with latent infection (untreated)	*rLatent*	1.7%	1.5%	1.8%	Smieja et al 2004	Risk of infection in control groups of included studies from meta analysis (n=33113). Various lengths of follow-up. Range shows 95% CI.
Relative risk of TB for latent cases with prophylaxis	*rrPro*	0.40	0.31	0.52	Smieja et al 2004	Relative risk with isoniazid treatment of 6 months or more (95% CI)

ANNEX 4: Input data and assumptions: QALY estimates

		Base case	Lower limit	Upper limit	Source	Comments
Quality of life values						
Population quality of life (0 to 1)	QoL	0.83	0.80	0.90	Health Survey for England 1996	Mean for 16+ population, men and women.
QoL loss due to adverse reactions to BCG	*QoLAR*	0.10	0.00	0.20	Assumption	
QoL loss during treatment for latent TB infection for latent infection	*QoLPro*	0.10	0.00	0.20	"	
QoL loss due to sick time at home with TB (not treated)	*QoLhome*	0.10	0.00	0.20	Schechter, Rose and Fahs 1990	Estimates by authors, not from patient survey. Ranges for sensitivity analysis assumed.
QoL loss due to near-death time in hospital with TB	*QoLND*	0.90	0.80	1.00	"	"
QoL loss due to time in hospital with non-fatal TB	*QoLIP*	0.50	0.40	0.60	"	"
QoL loss during outpatient treatment	*QoLOP*	0.10	0.00	0.20	"	"
Adverse reactions to BCG						
Incidence of adverse reactions to BCG	*pAR*	0.3%	0.0%	1.0%	Bannon 1999	Reported incidence of suppurative

						adenitis in older children
Mean duration of adverse reactions to BCG (years)	*dAR*	0.173	0.115	0.231	Marchant 1998	Says that localised lesions will heal within 6–12 weeks
QALY loss due to BCG adverse reactions	*qBCG*	0.000005	0.00000	0.00046	QoLAR*pAR*dAR	
Sickness during treatment for latent TB infection						
Mean duration of treatment for latent TB infection (years)	*dPro*	0.5	0.5	0.5	Guideline recommendations	
QALY loss for LI detected at school BCG	*qPro*	0.050	0.000	0.100	QoLPro*dPro	
QALY loss for LI detected from index cases (age 15–24)	*qPro10*	0.040	0.000	0.081		Discounted to age 15 (for index case) - assumes current distribution of incidence (age 15–24) for index case.
QALY loss for LI detected from index cases (age 15–29)	*qPro15*	0.036	0.000	0.073		Discounted to age 15 (for index case) - assumes current distribution of incidence (age 15–29) for index case.
Sickness for active cases						
Time to diagnosis: cases detected by school BCG (years)	*delayBCG*	0.083	0.042	0.125	Assumption	One month
Time to diagnosis: other cases (years)	*delay*	0.250	0.125	0.375	Assumption	Three months
QALYs lost prior to diagnosis	*Qho*	0.0	0.00	0.08	QoLhome*delay	

(per case)	*me*	3				
QALYs gained from early detection at BCG (per case)	*Qearly*	0.02	0.00	0.05	QoLhome*(delay-delayBCG)	
Proportion of cases admitted (all ages)	*pAdmit*	53%	40%	60%	HPA & DH data	Inpatient episodes/total TB cases
Mean length of stay for acute TB (days)	*LoS*	10.4	8.00	12.00	DH Reference Costs	HRG D18 non-elective episodes. Close to mean of 10 days for 18 non-MDR cases in White and Moore-Gillon 2000.
Proportion of time in hospital 'near death'	*pND*	20%	10%	30%	Assumption	
QALYs lost as inpatient for survivors	*QIPlive*	0.009	0.004	0.014	pAdmit*(LoS/365)*(pND*QoLND+(1-pND)*QoLIP)	
QALYs lost as inpatient for fatalities	*QIPdie*	0.026	0.026	0.026	(LoS/365)*QoLND	Assumes full time as inpatient is spent 'near death'.
Mean duration of outpatient treatment (years)	*dOP*	0.5	0.5	0.5	Guideline recommendations	Six months
QALYs lost as outpatient (per case)	*QOP*	0.050	0.000	0.100	QoLOP*dOP	
QALY loss due to morbidity for TB survivors	*QLive*	0.0838	0.0039	0.1892	Qhome+QIPlive+QOP	
QALY loss due to morbidity for TB fatalities	*QLdie*	0.0507	0.0257	0.1007	Qhome+QIPdie	
Total QALYs lost per active case						
QALY loss for TB (diagnosed early at school BCG)	*qTBearl*	0.1403	0.0309	0.3024	Q-Qearly	

	y					
QALY loss for TB (age 10–14)	*qTB*	0.1570	0.0345	0.3383	HPA mortality and incidence (1999–2003), GAD life expectancy (2000–2)	Includes estimated QALY loss due to mortality and morbidity (as estimated above) for primary cases aged 10 to 14.
QALY loss for primary case (age 15–24)	*qTB10*	0.1665	0.0366	0.3588		As above, but for primary cases aged 15–24 (mean weighted by incidence), discounted to age 15.
QALY loss for primary case (age 15–29)	*qTB15*	0.1634	0.0360	0.3522		As above, but for primary cases aged 15–29.
QALY loss for secondary case (index age 10–14)	*qSec*	0.6759	0.1487	1.4565		Mean QALY loss for secondary cases (mean for all ages weighted by incidence) given that index case occurs between age 10 and 14 and assuming time lag of 1 year for transmission.
QALY loss for secondary case (index age 15–24)	*qSec10*	0.5445	0.1198	1.1734		As above, but for index cases between 15 and 24,

						discounted to age 15 (for index case).
QALY loss for secondary case (index age 15–29)	*qSec15*	0.4930	0.1085	1.0625		As above, but for index cases aged 15 to 29.

ANNEX 5: Input data and assumptions: Cost estimates

		Base case	Lower limit	Upper limit	Source	Comments
School BCG						
Tuberculin per child	*ucTST*	£1.22			BNF 48, September 2004	0.1mL Tuberculin + £1 for disposables
Cost of vaccination (£ per child vaccinated)	*ucVaccine*	£3	£1	£5	Assumption	Not publicly available
Nurse for school BCG session (per hour)	*uNrs*	£28			PSSRU Unit Costs 2004	Assumed equivalent to health visitor cost (including qualification costs and overheads). Uprated for inflation.
Doctor for school BCG session (per hour)	*uDr*	£134			"	Assumed equivalent to GP per hour of patient contact (including overheads and qualification costs, but excluding costs for other direct care staff). Uprated for inflation.
School nurse time for skin testing session (hours per child)	*qNrs1*	0.08			Marchant 1998	Assumes 3 nurses for 3 hours per school, 117 children per school (estimated from DfES data).
School nurse time for vaccination session (hours	*qNrs2*	0.03			"	1 nurse for 3 hours per school.

per child)						
Doctor time for vaccination session (hours per child)	*qDr*	0.03			"	2 doctor for 3 hours per school.
Clinic visits for treatment of adverse reactions	*qOPAR*	2	1	3	Assumption by GDG	
GP visits for treatment of adverse reactions	*qGPAR*	1	0	2	Assumption by GDG	
Cost for first clinic visit (£)	*ucOP1*	£252	£214	£289		
Cost for subsequent clinic visits (£)	*ucOP2*	£128	£109	£146		
Cost per GP visit (£)	*ucGP*	£23	£10	£30		
Cost of school BCG programme (£ per child attending)	*cTST*	£8	£5	£32	ucTST+uNrs*qNrs1+uNrs*qNrs2+uDr*q Dr	Cost for both sessions (excluding vaccine). Upper limit from 2003/4 Reference costs
Cost of vaccination (£ per child vaccinated)	*cBCG*	£4	£1	£11	ucTST+pAR*IF(qOPAR>1,ucOP1+(qOP AR-1)*ucOP2,IF(qOPAR=1,ucOP1,0))	Includes cost of vaccine and cost of treating adverse reactions (assumes that there are no adverse reactions to the tuberculin test).
Cost of referral for strongly positive cases (£ per referral)	*cRefer*	£252	£214	£289	DH Tariff 2005/6	For respiratory medicine speciality. Range for adult and child.
Active cases						
Contact tracing						
Contact tracing (per contact)	*ucTrace*	£317	£164	£539	DH Reference costs 2003/4	Assumes one clinic visit per contact (infectious diseases, first visit). Range is interquartile range. Uplifted for inflation.

Mean number of contacts examined per primary case	*nContacts*	6.5	2.8	10.2	Review of Current Services (see guideline). Underwood et al 2003	Midpoint estimate from survey, lower limit from Underwood.
Cost of contract tracing (£ per primary case)	*cTrace*	£2,058	£466	£5,470	ucTrace*nContacts	
Inpatient care						
Cost of inpatient episode for acute TB (£ per spell)	*ucIP*	£3,457	£2,153	£6,040	DH Tariff 2005/6	HRG D18 non-elective (92% of FCEs in 2003/4). Lower limit for elective cases. Upper limit from White & Moore-Gillon 2000.
Proportion of cases admitted (all ages)	*pAdmit*	53%	40%	60%	HPA & DH Reference Costs	Inpatient episodes/total TB cases
Cost of inpatient care (£ per active case)	*cIP*	£1,835	£861	£3,624	ucIP*pAdmit	
Chemotherapy						
Cost of isoniazid (£ per month)	*ucIso*	£12.36	£6.18	£18.55	BNF 48, September 2004	Dose: 100, 200, 300mg daily, non-proprietary.
Cost of rifampicin (£ per month)	*ucRif*	£10.76	£5.45	£21.51	"	Dose: 150, 300, 600mg daily, non-proprietary.
Cost of ethambutol (£ per month)	*ucEth*	£18.48	£12.32	£22.89	"	Dose: 200,300,400 daily, non-proprietary.
Cost of pyrazinamide (£ per month)	*ucPyr*	£6.88	£4.58	£9.17	White and More-Gillon 2000	Dose: 1g, 1.5g, 2g daily
Duration of isoniazid (months)	*Iso*	6	6	6	GDG recommendation	Regimen for pulmonary TB (HIV-and non-MDR). Assumes full concordance with recommended regimen. No DOTS or

						other increased surveillance assumed.
Duration of rifampicin (months)	*Rif*	6	6	6	"	
Duration of ethambutol (months)	*Eth*	2	2	2	"	
Duration of pyrazinamide (months)	*Pyr*	2	2	2	"	
Cost of drugs (£ per active case)	*cdrugs*	£189	£104	£304	(Iso*ucIso+Rif*ucRif+Pyr*ucPyr+Eth*uc Eth)	Close to mean of £150 for 18 non-MDR cases reported in White and Moore-Gillon 2000.
Outpatient care						
Cost of outpatient consultation: first visit (£ per visit)	*ucOP1*	£252	£214	£289	DH Tariff 2005/6	For respiratory medicine speciality. Range for adult and child.
Cost of outpatient consultation: follow up visits (£ per visit)	*ucOP2*	£128	£109	£146	"	"
Cost of TB nurse home visit (£ per visit)	*ucNurse*	£22	£17	£34	PSSRU Unit Costs 2004	Assumed equivalent to district nurse/practice nurse/health visitor (including qualification costs and overheads). Uplifted for inflation.
Cost of GP consultation (£ per consult)	*ucGP*	£23	£10	£30	"	GP surgery consult lasting 9.36mins/primary care nurse consult/GP clinic consult lasting 12.6mins (includes qualification costs and overheads). Uplifted for inflation.

