The National Collaborating Centre

for Chronic Conditions

Funded to produce guidelines for the NHS by NICE

TUBERCULOSIS

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control

Published by

Royal College of Physicians

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- Dr Alistair Story, Health Protection Agency Centre for Infections
- All those involved in TB care who participated in our review of current services.

The following people acted as deputies for 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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- Mr Thomas Patterson, Patient & Carer Representative, London
- Dr Marko Petrovic, Consultant in Communicable Disease Control, Manchester.

Preface

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

The guideline has been commissioned by NICE as a successor to the British Thoracic Society's TB guidelines, which have been used with great benefit for many years as the principal source of advice on TB management in the UK. The scope of the guideline is unusually wide, and we were obliged to divide the work between two separate guideline development groups, one covering diagnosis and management, the other prevention and control. Both groups used what has become our standard methodology, first identifying the key aspects of the disease and then searching out and appraising the best relevant evidence. In some areas, particularly those around prevention and control, it has been unusually difficult to find strong evidence. In all cases the guideline groups have attempted to produce practical recommendations, however much or little evidence they had to work on. In addition, great efforts were made to link the advice contained in the guideline to that available from other sources, in particular advice from the Joint Committee on Vaccination and Immunisation.

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

The two guideline development groups have each had to meet their own challenges in the development of this document. Their sincere desire to get the best for patients with TB has been evident to those of us involved in the administration of the project, and we are grateful to them for this commitment as well as their expertise. Particular thanks are due to the clinical advisor,

Peter Ormerod, who sat on both groups. I believe their efforts have resulted in a comprehensive and authoritative guideline, which should serve the NHS well in the short and medium term and provide a firm basis for future development and improvement in TB management.

Dr Bernard Higgins MD FRCP
Director, National Collaborating Centre for Chronic Conditions

INTRODUCTION

1 Introduction

1.1 Background information

This guideline deals with activities undertaken by professionals in the NHS with the aims of diagnosing primary cases of tuberculosis (TB), identifying secondary cases, treating active disease, controlling latent infection and preventing further transmission. At a population level, the combined result of these activities should be to curb and then reverse the increase in TB seen in England and Wales in recent years. TB is a disease of poverty, and specific groups of the population are at heightened risk. To address this, the guideline provides recommendations, wherever there is evidence to support it, on ways of organising services efficiently to provide the best possible care. Almost all cases of TB are preventable, and almost all people with TB can be cured.

▷ What causes TB?

TB is caused by a bacterium called *Mycobacterium tuberculosis* ('*M. tuberculosis*' or '*M.Tb*'). It is spread by one person inhaling the bacterium in droplets coughed or sneezed out by someone with infectious tuberculosis. Not all forms of tuberculosis are infectious. Those with TB in organs other than the lungs are rarely infectious to others, and nor are people with just latent tuberculosis (see below). Some people with respiratory tuberculosis are infectious, particularly those with bacteria which can be seen on simple microscope examination of the sputum, who are termed 'smear positive'. The risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is. The risk is greatest in those with prolonged, close household exposure to a person with infectious TB.

▷ What happens after infection?

Once inhaled the bacteria reach the lung and grow slowly over several weeks. The body's immune system is stimulated, which can be shown by a tuberculin skin test (TST), a common diagnostic technique. In over 80% of people the immune system kills the bacteria and they are removed from the body. In a small number of cases a defensive barrier is built round the infection but the TB bacteria are not killed and lie dormant. This is called latent tuberculosis; the person is not ill and is not infectious. Sometimes at the time of the initial infection, bacteria get into the blood stream and can be carried to other parts of the body, such as bones, lymph glands or the brain, before the defensive barrier is built. One third of the world's population, two billion people, have latent tuberculosis.

If the immune system fails to build the defensive barrier, or the barrier fails later, latent tuberculosis can spread within the lung (pulmonary tuberculosis) or into the lymph glands within the chest (intrathoracic respiratory tuberculosis) or develop in the other part(s) of the body it has spread to (extrapulmonary tuberculosis). Only some of those with latent tuberculosis will develop symptoms ('active tuberculosis'). About half the cases of active tuberculosis develop within a few years of the original infection, particularly in children and young adults. The other half of active TB cases arise from reactivation of the latent infection many years later.

▷ Who catches TB?

Anyone can catch TB but those at particular risk are those who have been exposed to TB bacteria, and those who are less able to fight latent infection. They include:

- close contacts of infectious cases
- those who have lived in, travel to or receive visitors from places where TB is still very common
- those who live in ethnic minority communities originating from places where TB is very common
- those with immune systems weakened by HIV infection or other medical problems
- the very young and the elderly, as their immune systems are less robust
- those with chronic poor health and nutrition because of lifestyle problems such as homelessness, drug abuse or alcoholism
- those living in poor or crowded housing conditions, including those living in hostels.

▷ What are the symptoms of TB?

Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis.

Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend on the site, and may be accompanied by intermittent fever or weight loss. TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms.

▷ How is TB diagnosed?

TB is diagnosed in a number of ways. Tissue samples from biopsies may show changes which suggest TB, as do certain X-ray changes, particularly on chest X-rays. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. TST (Mantoux test) and interferon-gamma tests (IGTs) can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGTs involve taking a blood sample, which is processed at a laboratory.

▷ How is TB treated?

TB is completely curable if the correct drugs are taken for the correct length of time. Before drug treatment for TB nearly half of all persons with active tuberculosis died from it. Several antibiotics need to be taken over a number of months to prevent resistance developing to the TB drugs. The great majority of TB bacteria are sensitive to the antibiotics used (rifampicin, isoniazid, pyrazinamide and ethambutol). A minority of cases, 6–8% in England and Wales, are resistant to one of the antibiotics. Isoniazid and rifampicin are ineffective in 1% of cases. These cases are said to be of multi-drug resistant TB (MDR TB), which is harder to treat (see Appendix E for details of TB epidemiology).

TB bacteria grow very slowly and divide only occasionally when the antibiotics start to kill them, so treatment usually has to be continued for six months to ensure all active and dormant bacteria are killed and the person with TB is cured. People with respiratory TB are usually not infectious after two weeks of treatment. Drug-resistant forms of the bacteria require treatment for longer than six months. MDR TB is particularly serious, requiring prolonged (up to 24 months) treatment, with the infectious period lasting much longer.

In latent tuberculosis there are many thousand times fewer TB bacteria than in active tuberculosis. Treatment with a single drug for six months, or two drugs for a shorter time, is sufficient to kill the dormant bacteria, preventing the person developing active tuberculosis later in their life.

Following TB treatment, the disease can return (relapse) in a small number of people, because not all bacteria have been killed. This is obviously much more likely if the course of treatment has been interrupted, not completed or otherwise not followed. However, it is also possible to catch TB a second time, unlike some other infectious diseases.

1.2 Epidemiology of TB in England and Wales

Detailed information on the epidemiology of tuberculosis is provided in Appendix E. Up-to-date epidemiological information, including reports of notifications and enhanced surveillance, is available from the Health Protection Agency (**www.hpa.org.uk**).

▷ Historical trends

The TB notification system, implemented in 1913, showed that recorded TB rates peaked in England and Wales in the early part of the twentieth century, when 300 new cases per 100,000 people were reported every year. Since then, until the mid 1980s at least, the incidence of tuberculosis has been falling: in 1987 there were only 10 new cases per 100,000 people.

▷ Geographical variations in incidence

There are marked differences in the incidence of tuberculosis in different parts of England and Wales, with most new cases occurring in cities. For example, there were 38 new cases per year per 100,000 population in London in 2001, as compared to less than five in the south west of England. There are also substantial variations in incidence of TB within cities, with as much as a thirtyfold difference between different London boroughs.

▷ Variations in incidence by ethnicity and place of birth

Risk of TB is significantly higher in people from minority ethnic groups, as is evident in Table 1 (overleaf).

People born abroad were fifteen times more likely to contract tuberculosis as people born in England and Wales. The majority of cases in people born abroad occur after they have lived in the UK for several years.

Table 1 Tuberculosis rates by ethnicity in England and Wales, 2001

Ethnicity	TB cases per 100,000 population
Black African	211
Pakistani	145
Indian	104
White	4

2 Methodology

2.1 Aim

With this document the National Collaborating Centre for Chronic Conditions (NCC-CC) has aimed to provide a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:

- offers best practice advice for TB
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of the care provision for tuberculosis such as the diagnosis and management of both latent and active TB, and measures for its prevention and control
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences (full version, short version, quick reference guide and public version) in electronic or printed format.

In contrast to most clinical guidelines commissioned by NICE, the prevention and control sections of this guideline include recommendations on service organisation where good quality evidence exists to support them.

2.2 Scope

The guideline was developed in accordance with a specified scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of TB to be included and excluded.

Before development of the guideline began, the scope was subjected to stakeholder consultation in accordance with processes established by NICE.[1] The scope is given in Appendix D.

2.3 Audience

The guideline is intended for use with the following people or organisations:

- all healthcare professionals
- people with, or at risk from, tuberculosis, and their carers
- patient support groups
- commissioning organisations
- service providers.

▷ Involvement of people with TB

The NCC-CC was keen to ensure the views and preferences of people with TB and their carers informed all stages of the guideline. This was achieved by:

- consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline

- having two former TB patients and two user organisation representatives on the Guideline Development Group (GDG).