Number of outpatient clinic visits per case treated	*OP*	4	2	8	Marchant 1998	Assumptions by Marchant agreed by GDG. Upper limit is mean for 18 non-MDR cases in White and Moore-Gillon 2000.
Visits from TB nurse per case treated	*Nurse*	6	3	6	"	"
GP consultations per case treated	*GP*	0	0	1	Assumption	
Cost of non-drug outpatient care (£ per active case)	*cOP*	£764	£375	£1,544	IF(OP<1,0,IF(OP=1,ucOP1,ucOP1+(OP-1)*ucOP2))+Nurse*ucNurse+GP*ucGP	
Tests						
Cost of interferon gamma test (£ per test)	*ucIGtest*	£10	£5	£20	Internet, accessed 6/01/05	Low estimate: $10 price from US (may not be appropriate for UK, and may exclude labour costs).
Cost of culture tests (£ per test)	*ucCtest*	£7	£4	£11	DH Tariff 2005/6	Microbiology/bacteriology
Cost of chest X-ray (£ per X-ray)	*ucXray*	£16	£11	£18	DH Tariff 2005/6	Band A. Range from 2003/4 reference costs for range.
Interferon gamma test per case treated	*IGtest*	0	0	1	"	
Culture tests per case treated	*Ctest*	4	2	6	"	Assumed once per clinic visit
Chest X-ray per case treated	*Xray*	2	1	3	"	Assumed once every other clinic visit
Cost of tests (£ per active	*cTest*	£61	£18	£140	IGtest*ucIGtest+	

case)					Ctest*ucCtest+Xray*ucX ray	
MDR TB						
Proportion of active cases that are MDR	*pMDR*	1.1%	0.9 %	1.3%	HPA 2002	Upper limit is for resistance to more than one first line drug
Cost per MDR TB case	*cMDR*	£27,844	£20,000	£40,000	White & Moore-Gillon 2000	Baseline estimate is based on NHS Tariff costs (2005/6).
Total						
Cost for TB treatment for survivors (£ per case)	*cTBlive*	£5,160	£1,988	£11,458	pMDR*cMDR+(1-pMDR)*(cTrace+cIP+cdrugs+cOP+cTests)	Includes cost of contact tracing, inpatient care, outpatient care, tests and treating MDR cases
Cost for TB treatment for fatalities (£ per case)	*cTBdie*	£4,156	£1,495	£9,496	pMDR*cMDR+(1-pMDR)*(cTrace+cIP)	Includes contact tracing, inpatient care and MDR cases
Cost per primary case: age 10–14 (£ per case)	*cTB*	£5,157	£1,928	£11,598		Mean treatment cost for survivors and fatalities age 10–14 (weighted by incidence and case fatality rate)
Cost per primary case: age 15–24 (£ per case)	*cTB10*	£4,298	£1,607	£9,667		As above, but for cases aged 15–24
Cost per primary case: age 15–29 (£ per case)	*cTB15*	£3,891	£1,455	£8,751		As above, but for cases aged 15–29
Cost per secondary case (index age 10–14)	*cSec*	£5,098	£1,906	£11,466		Mean treatment cost for secondary cases resulting from index case aged 10–14 and assuming one year

						time lag for transmission.
Cost per secondary case (index age 15–24)	*cSec10*	£4,107	£1,535	£9,237		As above but for index cases age 15–24, discounted to age 15 for index case.
Cost per secondary case (index age 15–29)	*cSec15*	£3,719	£1,390	£8,364		As above but for index case aged 15-29.
Prophylaxis of latent cases						
Treatment for latent TB infection						
Cost of isoniazid (£ per month)	*ucIso*	£12.36	£6.18	£18.55	See previous table	
Cost of rifampicin (£ per month)	*ucRif*	£10.76	£5.45	£21.51		
Cost of ethambutol (£ per month)	*ucEth*	£18.48	£12.32	£22.89		
Cost of pyrazinamide (£ per month)	*ucPyr*	£6.88	£4.58	£9.17		
Duration of isoniazid (months)	*IsoP*	6	6	6	GDG recommendation	Regimen for pulmonary TB (HIV-and non-MDR). Assumes full concordance with recommended regimen. No DOTS or other increased surveillance assumed.
Duration of rifampicin (months)	*RifP*	0	0	0	"	
Duration of ethambutol (months)	*EthP*	0	0	0	"	
Duration of pyrazinamide (months)	*PyrP*	0	0	0	"	
Cost of treatment for latent TB infection (£ per latent	*cdrugsP*	£74	£37	£111	(IsoP*ucIso+RifP*ucRif+PyrP*ucP	

case treated)					yr+Eth P*ucEth)	
Outpatient care						
Cost of outpatient consultation: first visit (£ per visit)	*ucOP1*	£252	£214	£289	See previous table	
Cost of outpatient consultation: follow up visits (£ per visit)	*ucOP2*	£128	£109	£146	"	
Cost of TB nurse home visit (£ per visit)	*ucNurse*	£22	£17	£34	"	
Cost of GP consultation (£ per consult)	*ucGP*	£23	£10	£30	"	
Outpatient clinic visits per case treated	*OPP*	2	1	2	Assumption by GDG	
Visits from TB nurse per case treated	*NurseP*	0	0	6	Assumption	
GP consultations per case treated	*GPP*	0	0	1	"	
Cost of outpatient care (£ per latent case treated)	*cOPP*	£379	£214	£668	IF(OPP<1,0,IF(OPP=1,ucOP1,ucOP1+(O PP-1)*ucOP2))+NurseP*ucNurse+GPP*ucGP	
Tests						
Cost of interferon gamma test (£ per test)	*ucIGtest*	£10	£5	£20	See previous table	
Cost of culture tests (£ per test)	*ucCtest*	£7	£4	£11	"	
Cost of chest X-ray (£ per X-ray)	*ucXray*	£16	£11	£18	"	
Interferon gamma test per	*IGtest*	1	0	1	GDG	

case treated	*P*				recommendation	
Culture tests per case treated	*CtestP*	2	0	2	Assumption	Assumed once per clinic visit
Chest X-ray per case treated	*XrayP*	1	0	2	"	Assumed once every other clinic visit
Cost of tests (£ per latent case treated)	*ctests P*	£41	£0	£78	IGtestP*ucIGtest +CtestP*ucCtest +XrayP* ucXray	
Total						
Cost per latent case detected through school BCG	*cPro*	£494	£251	£857	cdrugsP+cOPP+ cTestsP	Mean cost of treatment for latent TB infection for latent cases resulting from index case aged 10–14, and detected through BCG
Cost per treated latent case (index age 15–24)	*cPro10*	£398	£202	£690		Discounted from age 22 (mid-way for range 15–29) to age 15.
Cost per treated latent case (index age 15–29)	*cPro15*	£360	£148	£504		Discounted from age 22 (mid-way for range 15–29) to age 15.
Economic parameters						
Inflation 2004/5 to 2005/6	*Ia*	8.7%				
Inflation 2003/4 to 2005/6	*Ib*	14.5 %			DH National Tariff 2005/6 Annex B	
Discount rate (health effects)	*drH*	3.5%			HMT recommended rates	
Discount rate (costs)	*drM*	3.5%			"	
Exchange rate (US-UK)	*ER*	0.51			Internet	

2.4 Appendix M – Guideline Development Group members 2006

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Specialist Registrar in Occupational Health, King's College Hospital

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- Mrs Delphine Antoine, Senior Scientist (epidemiology) – Tuberculosis Surveillance Co-ordinator, Health Protection Agency Centre for Infections
- Dr Sooria Balasegaram, Specialist Registrar in Public Health, seconded to the National Collaborating Centre for Chronic Conditions

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All those involved in TB care who participated in our review of current services.

The following people acted as deputies for the 2006 Guideline Development Group members unable to attend specific meetings:

Ms Jo Bloom, Breathe Easy, British Lung Foundation

Dr Ian Campbell and Dr John Moore-Gillon (acting as clinical advisors at one meeting on behalf of Professor Peter Ormerod)

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3.1 Appendix B: Clinical questions and search strategies 2011

REVIEW PROTOCOL FOR THE DIAGNOSIS OF LATENT TUBERCULOSIS USING INTERFERON GAMMA RELEASE ASSAY TESTS

KEY CLINICAL QUESTION 1		
	Details	**Comments**
REVIEW QUESTION 1	Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in Adults and Children who are recent arrivals from highly prevalent countries?	
OBJECTIVES	To determine the combination of diagnostic tools which would constitute the most accurate strategy to diagnose latent tb To determine which measure of effect is most appropriate to estimate utility of diagnostic tools especially in the absence of a gold standard	
CRITERIA FOR CONSIDERING STUDIES	PICO	No restrictions
POPULATION	Recent arrivals from highly prevalent countries People born in highly prevalent countries (are homeless and/or injecting drug users)	

DIAGNOSTIC TOOL	IGRA alone or with Mantoux	
COMPARATORS	Mantoux alone	
OUTCOMES	• Diagnosis of Latent tuberculosis • Acceptability of diagnostic strategies to this population. • Degree of concordance between TST and IGT • Prognostic Value of IGT in predicting the subsequent development of potential active tuberculosis • Health related quality of life associated with use of the diagnostic strategy • Resource use and costs	

KEY CLINICAL QUESTION 2		
	Details	**Comments**
REVIEW QUESTION 2	Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in children?	
OBJECTIVES	To determine whether it is appropriate to test all children regardless of BCG vaccination and to investigate the effect of BCG vaccination on the successful diagnosis of latent TB. To determine the combination of diagnostic tools which would constitute the most accurate strategy to diagnose latent tb To determine which measure of effect is most appropriate to estimate the utility of diagnostic tools especially in the absence of a gold standard	
CRITERIA FOR CONSIDERING STUDIES	PICO	No Restrictions
POPULATION	Children	
DIAGNOSTIC TOOL	IGRA alone or with Mantoux	
COMPARATORS	Mantoux alone	
OUTCOMES	• Diagnosis of Latent tuberculosis • Relationship between diagnostic utility of comparator strategies with BCG vaccination including the degree of concordance	

	between TST and IGT • Acceptability of diagnostic strategies to children • Adverse Events associated with diagnostic strategy • Health related quality of life associated with use of the diagnostic strategy • Resource use and cost	

KEY CLINICAL QUESTION 3		
	Details	**Comments**
REVIEW QUESTION 3	Which diagnostic strategy is most accurate in diagnosing latent TB in adults and children who have been in close contact with patients with active TB?	
OBJECTIVES	To determine the combination of diagnostic tools which would constitute the most accurate strategy to diagnose latent tb in adults and children who have been in close contact with patients with active TB. To determine which measure of effect is most appropriate to estimate accuracy of diagnostic tools especially in the absence of a gold standard	
CRITERIA FOR CONSIDERING STUDIES	PICO	No Restrictions
POPULATION	Adults and children who have been in prolonged close contact with active TB patients due to being • Healthcare workers • Prison and remand centre staff • In school or work with known active TB patients • In shared accommodation with people diagnosed with active TB o are homeless and/or	

	injecting drug users	
DIAGNOSTIC TOOL	IGRA alone or with Mantoux	
COMPARATORS	Mantoux alone	
OUTCOMES	• Diagnosis of Latent tuberculosis • Acceptability of diagnostic strategies to this population. • Degree of concordance between TST and IGT • Prognostic Value of IGT in predicting the subsequent development of potential active tuberculosis • Health related quality of life associated with use of the diagnostic strategy • Resource use and costs	

KEY CLINICAL QUESTION 4		
	Details	**Comments**
REVIEW QUESTION 4	Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients?	