The patient and carer representatives were present at every meeting of the GDG. They were therefore involved at all stages of the guideline development process and were able to consult with their wider constituencies.

2.4 Guideline limitations

These include:

- the diagnosis and treatment chapters of this guideline (5–10), except rapid diagnostic techniques (5.3 and 5.4), do not cover issues of service delivery, organisation or provision (as this was not specified in the remit from the DH)
- NICE is primarily concerned with health services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors
- generally the guideline does not cover rare, complex, complicated or unusual conditions.

2.5 Other work relevant to the guideline

Readers of this guideline should also be aware of the following publications:

- *Stopping tuberculosis in England and Wales*, the Chief Medical Officer's TB Action Plan[2]
- *Immunisation against infectious disease* (the 'Green Book')[3]
- *The clinical and cost-effectiveness of diagnostic tests for the detection of mycobacterial infection*, a health technology appraisal due for publication mid 2006 (see **www.ncchta.org**).

The National Knowledge Service is a relatively new national NHS body which is investigating ways of making patient and public information available to patients and the NHS, amongst other functions. One of the initial pilot projects is in tuberculosis, and is linked to this guideline. See **www.hpa.org.uk/tbknowledge** for more detail.

The Secretary of State for Health is advised on broader national policy on vaccination by the DH's Joint Committee on Vaccination and Immunisation (JCVI) (**www.advisorybodies.doh.gov.uk/jcvi**).

Information on TB epidemiology in the UK and abroad, as well as some background information for patients and the public, is available through the Health Protection Agency's website at **www.hpa.org.uk**. This is referred to at relevant points in this guideline.

2.6 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual[1] (**www.nice.org.uk/page.aspx?o=201982**) and the methodology pack[4] specifically developed by the NCC-CC for each chronic condition guideline (**www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm**). The developers' roles and remit are summarised below.

▷ National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the NICE.

A multiprofessional partners board inclusive of patient groups and NHS management governs the NCC-CC.

▷ NCC-CC technical team

The technical team met approximately two weeks before each GDG meeting and comprised:

- the GDG group leader
- the GDG clinical advisor
- an information scientist
- a research fellow
- a health economist
- a project manager
- administrative personnel.

▷ Guideline Development Group

The GDG met monthly for 15 months (2004 to 2005) and comprised a multidisciplinary team of professionals, service users, carers and user organisation representatives who were supported by the technical team.

The GDG membership details including patient representation and professional groups are detailed in the GDG membership section at the front of this guideline.

(Members of the GDG declared any interests in accordance with the NICE technical manual. A register is available from the NCC-CC for inspection upon request (**ncc-cc@rcplondon.ac.uk**).)

▷ Guideline Project Executive

The Project Executive was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

The Project Executive comprised:

- the NCC-CC director
- the NCC-CC manager
- an NCC-CC senior research fellow
- the NICE commissioning manager
- the technical team.

▷ Sign-off workshop

At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

2.7 The process of guideline development

There are ten basic steps in the process of developing a guideline.

▷ First step: Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions. See Appendix A for details of the questions.

▷ Second step: Systematically searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. Conference paper abstracts and non-English language papers were excluded from the searches. The research fellow identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

▷ Third step: Critically appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the Technical Manual[1]
- NCC-CC Quality Assurance document & Systematic Review paper available at **http://www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm**

▷ Fourth step: Distilling and synthesising the evidence and writing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available at **www.rcplondon.ac.uk**

▷ Fifth step: Grading the evidence statements and recommendations

The evidence statements and recommendations were graded in accordance with Table 2. The level of evidence and classification of recommendations were also included for diagnostic studies.

Table 2 Hierarchy of evidence and recommendation classification

Levels of evidence		Classification of recommendations	
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1–	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation.	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results. *or* extrapolated evidence from 1++ or 1+.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus *or* extrapolated from level 2 clinical evidence supplemented with health economic modelling.
		D (GPP)	A good practice point (GPP) is a recommendation based on the experience of the GDG.

Diagnostic study level of evidence and classification of recommendation was also included.

▷ Sixth step: Health economic evidence

Due to the appointment of the health economist midway through the guideline development, the areas for health economic modelling were considered after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they also commented on subsequent revisions.

▷ Seventh step: Agreeing the recommendations

The sign-off workshop employed formal consensus techniques[1] to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- seven key priorities for implementation
- eight key research recommendations
- five algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.

▷ Eighth step: Structure of the full version of the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and is described below:

The clinical introduction sets a succinct background and describes the current clinical context.

The methodological introduction describes any issues or limitations that were apparent when reading the evidence base.

Evidence statements provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.

Health economics presents an overview of the cost-effectiveness evidence base of relevance to the area under address.

'From evidence to recommendations' highlights the debate of the GDG. This section sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

The recommendations section provides stand-alone, action-orientated recommendations.

Evidence tables are not published as part of the full guideline but are available online at **www.rcplondon.ac.uk/pubs/books/TB/index.asp**. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

▷ Ninth step: Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed at the NICE website (**www.nice.org.uk**). Editorial responsibility for the full guideline rests with the GDG.

Table 3 describes the various versions of the guideline that are available.

Table 3 Versions of this guideline

Versions	Comments
Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at **www.rcplondon.ac.uk/pubs/books/TB/index.asp**
NICE version	Documents the recommendations without any supporting evidence. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Quick reference guide	An abridged version. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Information for the public	A lay version of the guideline recommendations. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**

▷ Tenth step: Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 30 November 2004 to be considered. The GDG agreed to make a special provision to extend this in one case where much new evidence was known to be forthcoming: interferon-gamma testing for latent tuberculosis, where published evidence was considered up to and including 21 July 2005. Future guideline updates will consider evidence published after these cut-off dates.

Two years after publication of the guideline, NICE will commission a national collaborating centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately four years after publication.

2.8 Healthcare needs assessment

In contrast to many NICE guidelines, the scope requires service guidance in the prevention and control chapters of this guideline (chapters 11–13) and for rapid diagnostic techniques (sections 5.3 and 5.4). The NCC-CC conducted a rapid and simple healthcare needs assessment in order to establish current practice and resources, and to identify areas where these did not match the clinical need. This collected information through a review of the epidemiology of TB in England and Wales, and a review of current service by questionnaire among a sample of TB service providers.

▷ Review of epidemiology

At the outset of the guideline development the prevention and control research fellow, Dr Ian Lockhart, compiled epidemiological data relevant to England and Wales from a number of national sources into a report to inform GDG discussions. This was refined through discussion at GDG meetings, is presented in this guideline in the Appendix E and in section 4.2, and will be described in a forthcoming paper.

▷ Survey of current services

The NCC-CC sought information on current service provision in terms of staffing, location of specific services and caseload. Dr Sooria Balasegaram coordinated this survey through TB nurses and the Health Protection Agency's local and regional services. Further details are given in section 4.2 and will be described in a forthcoming paper.

2.9 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The British National Formulary (BNF)[5] should be consulted alongside any drug recommendations cited in this guideline and note taken of the indications, contraindications, cautions and product characteristics.

NICE guidelines will normally only make drug recommendations that fall within licensed indications. If a drug is recommended outside of its licensed indication this will be made clear in the guideline. This guideline contains recommendations for prescribing the following, all of which are within current licensed indications:

- ethambutol, for treating active tuberculosis
- isoniazid, for treating both latent and active tuberculosis
- pyrazinamide, for treating active tuberculosis
- rifampicin, for treating both latent and active tuberculosis
- streptomycin, for treating isoniazid mono-resistant active TB
- any glucocorticoid, for treating inflammation associated with active tuberculosis of the meninges or central nervous system (CNS).

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Key priorities for implementation

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

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

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

Patients with active meningeal TB should be offered:

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

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

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

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

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

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

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

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

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

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

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

3.2 Algorithms

The following algorithms appear in this document:

- algorithm showing isolation decisions for patients with suspected TB (*see* Fig 2, p61)
- algorithm for testing and treating asymptomatic children aged between four weeks and two years old who are contacts of people with sputum smear-positive TB (*see* Fig 8, p148)
- algorithm for asymptomatic household and other close contacts of all cases of active TB (*see* Fig 9, p149).
- algorithm for new entrant screening (*see* Fig 10, p172)
- algorithm for new NHS employees (*see* Fig 11, p180).

3.3 Audit criteria

Table 4 Audit criteria

Key priority for implementation	Criteria	Exception	Definition of terms
A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in: • adults not known to be HIV positive **A** • adults who are HIV positive **B** • children. **B** This regimen is referred to as 'standard recommended regimen' in this guideline.	a) Process measure: percentage of patients with active TB receiving rifampicin, isoniazid, pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Outcome measure: percent cure and completion rate.	Contraindications, meningeal TB, CNS involvement, drug resistance.	
Patients with active meningeal TB should be offered: • a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period **D(GPP)** • a glucocorticoid at the normal dose range • adults – equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg **A** • children – equivalent to prednisolone 1–2 mg/kg, maximum 40 mg **D(GPP)** with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation.	a) Process measure: percentage of patients with meningeal TB receiving rifampicin, isoniazid, pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Process measure: percent receiving/having received glucocorticoids. c) Outcome measure: percent cure and completion rate (12 months).	Contraindications, drug resistance.	b) Any patient who received glucocorticoids for at least two weeks.
Use of DOT is not usually necessary in the management of most cases of active TB. **A** All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular: • street- or shelter-dwelling homeless people with active TB **B** • patients with likely poor adherence, in particular those who have a history of non-adherence. **D(GPP)**	Process measure: percentage of patients with active TB who are treated with DOT.		A 'patient on DOT' is any patient who has been prescribed anti-TB drugs as directly observed therapy (regardless of observer) for part or all of their treatment.