OBJECTIVES	To determine the combination of diagnostic tools which would constitute the most accurate strategy to diagnose latent tb in adults and children who are immunocompromised To determine which measure of effect is most appropriate to estimate utility of diagnostic tools especially in the absence of a gold standard	
CRITERIA FOR CONSIDERING STUDIES	PICO	No Restrictions
POPULATION	Adults and children who are immunocompromised due to • Prolonged steroid use (equivalent to 15mg daily prednisolone for at least a month) • TNF alpha antagonists such as infliximab and etanercept • anti-rejection therapy such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine • Presence of co-morbid states which affect the immune system such as HIV, Chronic renal disease, many haematological and solid cancers and diabetes	

	o (are homeless and/or injecting drug users)	
DIAGNOSTIC TOOL	IGRA alone or with Mantoux	
COMPARATORS	Mantoux alone	
OUTCOMES	• Diagnosis of Latent tuberculosis • Acceptability of diagnostic strategies to this population. • Degree of concordance between TST and IGT • Prognostic Value of IGT in predicting the subsequent development of potential active tuberculosis • Health related quality of life associated with use of the diagnostic strategy • Resource use and costs	

Appendix L – Health economic model - 2011

Cost Effectiveness Analysis of Interferon Gamma Release Assay (IGRA) Testing for Latent Tuberculosis

INTRODUCTION

The department of health formally requested the National Institute for Health and Clinical Excellence to produce a short clinical guideline on interferon gamma immunological testing for diagnosing latent TB (partial review of CG 33).

This appendix will highlight the parts that have been updated from the previous economic evaluation that was constructed for the full TB guideline, as many of the assumptions, model structure, and in put parameters are similar.

This analysis, like the previous, addresses the question of whether the newer interferon gamma tests (IGT) based on ESAT-6 and CFP-10 antigens offer a more cost-effective means of identifying patients with suspected latent infection to receive treatment for latent TB infection compared with conventional tuberculin skin tests (TST) based on purified protein derivative (PPD). This partial update does not compare different types of skin tests or different types of interferon gamma tests. Thus, throughout this paper the term 'TST' refers to either Heaf or Mantoux skin tests using PPD and standard rules for interpretation of the result in the presence of absence of prior BCG, and 'IGT' refers to either T-Spot or QuantiFERON-TB Gold or Gold InTube commercial immunological tests, which use a combination of ESAT-6 and CFP-10 antigens.

A decision model was used to compare the expected costs (£) and health effects (QALYs) of four strategies of testing for people suspected with TB in England and Wales. The strategies compared are: a) TST; b) IGT; c) TST followed by IGT for patients with a positive TST; and d) no test (to inform and advise only). There is considerable uncertainty over the relative accuracy of the TST and IGT tests, as well as over some of the other model parameters. A

deterministic sensitivity analysis was used to explore the impact of such variations and uncertainties.

The model used is a decision tree, which does not account for the dynamics of disease transmission within the population. Instead, for simplicity, we assume that each primary case of active disease is associated with a fixed number of secondary cases. This is probably a reasonable assumption when comparing tests with similar sensitivity, since the absolute difference in false negatives, and hence in opportunities for transmission within the community, will be small.

In summary, the following decision problem was considered:

	Scope	Approach taken
Population	• Individuals suspected with latent tuberculosis • Contacts (Healthcare workers)	Those from high prevalence countries.
Interventions	Interferon Gamma Release Assay	T-Spot, QFT-Gold or QFT-Gold InTube
Comparators	Mantoux test	Mantoux test
Outcome(s)	Costs, QALYs and Cost per QALY	Cost per QALY

- ***Population***

The following populations were evaluated using a cost-effectiveness model:

1. Adults from high prevalence countries

2. Contacts (Healthcare workers)

The population considered within the economic evaluations consisted of adults (over 16). Therefore, all the costs, QALYs and effectiveness data comes are in relation to this population. No age cut-off was used within the model, as it does not affect the modeling of which testing strategy should be used.

Furthermore, due to an absence of evidence the following populations were not analysed: all children populations, screening new NHS employees and immunocompromised populations. For children, the almost complete absence of sensitivity and specificity information and quality of life data meant that a useful analysis could not be produced. For screening new NHS employees and the immunocompromised adult populations there was no new data on prevalence or on the potential outcomes from latent TB resulting so any new analysis would add very little value. Therefore, results from the other analyses will be extrapolated to these populations in the guideline.

- ***Interventions***

Current information from the Tuberculosis Guidelines CG 33 and Health Protection Agency recommend that people suspected with latent Tuberculosis should be diagnosed using a dual strategy which consists of a skin test and interferon gamma release assay (IGRA). The evidence used for the analysis was based on assumptions of the relative accuracy of the following commercially available IGRAs: Quantiferon TB Gold, Quantiferon TB Gold InTube, and T-Spot.TB.

- ***Comparators***

There is currently no gold standard for the diagnosis of latent tuberculosis and therefore assessment has routinely been the use of a skin test (Mantoux test) using PPD. Therefore, the comparator was a TST.

- ***Outcomes***

In line with the NICE reference case we use a cost effectiveness analysis to determine the cost effectiveness of IGRA. Because this is an update of a guideline that had an existing analysis, it was deemed appropriate to review new evidence and update the relevant sections of the model. This requires the calculation of resource use and QALYs to assess effectiveness.

- **Review of cost effectiveness literature**

The following sections summarises the results of the literature search for new analyses. Checklists for mentioned studies are provided in Annex 6.

- ***Review of Cost effectiveness studies – HPC***

A search for cost-effectiveness studies identified no cost utility papers that examined the use of IGT in this cohort of patients suspected with latent tuberculosis infection. Two papers examined costs only; Hardy et al 2009 calculated the actual costs of implementing CG 33 for screening people from high prevalence countries and concluded that IGT was cheaper than TST. Oxlade et al 2007concluded that TST or IGT test was of little added value in preventing future cases, but at the expense of significant investment.

- ***Review of Cost effectiveness studies – Contacts(HCW)***

A search for cost-effectiveness studies identified two cost utility papers that examined the use of IGT in the cohort of patients with suspected latent tuberculosis infection, de Perio et al 2009 and Kowada et al 2008. Both papers concluded that IGT was the cheaper and more effective screening strategy than TST or TST/IGT. Pooran et al 2010 examined costs only for the UK and concluded that IGT alone or in combination with TST were less expensive and more cost effective per active TB case prevented than TST alone. The combined strategy was less effective in detecting TB cases but cheaper than IGT alone, therefore, becoming the optimum choice. All the analyses commented on the importance of prevalence as a key factor to interpreting the results.

- ***Conclusion of studies***

None of the studies exactly matches the decision problem and therefore, the analysis conducted for CG 33 will be updated.

- **Modelling approach**

The key areas that were updated were the test accuracies and the relevant costs. All costs were updated to current prices and were validated by the GDG. The test accuracies were based on published reviews which calculated sensitivities and specificities. The published reviews identified were Pai et al 2008, Girardi et al 2009, and Diel et al 2010. Given that there was no

differentiation between IGT tests, midpoints were used for the test accuracy estimates.

The assumptions made in the initial guideline are still applicable unless stated otherwise. Whenever possible, input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and Guideline Development Group (GDG). The model considers the QALYs lost due to infection, adverse events and so on. Therefore, the interventions with the smallest QALY loss are the most effective. Throughout the analysis ICERs will either be compared to a common base line (usually no test) and net monetary benefits will be calculated. Net monetary benefit quantifies which treatment option provides the greatest health benefit for a given threshold. In this analysis the £20,000 and £30,000 per QALY threshold will be used. Probabilistic sensitivity analysis was considered, however the mean value for a number of variables were unknown or highly uncertain so a probabilistic sensitivity analysis was considered to be of little added value.

- The analysis is conducted from an NHS perspective. A time horizon of 15 years is used for the analysis, chosen to reflect the duration of BCG protection. The costs and outcomes are discounted using an annual rate of 3.5%. We assume an average time delay of *lagLatent* years before people with latent infection go on to develop active disease. Similarly, where TB occurs in later life for people without current latent infection, this is assumed to occur after an average time delay of *lagNoInf* years. We assume that each case of active disease is associated with *nSec* secondary cases, which occur on average *lagSec* years after the index case. However, the number of secondary cases is assumed to be reduced (by a proportion *pSec*) when the index case is detected early through contact tracing.

- As it is beyond the scope of this update to consider the clinical and cost effectiveness of different regimens for the treatment of latent tuberculosis, the analysis only considers the current treatment regimen of three months of rifampicin and isoniazid (3RH).

ADULTS FROM HIGH PREVALENCE COUNTRIES (HPC)

- ## Introduction – HPC

The magnitude of human migration from high TB incidence regions to low incidence regions has reached an unprecedented scale worldwide. Two studies have estimated that 20-30% of all TB cases in England were among foreign-born permanent residents-attributed to the re-exposure during return visits(McCarthy OR 1984;Ormerod LP et al. 2001).

- ## Model Structure – HPC

Figure 1 shows the basic outline of the modified model with the main features highlighted. The main components are the diagnostic strategy and treatment outcomes (true positive, false positive, false negative and true negative and no test).

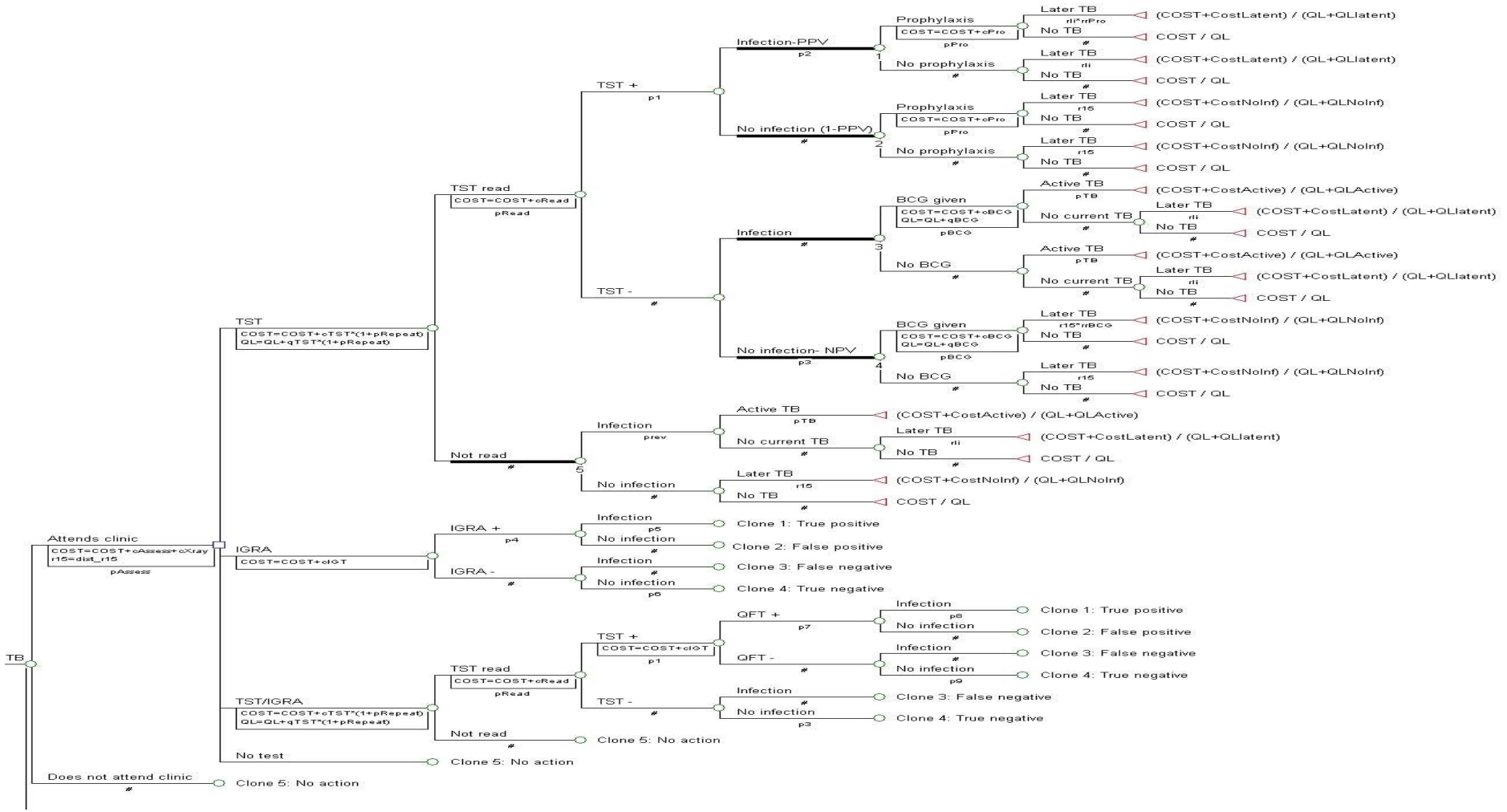


Figure 1 Modified economic evaluation for adults from high prevalence countries suspected with latent tuberculosis