continued over

Table 4 Audit criteria – *continued*

Key priority for implementation	Criteria	Exception	Definition of terms
The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. **D(GPP)**	Process measure: percentage of TB patients in possession of current correct key worker's details.	Hospital inpatients.	Key worker will have been named as specified in recommendations.
New entrants should be identified for TB screening from the following information: • port of arrival reports **D(GPP)** • new registrations with primary care **B** • entry to education (including universities) **D(GPP)** • links with statutory and voluntary groups working with new entrants. **D(GPP)**	a) Process measure: percentage of new entrants referred or recorded who are contacted for screening. b) Process measure: percent of new entrants contacted for screening, who complete the screening. c) Process measure: percent of new entrants contacted for screening, who are referred to secondary care TB teams.	a) Any people sought but not found. b) Any people sought but not found. Loss to follow-up, including not returning for TST to be read, chest X-ray to be taken, treatment for latent TB infection to be started, etc.	b) Any person who completes the screening process according to the algorithm is counted.
Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. **D(GPP)** Primary care organisations with a high incidence of TB* should consider vaccinating all neonates soon after birth. **D(GPP)**	a) Process measure: percentage of neonates vaccinated with BCG. b) Process measure: percentage of eligible neonates vaccinated with BCG.	Informed refusal, HIV.	

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

4 Aims and principles of tuberculosis care

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

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

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

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

4.1 Current service organisation

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

Centralised

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

Central with satellites

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

General hospital/community model

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

Specialist hospital-based model

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

▷ Staffing levels

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

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

▷ Other information on current services

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

- dedicated TB clinics (section 6.1)
- nurse-led follow-up clinics (section 6.1)
- specialist HIV/TB clinics (section 6.1)
- specialist paediatric TB clinics (section 6.1)

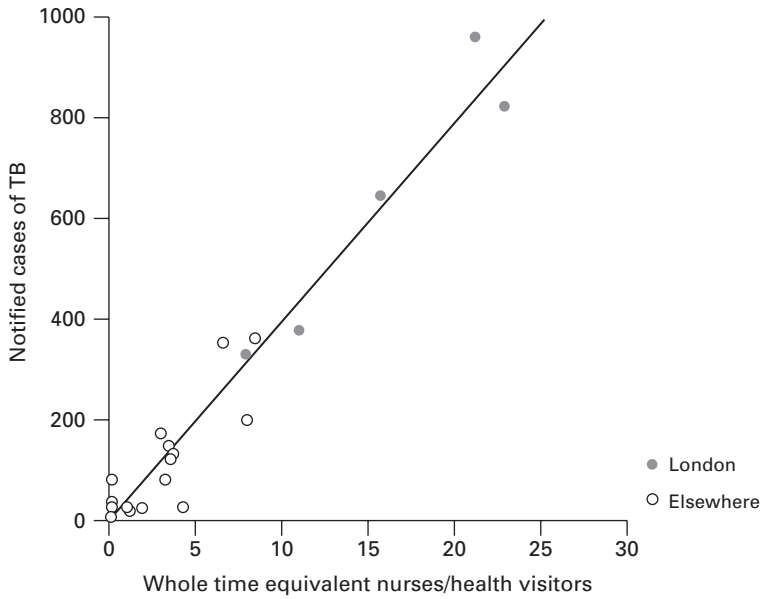

Figure 1: Staffing levels of nurses/health visitors *vs* notified cases of TB. The line represents one whole time equivalent per 40 cases

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

4.2 Communication and patient information

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

- a single national source of high-quality TB information in relevant languages, and formats for vision- or hearing-impaired people
- TB services to assess local language and other communication needs, and accordingly make information from the national source available locally
- clear discussion between healthcare professionals, people with (or at risk from) TB and their carers about tests, treatment, contact tracing and infection control measures, to enable understanding

- people with both HIV and TB to be provided with information about the different specialties who may provide care during and after their treatment for TB
- contact tracing explained and handled sensitively to avoid misunderstanding and stigma
- information set out so as not to medicalise the patient
- TB services providing each patient completing anti-tuberculosis treatment with clear 'inform and advise' information

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

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

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

Recommendations are therefore given under section 6.2.

4.3 HIV co-infection

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

THE GUIDELINE: DIAGNOSIS AND TREATMENT

5 Diagnosis

5.1 Diagnosing latent tuberculosis

5.1.1 Clinical introduction

In asymptomatic persons exposure to, and potential infection with, tuberculosis is demonstrated by a positive skin test, or more recently from a positive blood-based immunological (interferon-gamma) test. Those with a strongly positive skin test are then regarded as having been infected with tuberculosis. Of these people presumed infected, there is a 10–15% chance of developing clinical disease at some point in their lives. If a co-morbidity develops which reduces the immune system (see section 10.2), that risk is increased. The majority of exposed persons will kill off the inhaled bacteria, and be left only with a positive skin test as a marker of exposure. About half of those who develop the clinical disease will do so within five years of the initial infection. In cases where a long period elapses between infection and development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can 'reactivate' in favourable circumstances for the organism.

Until recently, only TST (Mantoux and Heaf tests) was available to give evidence of exposure. The tuberculin tests had the advantage of being cheap and relatively easy to perform, but suffered from a number of problems. The test results have to be interpreted within a certain timescale, and patients who do not return, or delay returning, will have either no result or a possibly inaccurate one. False positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or opportunist environmental mycobacteria. False negative results can occur due to anything reducing immunity, particularly co-infection with HIV, but also treatments such as cytotoxics, or immunosuppression. Extensive tuberculosis (pulmonary or miliary) can itself also temporarily depress the immunity, and can lead to a paradoxically negative TST. More recently, selective immunological (interferon-gamma) tests have been developed using the tuberculosis antigens 'early secretion antigen target 6' (ESAT-6) and 'culture filtrate protein 10' (CFP-10), which are not present in BCG, and are found in only a few species of environmental mycobacteria. These can be done on either cells or cell products derived from whole blood tests. These tests aim to be more specific by removing false positive results, and to be better correlated with latent infection or dormant organisms.

5.1.2 Methodological introduction

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

Studies were excluded if the interferon-gamma immunological test under consideration used purified protein derivative as an antigen (as used in the TST) as these tests were phased out to make way for the newer tests based on more specific antigens.

Eleven diagnostic studies were identified which compared interferon-gamma immunological tests with the TST for the diagnosis of latent infection.[9–19] One of the studies included an HIV-positive population, but this study was excluded due to methodological limitations.[10]

It should be noted that three of the studies used an IGT which only included the ESAT-6 antigen.[14,16,17] Although such a test is not commercially available, the studies further elucidate the effectiveness of tests based on such antigens compared to the TST.

A recent systematic review[20] of interferon-gamma assays in the immunodiagnosis of TB included comparisons with the TST; however this review included studies already considered here and did not attempt a meta-analysis (as meta-analysis methods are not well defined for heterogeneous diagnostic studies). This review has therefore not been considered.

There is no gold-standard test for latent tuberculosis. Diagnosis has in the past been reliant on the TST but this has poor specificity if there has been BCG vaccination or environmental mycobacterial exposure, which can lead to false positive results. In the absence of a gold-standard reference test, it is not possible to measure directly the sensitivity and specificity of a new test for latent tuberculosis. The studies included here have thus focused on whether interferon-gamma immunological tests correlate better with exposure to *M. tuberculosis* than the TST.

There is a lack of evidence available on the use of these tests in those who are HIV positive, in other immunocompromised individuals and in younger children. Furthermore, there is an issue of the generalisability of non-UK studies.

5.1.3 Evidence statements

▷ Test results and TB exposure

In a UK study[17] of healthy adults in a contact tracing clinic, IGT (ESAT-6 ELISPOT assay) results had a strong positive relationship with increasing intensity of contact exposure (OR 9.0 per unit increase in exposure, 95%CI 2.6 to 31.6, p=0.001), whereas TST results had a weaker relationship with exposure (OR 1.9, 95%CI 1.0 to 3.5, p=0.05). (**2**)

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

In contacts of index cases in the Gambia,[13] with increasing *M. tuberculosis* exposure, the percentage of participants who were tuberculin positive and interferon gamma test (ESAT-6/CFP-10 ELISPOT assay) negative increased from 11% of those sleeping in a different house from the index case to 32% of those sleeping in the same room (p<0.001). (**3**)

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

In Korea where BCG vaccination is mandatory,[15] a study found that the odds of a positive test result per unit increase in exposure across four groups, increased by a factor of 5.31 (95%CI 3.62 to 7.79) for the IGT (QuantiFERON-TB Gold) and by a factor of 1.52 (95%CI 1.2 to 1.91) for the TST ($p<0.001$). (**2**)

▷ Test results and BCG status

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

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

In a UK study[16] of healthy household contacts and healthy unexposed controls, ESAT-6 peptide-specific interferon-gamma-secreting cells were detected in 85% of the healthy household contacts who were tuberculin positive. None of the healthy control subjects without a history of TB exposure, responded to this IGT even though all unexposed control subjects were BCG vaccinated. (**3**)