- ***Updated/modified Input Parameters – HPC***

The parameters listed in table xx below reflect the input parameters that have been updated/modified from the full CG36 Tuberculosis guideline. For a complete list of input parameters, including those discussed in this appendix but not in listed in the table below; please refer to the full CG 36 appendices. Where possible, updated/modified parameter values are based on best available evidence from the literature; however, where values were not available consensus was reached by the GDG. The base case, range for sensitivity analysis, and source for each updated input parameter is listed in table 1.

Table 1: Updated/modified input parameters

		Base case	Lower limit	Upper limit	Source
POPULATION AND BASELINE RISKS					
Prevalence of infection in cohort	*prev*	30%	0	50%	(Ewer et al. 2003;Shams et al. 2005;Tsevat et al. 1988) and GDG consensus
Proportion of infected patients with active disease	*pTB*	0.5%	0.1	0.5	GDG consensus
Mean number of secondary cases per primary case	*nSec*	0.5	0	1	GDG consensus
EFFECTIVENESS OF PREVENTIVE INTERVENTIONS					
Proportion of TST results read (at first or second attempt)	*pRead*	90%	0	1	(Diel et al. 2006) (Bothamley et al. 2002) and GDG consensus
Proportion of those offered prophylaxis who start treatment	*pPro*	80%	0.55	0.95	Taylor et al 2000 (for adults) and GDG consensus
ACCURACY OF TESTS					
Sensitivity of Interferon Gamma tests	*Se*	0.775	0.55	1	(Pai et al. 2008)
Specificity of Interferon Gamma tests	*Sp*	0.915	0.83	1	(Pai, Zwerling, & Menzies 2008)
Sensitivity of TST	*SeTST*	0.785	0.57	1	(Pai, Zwerling, & Menzies 2008)
Specificity of TST	*SpTST*	0.35	0.675	1	(Pai, Zwerling, & Menzies 2008)
Sensitivity of Interferon Gamma tests	*Se*	0.765	0.53	1	(Diel et al. 2010)
Specificity of Interferon Gamma tests	*Sp*	0.915	0.83	1	(Diel et al. 2010)
Sensitivity of TST	*SeTST*	0.575	0.25	0.9	(Diel et al. 2010)
Specificity of TST	*SpTST*	0.675	0.35	1	(Pai, Zwerling, & Menzies 2008)
COSTS					
Cost of Assessment for active disease (£ per patient)	cAccess	257	257	257	DH Tariff 2010/11
Cost of the Interferon Gamma Tests (£ per patient)	cIGT	50	40	100	Cost includes kit, consumables, processing and phlemobotmy per test (Pooran et al 2010 and GDG consensus)
Cost of chemoprophylaxis (£ per patient)	cPro	413			Various
Cost of chemotherapy (£ per case of active TB)		222	122	376	Various
Cost of chemoprophylaxis (£ per latent case treated) 3RH		86	44	156	Various

- ***Population and baseline risks***

The model constructed for adults from high prevalence countries, uses a prevalence of 30% for latent tuberculosis.

- ***Effectiveness of preventative interventions***

The probability of being fully cured is based on the efficacy of either a complete or incomplete course of 3RH regimen. It was estimated by the GDG that nearly 80% of those offered preventative treatment actually start the treatment, therefore, a baseline value of 80% was used.

- ***Accuracy of tests***

- As there is no gold standard for the diagnosis of latent tuberculosis infection, test accuracy values for this population were obtained from two studies, Pai et al 2008 and Diel et al 2010, midpoints were used for the test accuracy estimates. The Diel et al 2010 study was identified during consultation and incorporated to examine the effect of more up-to-date results. As the Diel et al. paper did not report TST specificity; the value from the Pai paper was used.

- ***Quality of Life***

The morbidity and mortality impact of each case of TB is analysed in terms of quality adjusted life years (QALYs). In this cohort we used an estimate based on the expected QALY loss due to TB-related mortality and morbidity. Early and correct diagnosis can improve outcomes: prevention of future active TB disease due to the use of prophylactic treatment of people with latent infection. Early diagnosis is known to enhance the quality of life and reduce the morbidity and mortality impact of TB for the index case by *qEarly* QALYs. Similarly early diagnosis will also reduce the number of secondary cases by a proportion *pEarly*. Cases prevented by early prophylaxis yield a QALY gain for the index case, and also for expected secondary cases.

- ***Resource Use: Costs***

- The analysis was undertaken from the NHS and Personal Social

Service (PSS) perspective in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated using the 2008/2009 prices. Where costs have been taken from sources using a different price year, they have been inflated using the hospital and community Health Services Pay and Price Index (PSSRU, 2008/2009).

- The costs of diagnosing LTBI using the various strategies were obtained from the published literature. Asymptomatic infection is assumed to produce no cost (except the cost of testing, which would have been incurred irrespective of infection). The costs of testing comprised labour cost for the staff performing the TST, as well as the costs of IGRAs, comprised of the kit, associated consumables, processing and phlebotomy.

- Treatment costs include initial chest radiography to rule out active TB prior to treatment (*cXray*), an initial cost of visiting a respiratory assessment team (*cAccess*), costs of 3 months' of Rifampicin and Isoniazid, cost of 6 months of active TB. Side-effects from the three months regime of Rifampicin and Isoniazid were ignored, and all patients were assumed to complete the full course of therapy.

- **Results – HPC**

Table 2 Cost effectiveness results for new entrants from high prevalence countries

Strategy	Cost (£)	Effect (QALY loss)	ICER compared with no test (£)	Net monetary benefit	
				£20,000	£30,000
Pai et al 2008					
No test	£315.8	9.98686	-	-	-
TST/IGT	£403	9.99015	£26,641	-22	11
IGT	£452.2	9.99156	£29,043	-43	5
TST	£458.4	9.99107	Dominated	Dominated	Dominated
Diel et al 2010					
No test	£315.8	9.98686	-	-	-
TST/IGT	£387.4	9.98925	Extended dominance	Extended dominance	Extended dominance
IGT	£451.3	9.98994	£29,211.57	-42.8	3.6
TST	£442.0	9.99150	Extended dominance	Extended dominance	Extended dominance

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

These results demonstrate that TST/IGT and IGT are associated with ICERs which are just under £30,000 per QALY and suggest that these two tests are potentially cost effective, but that further consideration is required on key parameters before a decision can be made.

The prevalence of LTBI in this population and the transformation rate of latent TB to active TB are presented below since the GDG considered them two of the key parameters in the model.

Table 3 Cost effectiveness results for new entrants from high prevalence countries with varying prevalence of LTBI

	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
Prevalence	**TST/IGT**	**IGT**	**TST**	**TST/IGT**	**IGT**	**TST**
Pai et al 2008						
0.01	-34	-73	Dominated	-32	-70	Dominated
0.05	-32	-69	Dominated	-26	-60	Dominated
0.1	-30	-64	Dominated	-19	-47	Dominated
0.15	-28	-58	Dominated	-11	-34	Dominated
0.2	-26	-53	Dominated	-4	-21	Dominated
0.25	-24	-48	Dominated	4	-8	Dominated
0.3	-22	-43	Dominated	11	5	Dominated
Diel et al 2010						
0.01	-34	-74	Dominated	-33	-71	Dominated
0.05	-33	-69	Dominated	-28	-60	Dominated
0.1	-31	-64	Dominated	-23	-48	Dominated
0.15	-30	-60	Dominated	-17	-34	Dominated
0.2	-27	-53	Dominated	-11	-22	Dominated
0.25	Extended Dominated	-48	Extended Dominated	Extended Dominated	-9	Extended Dominated
0.3	Extended Dominated	-43	Extended Dominated	Extended Dominated	4	Extended Dominated

Table 4 Cost effectiveness results for new entrants from high prevalence countries with varying transformation rate of latent TB to active TB

	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
Latent TB to active TB	**TST/IGT**	**IGT**	**TST**	**TST/IGT**	**IGT**	**TST**
Pai et al 2008						
0.01	-60	-97	Dominated	-46	-76	Dominated
0.05	-9	-24	Dominated	30	31	Dominated
0.1	55	66	Dominated	125	166	Dominated
0.15	119	157	Dominated	220	301	Dominated
0.2	183	247	Dominated	315	435	Dominated
0.25	247	338	Dominated	411	570	Dominated
0.3	311	428	Dominated	506	704	Dominated
Diel et al 2010						
0.01	Extended dominance	-96.87	Extended dominance	Extended dominance	-76	Extended dominance
0.05	Extended dominance	-15.12	Extended dominance	Extended dominance	30	Extended dominance
0.1	Extended dominance	67.08	Extended dominance	Extended dominance	163	Extended dominance
0.15	Extended dominance	149.27	Extended dominance	Extended dominance	296	Extended dominance
0.2	Extended dominance	231.46	Extended dominance	Extended dominance	429	Extended dominance
0.25	Extended dominance	333.66	Extended dominance	Extended dominance	562	Extended dominance
0.3	Extended dominance	415.85	Extended dominance	Extended dominance	695	Extended dominance

These results suggest that if the prevalence of TB and the conversion rate of TB are high then the tests will be cost effective. Among the different test strategies, IGT appears to be the optimum choice. However, the results indicate that relatively small differences in the variables could result in TST/IGT being optimal. Additionally, it is still a cost effective option.

- ***Sensitivity Analysis-HPC***

The following key variables are examined in deterministic sensitivity analysis: costs of the IGRAs, return rate of the skin tests, secondary cases and test accuracies. The results are presented using both the Pai et al and Diel et al test accuracies to populate the model.