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

High school contacts in a TB outbreak in Denmark[9] who had high exposure to an index case and were not BCG vaccinated, had agreement between TST and IGT (QuantiFERON-TB Gold) results of 93% (95%CI 86 to 100%). This was 95% (95%CI 88 to 102%) in the low exposure group and an overall agreement between the two tests of 94% (95%CI 89 to 99%) in all subjects tested. The kappa value was 0.866, indicating high agreement between the two tests. (**3**)

In an Italian study[19] of contacts of an index case on a maternity unit, IGT (ESAT-6/CFP-10 ELISPOT assay) results were independent of BCG vaccination status. (**3**)

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

In a study of healthcare workers conducted in India[18] (where non-tuberculous mycobacteria are highly prevalent), previous BCG vaccination was not associated with TST or IGT (QuantiFERON-TB Gold) positivity. (**3**)

▷ Indeterminate test results

An Italian study[12] found that indeterminate IGT results (QuantiFERON-TB Gold) were significantly over-represented in patients with a negative TST (28.6% *vs.* 6.6% in tuberculin positive patients, $p<0.001$) and were more frequent in patients receiving immunosuppressive therapies than in those who were not receiving such treatments (OR 3.35, 95%CI 1.84 to 6.08, $p<0.0001$). Immunosuppressive therapy was defined as cancer chemotherapy, systemic steroids, or anti-tumour necrosis factor alfa agents at the time of testing. (**3**)

5.1.4 Health economics

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

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

It was assumed that treatment followed current policy: with appropriate therapy for people diagnosed with active TB or testing positive for latent infection, and BCG when appropriate for others. The analysis did not compare different types of skin tests or different types of IGT.

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

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

▷ Cost-effectiveness of testing strategies in contact tracing

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

▷ Variation in optimal strategy with context of contact tracing

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

Table 5 Cost-effectiveness of diagnostic strategies

Prevalence of infection	Strategy	Cost (£)	Effect (QALYs lost)	ICER* (£ per QALY gained)
0	No test	£31	0.00409	–
	TST/IGT	£58	0.00394	£178,835
	IGT	£102	0.00394	(Dominated)
	TST	£139	0.00404	(Dominated)
10%	No test	£191	0.02533	–
	TST/IGT	£240	0.02323	£23,351
	IGT	£282	0.02290	£126,813
	TST	£314	0.02310	(Dominated)
20%	No test	£351	0.04658	–
	TST/IGT	£423	0.04252	£17,575
	IGT	£463	0.04185	£60,073
	TST	£489	0.04217	(Dominated)
30%	No test	£512	0.06782	–
	TST/IGT	£605	0.06182	£15,553
	IGT	£643	0.06081	£38,081
	TST	£664	0.06123	(Dominated)
40%	No test	£672	0.08907	–
	TST/IGT	£788	0.08111	£14,522
	IGT	£824	0.07976	£27,132
	TST	£838	0.08029	(Dominated)
50%	No test	£832	0.11031	–
	TST/IGT	£970	0.10040	£13,898
	IGT	£1,005	0.09872	£20,578
	TST	£1,013	0.09936	(Dominated)

* ICER = incremental cost-effectiveness ratio

▷ Uncertainty over optimal testing strategy for contact tracing

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

5.1.5 From evidence to recommendations

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

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

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

RECOMMENDATIONS

Evidence is emerging on the performance of interferon-gamma tests. If this new evidence is significant, NICE will consider updating the guideline.

R1 To diagnose latent TB: **D**

- Mantoux testing should be performed in line with the 'Green Book'[21]
- those with positive results (or in whom Mantoux testing may be less reliable) should then be considered for interferon-gamma immunological testing, if available
- if testing is inconclusive, the person should be referred to a TB specialist (see chapter 10 for management of latent TB).

Cross-referring:
For details of people more likely to develop active TB, see section 10.2.
For people with negative tuberculin skin test results, see BCG vaccination under chapter 11.
For people with latent TB, see treatment of latent TB infection under section 10.1.

5.2 Diagnosing active tuberculosis

5.2.1 Clinical introduction

▷ Signs and symptoms of respiratory TB

Primary respiratory tuberculosis is often asymptomatic, but the fact that infection has occurred is shown by the development of a positive tuberculin skin test or interferon-gamma blood test. A history of recent contact with a person with TB is the most important factor in making the diagnosis. Occasionally, tuberculin conversion is accompanied by erythema nodosum or phlyctenular conjunctivitis. Mediastinal nodal enlargement as part of the primary complex can sometimes press on or discharge into a bronchus causing collapse of the distal lung or bronchial narrowing leading to wheeze or obstruction with distal over-inflation.[22]

In children with primary TB, weight loss, or weight loss and cough, are symptoms associated with culture confirmed TB. However, about half of all children with primary TB will have no symptoms.