Table 5 Cost effectiveness results for new entrants from high prevalence countries with varying costs of IGRA

Cost of IGGT	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Pai et al 2008						
0	Dom	8	Ext Dom	Dom	55	Ext Dom
10	Dom	-2	Ext Dom	Dom	45	Ext Dom
20	Dom	-12	Ext Dom	Dom	35	Ext Dom
30	Dom	-22	-14	Dom	25	19
40	Dom	-32	-18	Dom	15	15
50	Dom	-42	-22	Dom	5	11
60	Ext Dom	-52	-26	Ext Dom	-5	7
70	Ext Dom	-62	-30	Ext Dom	-15	2
80	-59	-72	-34	-17	-25	-1
90	-59	-82	-39	-17	-35	-6
100	-59	-92	-43	-17	-45	-10
Diel et al 2010						
0	Dom	7	Ext Dom	Dom	54	Ext Dom
10	Dom	-3	Ext Dom	Dom	44	Ext Dom
20	Dom	-13	Ext Dom	Dom	34	Ext Dom
30	Dom	-23	Ext Dom	Dom	24	Ext Dom
40	Dom	-33	Ext Dom	Dom	14	Ext Dom
50	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
60	Ext Dom	-53	Ext Dom	Ext Dom	-6	Ext Dom
70	Ext Dom	-63	-31	Ext Dom	-16	-7
80	Ext Dom	-73	-35	Ext Dom	-26	-10
90	Ext Dom	-83	-38	Ext Dom	-36	-14
100	Ext Dom	-93	-42	Ext Dom	-46	-18

IGT becomes cost ineffective at approximately £50 to 60 per test. This only includes the acquisition cost of the test and not administration. The GDG considered that the price of IGT was likely to be lower than £50 per test. Potentially close to £20 to £30.

Table 6 Cost effectiveness results for new entrants from high prevalence countries with varying return rates of TST

%	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Pai et al 2008						
50	Dom	-43	-25	Dom	5	8
60	Dom	-43	-24	Dom	5	9
70	Dom	-43	-23	Dom	5	9
80	Dom	-43	-22	Dom	5	10
90	Dom	-43	-21	Dom	5	11
100	Dom	-43	-21	Dom	5	12
Diel et al 2010						
50	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
60	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
70	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
80	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
90	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
100	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom

The rate of TST return rate did not have significant impact on the results of the cost effectiveness analysis.

Table 7 Cost effectiveness results for new entrants from high prevalence countries with varying number of secondary cases

	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Pai et al 2008						
0	Dom	-52	-29	Dom	-9	2
0.25	Dom	-47	-25	Dom	-2	6
0.5	Dom	-42	-22	Dom	5	11
0.75	Dom	-37	-18	Dom	11	16
1	Dom	-32	-15	Dom	18	20
Diel et al 2010						
0	Ext Dom	-52	Ext Dom	Ext Dom	-9	Ext Dom
0.25	Ext Dom	-48	Ext Dom	Ext Dom	-3	Ext Dom
0.5	Ext Dom	-43	Ext Dom	Ext Dom	4	Ext Dom
0.75	Ext Dom	-38	Ext Dom	Ext Dom	10	Ext Dom
1	Ext Dom	-33	Ext Dom	Ext Dom	17	Ext Dom

These results indicate that the greater the number of secondary cases the more improved the cost effectiveness results. Since the model is not dynamic and therefore, cannot account for potential variation in the number of

secondary cases, it could be concluded that the number of secondary cases has been underestimated. Therefore, the cost effectiveness estimates could improve.

- ***Two way sensitivity analysis***

The net monetary results at £20,000 and £30,000 per QALY are presented in the following figures for the varying sensitivity and specificity of IGT and TST. At £20,000 per QALY all combinations of IGT sensitivity and specificity resulted in no test being the optimum choice ergo the results are not presented here.

Figure 2 Cost effectiveness results for new entrants from high prevalence countries with varying sensitivity and specificity of IGT

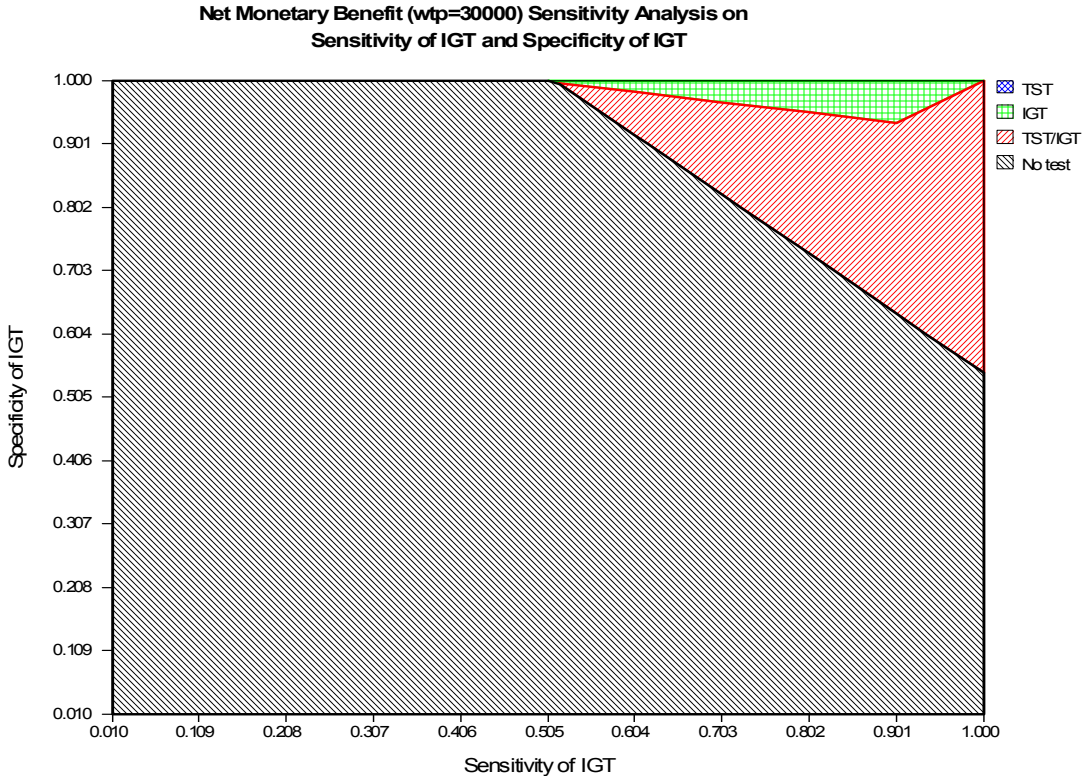


Figure 3 Cost effectiveness results for new entrants from high prevalence countries with varying sensitivity and specificity of TST

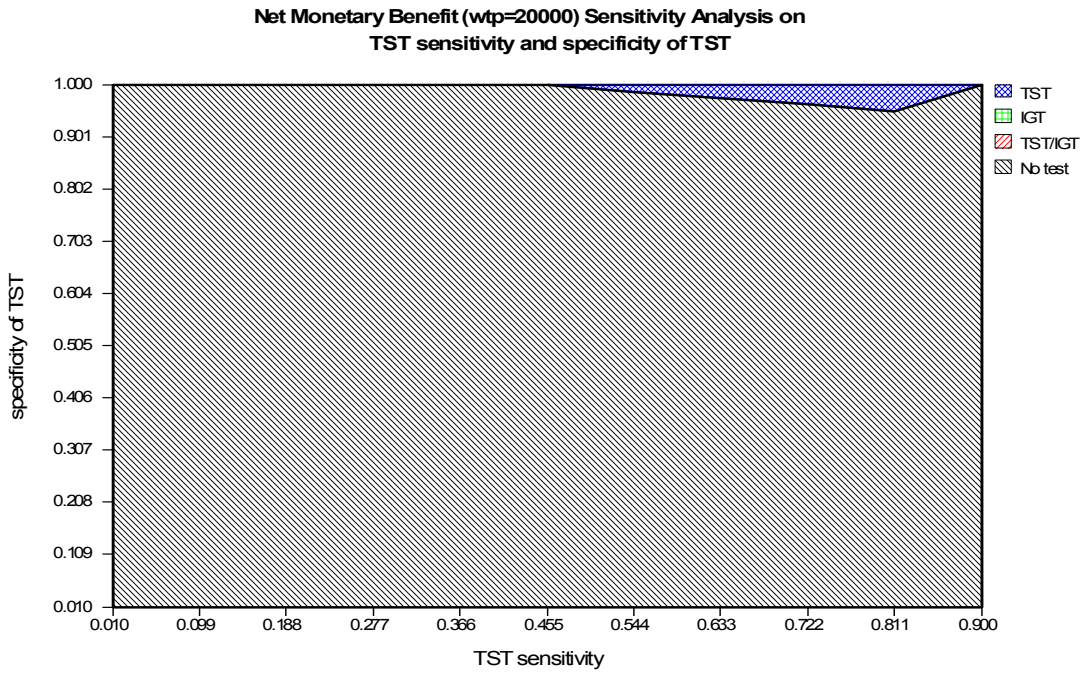
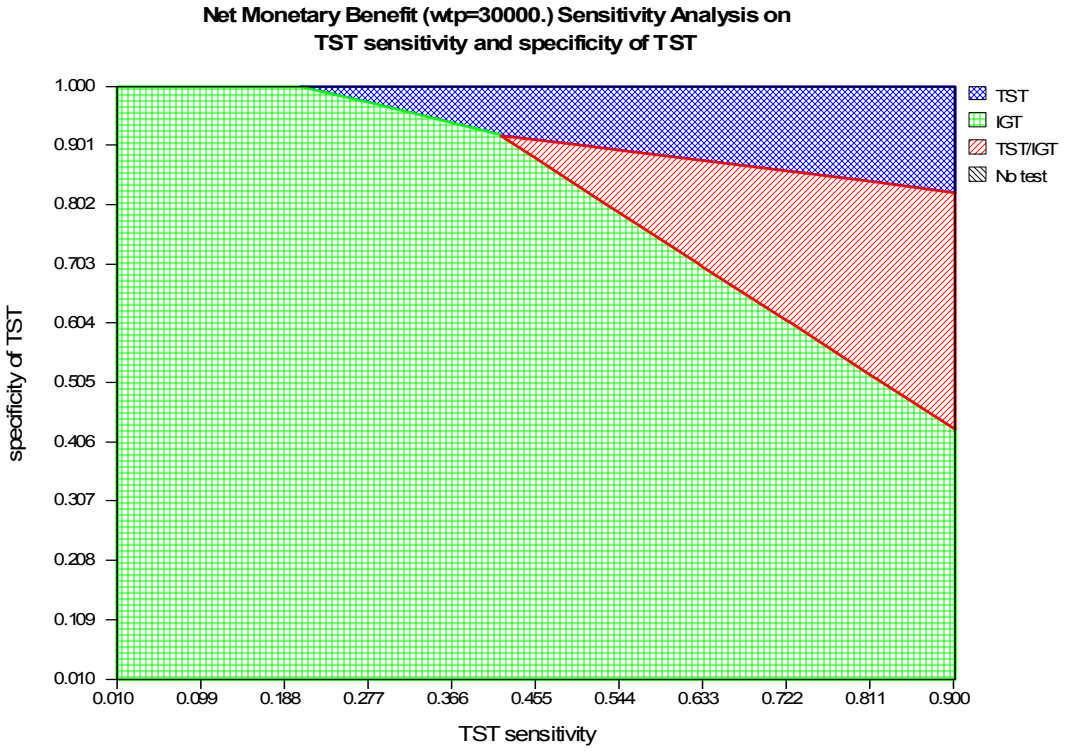


Figure 4 Cost effectiveness results for new entrants from high prevalence countries with varying sensitivity and specificity of TST



These results indicate that for IGT, relatively high levels of specificity are required for IGT to be considered cost effective at £30,000 per QALY gained. For TST, again, no test is likely to be cost effective at £20,000 per QALY but at £30,000 per QALY for TST alone to be cost effective the specificity has to be over 80% and for the combined strategy IGT and TST specificity need to be quite low.

- ***Validation***

Validating models requires checking the internal and external validity. Internal validity is ensuring that the model is mathematically correct and that all the calculations are correct. All the calculations have been checked by following the numbers in the cohort and double checking the calculations.

- ***Discussion - HPC***

The economic evaluation for adults from high prevalence countries indicated that none of the tests were associated with ICERs of below £20,000 per QALY gained. In addition, it appears that these results are likely to be highly uncertain with small changes in a number of parameters having a large impact

on the cost effectiveness results. However, the GDG considered that the mean rate of transformation from latent TB to active TB was underestimated and that the true rate was closer to 16% over 15 years. At estimates this high, IGT alone is the most cost effective option, followed by the TST/IGT dual strategy. The GDG considered that while IGT alone appeared to be the most cost effective option that the dual strategy should remain as an alternative as 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 inter subject variability.

- ***Conclusion-HPC***

These results demonstrate that TST/IGT and IGT are associated with ICERs which are just under £30,000 per QALY. These results suggest that these two tests are potentially cost effective. Research into the epidemiology of latent TB and test accuracies can improve confidence around the results.

CONTACTS (HEALTH CARE WORKERS)

• Introduction – Contacts (HCW)

Healthcare workers represent an important target population for latent tuberculosis infection screening programmes. The effectiveness of these programmes, however, this has been limited by the fact that the standard tool used to diagnose latent tuberculosis infection, the tuberculin skin test, has a limited diagnostic accuracy, mainly because it relies on the use of protein purified derivative (PPD), which is a mixture of antigens shared by many pathogenic and non-pathogenic mycobacteria. A number of clinical studies have evaluated IGRA, in comparison to TST, as a tool for screening latent tuberculosis infection among healthcare workers (Drobniewski et al. 2007;Mirtskhulava et al. 2008;Pai et al. 2005;Stebler et al. 2008).

• Model Structure – Contacts (HCW)

Figure 5 shows the basic outline of the modified model with the main features highlighted. The main components are the diagnostic strategy and treatment outcomes (true positive, false positive, false negative and true negative and no test.

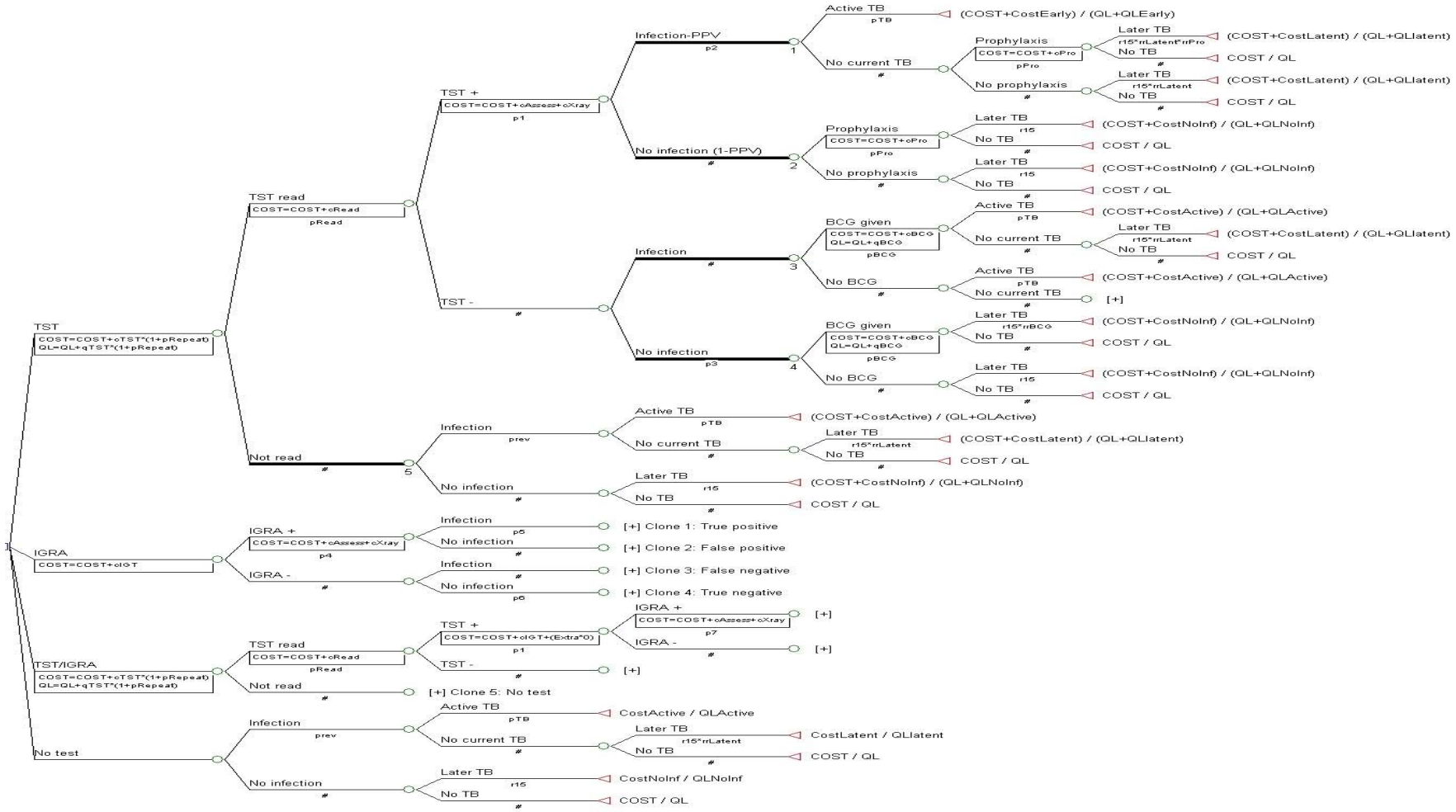


Figure 5 Modified economic evaluation of IGRA for contacts (healthcare workers)

- ***Updated/modified input parameters – Contacts (HCW)***

The economic model uses the same structure, costs and health related quality of life values as those in the adults from high prevalence countries. However, the difference is in the estimates of the test accuracy and the prevalence of LTBI in this cohort. The test accuracy for this population was based on Girardi et al. 2009 and Diel et al 2010. The treatment regimen is the same. We have also assumed that diagnosing and screening for latent tuberculosis is done in an outpatient setting.

Table 8: Updated/Modified input parameters

		Base case	Lower limit	Upper limit	Source
POPULATION AND BASELINE RISKS					
Prevalence of infection in cohort	*prev*	20%	0.01	0.3	GDG consensus
Proportion of infected patients with active disease	*pTB*	0.25%	0.1	0.5	GDG consensus
Mean number of secondary cases per primary case	*nSec*	0.4	0	1	GDG consensus
ACCURACY OF TESTS					
Sensitivity of Interferon Gamma tests	*Se*	0.865	0.763	0.967	Girardi et al
Specificity of Interferon Gamma tests	*Sp*	0.896	0.856	0.936	Giradi et al
Sensitivity of TST	*SeTST*	0.99	0.95	1	Girardi et al
Specificity of TST	*SpTST*	0.642	0.53	0.741	Girardi et al
COSTS					
Cost of contact tracing (£ per case)		2, 058	466	5, 470	Various
Cost of outpatient care (£ per active case)		777	439	1, 406	Various
Cost of outpatient care (£ per latent case)		695	350	777	Various

- **Results – Contacts (HCW)**

Table 9 Cost-effectiveness of testing strategies for contacts

Strategy	Cost (£)	Effect (QALY loss)	ICER compared with no test (£)	Net monetary benefit (£20,000 per QALY)	Net monetary benefit (£30,000 per QALY)
Girardi et al. 2009					
No test	379.9	9.9393	-	-	-
TST/IGT	476.3	9.9473	12,037	64	144
IGT	531.4	9.9483	16,833	29	119
TST	604.2	9.9484	24,637	-42	49
Diel et al 2010					
No test	379.9	9.9393	-	-	-
TST/IGT	444.5	9.9435	15,173.74	21	64
IGT	515.1	9.9473	16,243.9	27	108
TST	567.3	9.9447	Dominated	Dominated	Dominated
QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. TST = tuberculin skin test. IGT = inferferon gamma test					

These results indicate that TST/IGT and IGT alone are both cost effective testing options and that depending on the test accuracies used either option could be the optimum choice.

- ***One-to-one sensitivity analysis***

The prevalence of LTBI in this population and the transformation rate of latent TB to active TB are presented below since the GDG considered them two of the key parameters in the model.

Table 10 Cost-effectiveness of testing strategies for contacts with varying prevalence rates

Prevalence	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST/IGT	IGT	TST	TST/IGT	IGT	TST
Girardi et al. 2009						
0.01	-36	-97	Dominated	-28	-88	Dominated
0.05	-15	-71	Dominated	8	-45	Dominated
0.1	11	-37	Dominated	53	10	Dominated
0.15	38	-4	-83	99	65	-14
0.2	64	29	-42	144	119	49
0.25	90	62	-1	189	174	112
0.3	116	95	40	235	228	175
Diel et al 2010						
0.01	-31	-85	Dominated	-25	-76	Dominated
0.05	-20	-61	Dominated	-7	-38	Dominated
0.1	-7	-33	Dominated	17	10	Dominated
0.15	7	-3	Dominated	40	58	Dominated
0.2	21	25	Dominated	63	106	Dominated
0.25	34	54	Dominated	86	153	Dominated
0.3	48	83	Dominated	116	202	Dominated

At £20,000 per QALY the prevalence has to be over 10% for testing to be cost effective. At a £30,000 per QALY threshold the lowest prevalence rate that testing remains cost effective is 6%.

Table 11 Cost-effectiveness of testing strategies for contacts with varying transformation rate of latent TB to active TB

Relative Risk of Latent TB to active TB	£20,000 per QALY gained			£30,000 per QALY gained		
	TST/IGT	IGT	TST	TST/IGT	IGT	TST
Girardi et al. 2009						
0	18	-23	-96	75	42	-31
1	29	-10	-82	92	61	-11
2	41	3	-69	110	81	9
3	52	16	-56	127	100	29
4	64	29	-42	144	119	49
5	75	42	-29	161	138	69
6	87	55	-16	178	158	88
Diel et al 2010						
0	-3	-20	Dominated	28	37	Dominated
1	3	-9	Dominated	37	54	Dominated
2	9	2	Dominated	46	72	Dominated
3	15	14	Dominated	54	89	Dominated
4	21	25	Dominated	63	106	Dominated
5	27	36	Dominated	72	123	Dominated
6	32	48	Dominated	81	140	Dominated

In the contacts model, the transformation from latent to active TB was implemented via a relative risk (please see 2006 guideline appendix for more details).

The transformation rate did not appear to be a major variable in the model. These results indicate that if the risk of latent TB becoming active is high then the cost effectiveness results improve.

- ***Sensitivity Analysis-Contacts(HCW)***

The following key variables will be examined in deterministic sensitivity analysis: Costs of the IGRAs, return rate of the skin tests, secondary cases and test accuracies. The results are presented using both the Girardi et al and Diel et al paper.

Table 12 Cost effectiveness results for contacts with varying costs of IGT

Cost of IGT	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Girardi et al 2009						
0	-42	79	86	49	169	166
10	-42	69	81	49	159	161
20	-42	59	77	49	149	157
30	-42	49	73	49	139	153
40	-42	39	68	49	129	148
50	-42	29	64	49	119	144
60	-42	19	59	49	109	140
70	-42	9	55	49	99	135
80	-42	-1	51	49	89	131
90	-42	-11	46	49	79	126
100	-42	-21	42	49	69	122
Diel et al 2010						
0	Dom	75	Ext Dom	Dom	156	Ext Dom
10	Dom	65	Ext Dom	Dom	146	Ext Dom
20	Dom	55	26	Dom	136	73
30	Dom	45	22	Dom	126	70
40	Dom	35	19	Dom	116	67
50	Dom	25	15	Dom	106	63
60	Dom	15	12	Dom	96	60
70	Dom	5	5	Dom	86	56
80	Dom	-5	5	Dom	76	53
90	Dom	-15	2	Dom	66	50
100	Dom	-25	-1	Dom	56	46

These results indicate that the cost of IGT at which it becomes cost ineffective is £80 if a threshold of £20,000 per QALY is used. At £30,000 per QALY it appears not to be a factor. The GDG considered that in UK clinical practice IGT tests could be acquired for less than £50**.** Therefore, the cost of IGT does not appear to be a major factor.

Table 13 Cost effectiveness results for contacts with varying return rates of TST

%	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Girardi et al 2009						
50	-45	29	61	45	119	140
60	-45	29	61	46	119	141
70	-44	29	62	47	119	142
80	-43	29	63	48	119	143
90	-42	29	64	49	119	144
100	-41	29	64	50	119	145
Diel et al 2010						
50	Dom	27	17	Dom	105	60
60	Dom	27	18	Dom	105	61
70	Dom	27	19	Dom	105	62
80	Dom	27	20	Dom	105	63
90	Dom	27	21	Dom	105	64
100	Dom	27	21	Dom	105	65

The rate of TST return does not affect the conclusions of the cost effectiveness analysis. IGT remains the optimum choice followed by TST/IGT. However, low rates of TST return would improve the probability that IGT is the optimum choice.

Table 14 Cost effectiveness results for contacts with varying number of secondary cases

	NMB at £20,000 per QALY			NMB at £30,000 per QALY		
	TST	IGT	TST/IGT	TST	IGT	TST/IGT
Girardi et al 2009						
0	Dom	-127	-75	Dom	-75	-46
0.25	-102	-30	12	-34	39	73
0.5	-2.21	68	99	104	173	192
0.75	98	165	185	241	306	311
1	198	263	272	379	440	429
Diel et al 2010						
0	Dom	-113	-51	Dom	-83	-35
0.25	Dom	-26	-6	Dom	35	26
0.5	Dom	59	38	Dom	153	88
0.75	Dom	146	83	Dom	271	149
1	Dom	232	128	Dom	389	210

Varying the number of secondary cases does not affect which test is optimum, but a higher number of secondary cases would result in improved and more

certain estimates of cost effectiveness. As the model may underestimate the number of secondary cases especially in outbreak situations there is the possibility that the cost effectiveness results could improve considerably compared to the base case.

- ***Two way sensitivity analysis***

The net monetary results at £20,000 and £30,000 per QALY are presented in the following figures for varying the sensitivity and specificity of IGT and TST.

Figure 5 Cost effectiveness results for contacts with varying sensitivity and specificity of IGT (WTP = 20, 000)

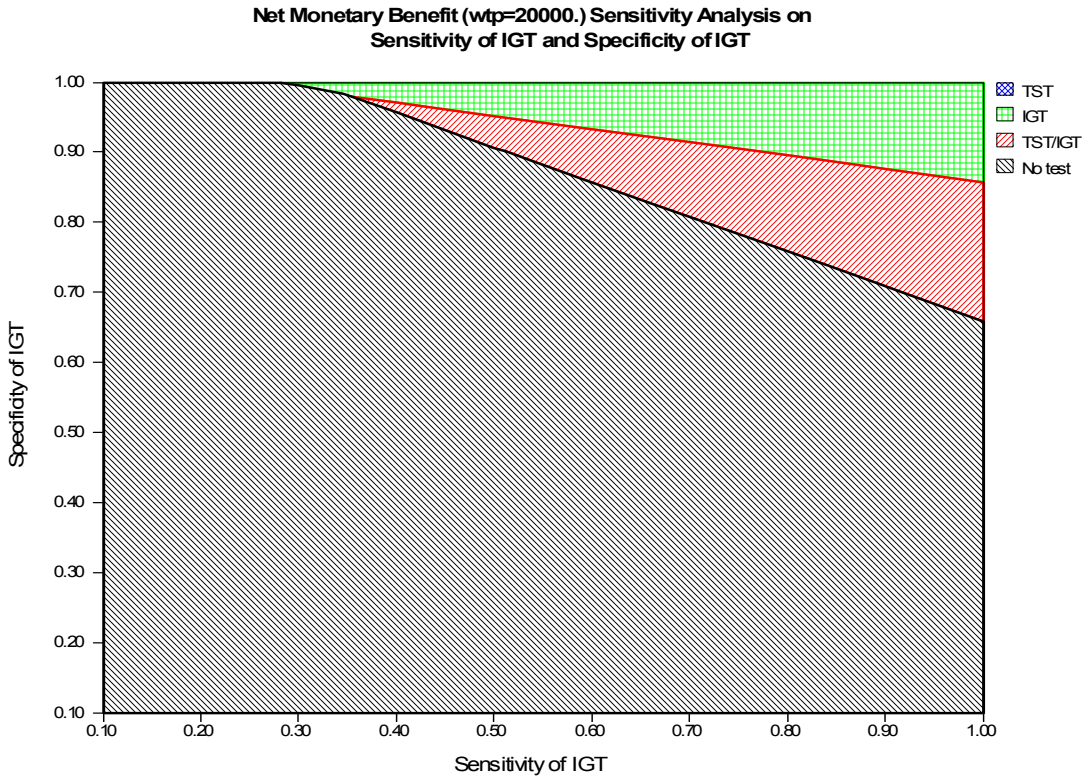


Figure 6 Cost effectiveness results for contacts with varying sensitivity and specificity of IGT (WTP = 30,000)

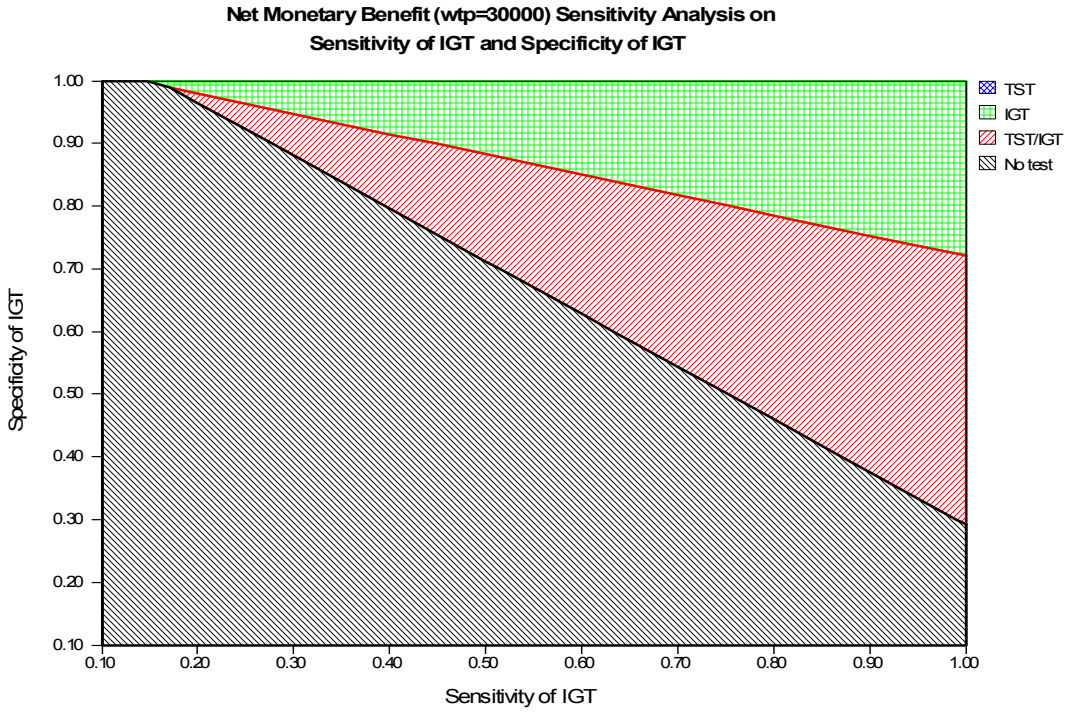


Figure 7 Cost effectiveness results for contacts with varying sensitivity and specificity of TST (WTP = £20,000)

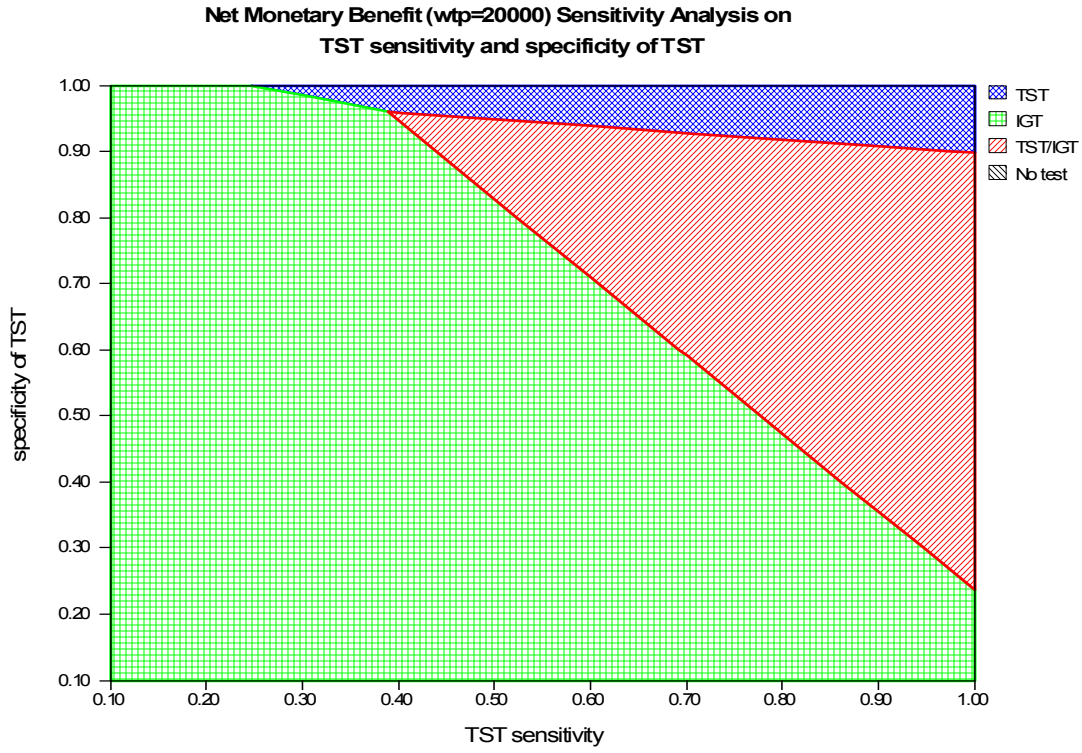
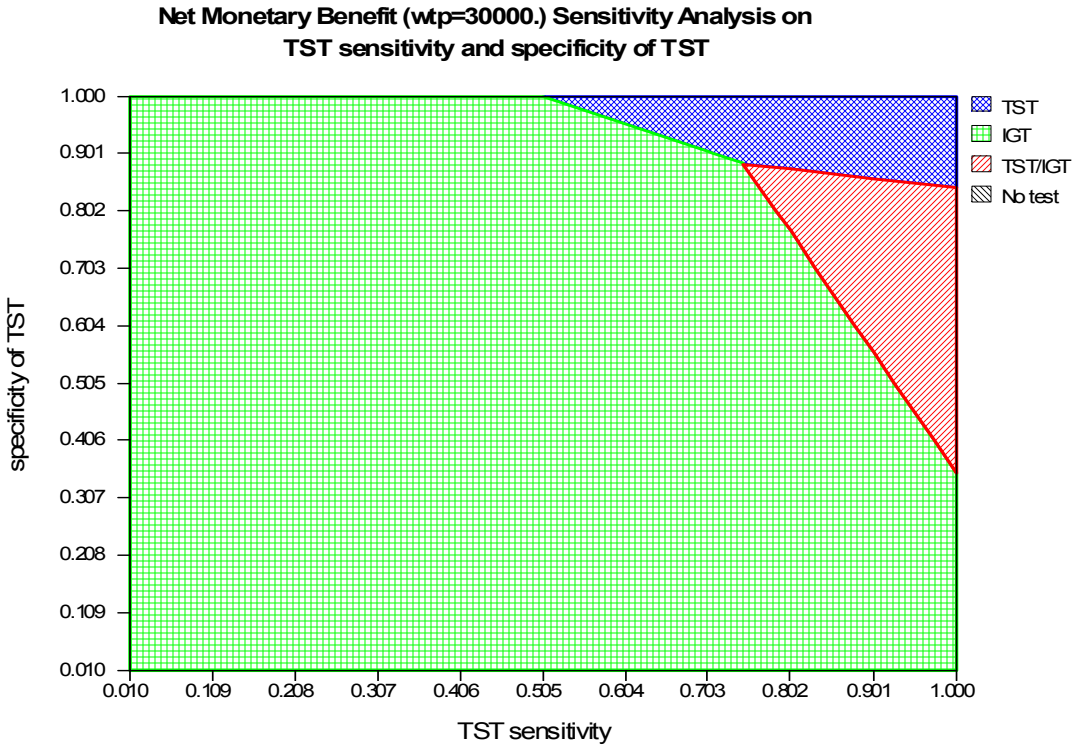


Figure 8 Cost effectiveness results for contacts with varying sensitivity and specificity of TST (WTP = £30,000)



These results indicate that IGT specificity is the most important test accuracy parameter to determining the cost effectiveness of IGT in testing strategies. Under a specificity of 80% to 90% TST/IGT is the optimum strategy (with corresponding sensitivities) however below 70% to 30% no test is the optimum. These results suggest that the combined strategy is more likely to be cost effective given uncertainty in IGTs test accuracy. For TST, the various combinations of sensitivity and specificity demonstrate that for TST alone to be optimum, the specificity has to be over 90%, which is highly unlikely given the clinical data. For TST/IGT at high sensitivity and specificity it is the optimum choice. However, overall IGT is the optimum choice at most combinations of sensitivity and specificity.

- ***Validation***

Validating models requires checking the internal and external validity. Internal validity is ensuring that the model is mathematically correct and that all the calculations are correct. All the calculations have been checked by following the numbers in the cohort and double checking the calculations.

- ***Conclusion – Contacts (HCW)***

The results of the analysis suggest that IGT and TST/IGT are very likely to be cost effective options for testing contacts. The results indicate that these conclusions are robust to variation in a number of key parameters. However, there was uncertainty over which testing strategy was the optimal choice. This was dependant on a number of factors including the sensitivity and specificity used for TST in the analysis. Given this uncertainty, the GDG considered that both tests should be offered and that depending on the operational issues the most appropriate should be used.

- ***References***

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- # Annex 6: Health economic checklists

Checklist 1

Clinical diagnosis and management of tuberculosis and measures for its prevention and control (The National Collaborating Centre for Chronic Conditions. 2006)		
Guideline topic: TB update	Question no:1,2	
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
1.1 Is the study population appropriate for the guideline?	Yes	Hypothetical model
1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK NHS
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Partly	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	QALY values reported in EQ5D
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	The studies referenced directly elicited values from patients
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	Valued by the public
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Applicable		
Other comments The economic model built in the guideline was based on a contact tracing strategy in that, each primary case of active disease is associated with a fixed number of secondary cases. The model used was a decision tree which did not account for the dynamics of disease transmission within the population. The rationale for this approach was twofold: lack of resources and time. Suffice to say that the estimates of the cost effectiveness of contact tracing per se are less robust and be treated with caution.		

Checklist 2

Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries(Hardy et al. 2009)		
Guideline topic: TB update		Question no:1 contacts
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
1.1 Is the study population appropriate for the guideline?	Yes	Based on actual data
1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Partly	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	Not considered
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	No	Outcome measure based on LTBI detected
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments No sensitivity or specificity was considered in this economic paper. The paper is a cost impact analysis rather than a cost utility analysis.		

References

Hardy, A. B., Varma, R., Collyns, T., Moffitt, S. J., Mullarkey , C., & Watson, J. P. Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-

effective for immigrants from high burden countries. Thorax 65, 178-180. 2009.

Checklist 3

Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis (Oxlade et al. 2007)		
Guideline topic: TB update	Question no:1 contacts	
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
• 1.1 Is the study population appropriate for the guideline?	Yes	Hypothetical model
• 1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA Chest X ray
• 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	Canada
• 1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	
1.5 Are all direct health effects on individuals included?	Partly	
• 1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	
• 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	No	Based on cases detected and persons screened
• 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	
• 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not Applicable		
Other comments Markov modelling was used to compare the expected TB cases and costs over 20 years following screening for TB with different strategies among hypothetical cohorts of foreign-born entrants to Canada, or contacts of TB cases. Sequential screening with TST then QFT was more cost effective than QFT alone in all scenarios and more cost-effective than TST alone in selected subgroups.		

Checklist 4

Cost effectiveness of Interferon-gamma release Assay for Tuberculosis Contact Screening in Japan(Kowada et al. 2008)		
Guideline topic: TB update	Question no: 2 (contacts)	
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
• 1.1 Is the study population appropriate for the guideline?	Yes	Hypothetical model
• 1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA TST and then IGRA
• 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	Japan
• 1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	Direct and indirect costs were considered
1.5 Are all direct health effects on individuals included?	Partly	
• 1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3%
• 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
• 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	Patients
• 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments The analysis showed that the most cost effective strategy was the QFT followed by the dual strategy. In the base case analysis (20year old cohort), the QFT-alone strategy was the least expensive ($471.54) and the most effective (28.1099 QALYs), compared to the TST/QFT strategy ($500.55; 28.1087QALYs) and the TST-alone strategy ($573.98; 28.1079QALYs). The ICER of the QFT-alone strategy resulted in a cost saving of US$23,043/QALY gained compared with the TST/QFT strategy. This analysis was done across the following age groups 20 years, 40 years and 60years. The relationship between age and cost effectiveness of the strategy was inverse with age, in that QFT was a more effective approach in the elderly compared to the young-this is because the QFT decreased costs in the elderly adults.		

Checklist 5

Cost effectiveness of Interferon Gamma Release Assays vs Tuberculin Skin Tests in Health Care Workers(Perio et al. 2009)		
Guideline topic: TB update		Question no:2 (contacts)
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
• 1.1 Is the study population appropriate for the guideline?	Yes	Hypothetical model
• 1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA
• 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	No	USA
• 1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	Direct and indirect costs were considered
1.5 Are all direct health effects on individuals included?	Yes	
• 1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% was used
• 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	QALY values
• 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	The studies referenced directly elicited values from patients
• 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Not stated	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not Applicable		
Other comments A markov state-transition decision analytic model using the societal perspective and life time horizon was constructed to compare costs and QALYs associated with the 3 strategies for hypothetical 35-year old Healthcare workers with or without prior BCG vaccination. However, there was no consideration for a dual strategy and therefore deemed not applicable for this guideline.		

Checklist 6

Different screening strategies (single or dual) for the diagnosis of suspected

latent tuberculosis: a cost-effectiveness analysis (Pooran et al. 2010)		
Guideline topic: TB update		Question no: 2 (Health care Workers)
Check list completed by Edward Mwarangu		
Section 1: Applicability	Yes/ Partly/ No/ Unclear/ NA	Comments Partly applicable
• 1.1 Is the study population appropriate for the guideline?	Yes	Hypothetical model
• 1.2 Is/are the intervention(s) appropriate for the guideline?	Yes	TST, IGRA-both types TST and then IGRA
• 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	UK NHS
• 1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Partly	
• 1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
• 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	No	Outcome measure based on the Number of active TB cases prevented
• 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	
• 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not Applicable		
Other comments The economic model built in the guideline was based on a contact tracing strategy in that, each primary case of active disease is associated with a fixed number of secondary cases. The modelling approach is very similar to that reported in this analysis. The paper provided very robust data on the source of cost.		

3.3 Appendix N – Guideline Development Group members and NICE staff 2011

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Declarations of interest: TB Update.

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Ibrahim Abubakar	I co-wrote the HPA position statement on Interferon Gamma Release Assays.	Personal Non-Pecuniary	Declare and can participate in discussions on all topics.
	I am the chief investigator for the NIHR funded study on the prognostic value of IGRAs (this call was suggested by the Department of Health as a response to the recommendations of NICE clinical guidelines 33). The	Personal Non-Pecuniary	

	research is fully funded by the Department of Health/NHS with no commercial involvement. It will be necessary that I hold an objective view of the potential outcome of this research and I therefore do not have a formed/expressed view on the matter that differs from the recommendations on NICE clinical guidelines 33. The views expressed in the HPA position statement are also largely consistent with (and based on) NICE clinical guidelines 33.		
	Membership of the National Knowledge service for TB which develops guidelines.	Personal Non-Pecuniary	
	Publications on the role of IGRA's in TB.	Personal Non-Pecuniary	
Ann Chapman	Member of advisory panel for a pharmaceutical company relating to the development of Outpatient Parenteral Antibiotic Therapy, with occasional fees paid. This work is unrelated to TB.	Personal pecuniary, non-specific.	
Tim Collyns	Have attended symposia with educational grants from a range of pharmaceutical companies and given lectures/attended advisory board, for pharmaceutical companies none related to tuberculosis/diagnostic methods being discussed.	Personal pecuniary, non-specific.	
	Both commercial companies have provided some test kits at reduced cost to the laboratory to 'try out', no conditions attached. Provide both IGRA's to other local NHS trusts.	Non Personal pecuniary, non-specific.	
Francis Drobniewski	Health Technology Assessment Grant to evaluate two commercial IGRA systems in a pan-London clinical study. Grant to HPA	Non Personal pecuniary, specific.	

	Director Health Protection Agency National Mycobacterium Reference Laboratory which operates a not-for profit service for diagnosis of latent TB infection and active TB using Quantiferon Gold. Materials are purchased at normal price.	Non Personal pecuniary, non-specific.	
Sandy Moffitt	Co-author of paper – audit of New Entrant TB screening using Quantiferon Gold in Leeds. (lead author Dr Andrew Hardy)	Personal Non-Pecuniary	
	Husband receives 'financial payment from the healthcare industry' – he is a consultant orthopaedic surgeon.	Personal family interest, non-specific.	

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