Post-primary tuberculosis may be asymptomatic in the early stages, but symptoms, which can be either constitutional or respiratory, soon develop. Malaise, weight loss, fever and night sweats are the common constitutional symptoms. Cough is the commonest respiratory symptom, which is initially dry and non-productive but may later become productive, with haemoptysis in a small minority of cases. Breathlessness is a late feature, usually only occurring when a substantial amount of lung is destroyed or there is a significant pleural effusion. Chest pain is relatively uncommon, but can be pleuritic if peripheral lesions are present, or of dull ill-localised nature.

A study in Sudan, grading sputum smear positivity with clinical features showed multiple chest symptoms were positively correlated with sputum smear positivity. Also, the longer the duration of symptoms, the more this correlated with sputum smear positivity.[23] A comparison of the 'classic' symptoms of tuberculosis in patients with and without tuberculosis[24] is summarised in Table 6.

Table 6 Classic symptoms of tuberculosis

Symptom	TB (n=47)	Non-TB (n=516)	Odds ratio (95% CI)
Cough	81%	77%	1.27 (0.58–2.69)
Fever	70	59	1.64 (0.85–3.15)
Weight loss	64	27	4.74 (2.53–8.86)*
Night sweats	55	27	3.29 (1/79–6.04)*
Dyspnoea	47	50	0.88 (0.48–1.60)
Chest pain	27	26	1.08 (0.55–2.11)

* significant difference

A multivariate analysis[25] showed that the following features were positively associated with culture proven tuberculosis:

- the presence of TB risk factors or symptoms (OR 7.9)
- a positive skin test for tuberculosis (OR 13.2)
- a high temperature (OR 2.8)
- upper lobe disease on a chest radiograph (OR 14.6)

and that the following were negatively correlated with tuberculosis:

- shortness of breath (OR 0.2)
- crackles on physical examination of chest (OR 0.29).

▷ Signs and symptoms of non-respiratory TB

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

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

▷ Signs and symptoms of lymph node TB

Nearly half of all non-respiratory TB in England and Wales occurs in peripheral lymph nodes, mainly cervical.[26,27] The nodal enlargement in TB is usually gradual and painless, but can be painful if rapid. The usual absence of erythema and warmth makes the classical 'cold abscess'. The nodes originally are discrete and firm, but may later mat together and become fluctuant as necrosis develops, which can discharge through the skin with sinus formation and superficial ulceration. Persistent lymphadenopathy of over four weeks duration in people other than white UK-born should be regarded as TB until proven otherwise and investigated appropriately.

▷ Signs and symptoms of bone and joint TB

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

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

pain and/or neurological signs should have an infective process in the differential diagnosis, particularly in ethnic minority groups.

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

▷ Signs and symptoms of gastrointestinal TB

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

▷ Signs and symptoms of genitourinary TB

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

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

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

▷ Signs and symptoms of disseminated (including miliary) TB

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

▷ Signs and symptoms of central nervous system TB

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

▷ Signs and symptoms of skin TB

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

▷ Signs and symptoms of pericardial TB

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

▷ Signs and symptoms of TB at other sites

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

▷ Diagnosing active respiratory tuberculosis

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

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

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

▷ Diagnosing active non-respiratory tuberculosis

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

The yield of histology/cytology depends on tissue sample size, which is much smaller with aspiration cytology than biopsy, and on the level of immune response which generates the histological appearances. In HIV-positive individuals the histological response depends on the

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

In some cases of non-respiratory tuberculosis, the diagnosis of TB is not entertained in the differential diagnosis, and the doctor, usually a surgeon, does not send any material for culture, instead placing the entire sample in formalin. This then completely precludes any attempt at bacterial culture, although if AFB are seen histologically it still allows PCR-based techniques to be used (see section 5.3). The same histological and cytological criteria apply as in Table 7. Tuberculin skin tests or whole blood interferon-gamma based tests may be needed to assist with histological appearances that are not fully diagnostic.

5.2.2 Methodological introduction

▷ Diagnosing active respiratory TB: testing while awaiting culture results

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

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

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

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

Three studies considered the diagnostic accuracy of gastric washings in children.[53–55] Two of the studies were performed more than ten years ago in developing countries in populations with a high proportion of malnourished children, thus their applicability to the UK today is

highly questionable. A more recent study performed in Cape Town, South Africa[55] compared gastric lavage and induced sputum samples from children in terms of their diagnostic yield, reporting how many cases were culture positive, smear positive or both.

Methodological considerations include the following:

- In terms of sputum smear microscopy, serial testing of sputum samples will increase the sensitivity and specificity of the test.
- Sensitivity and specificity values are calculated in different ways, either on a patient basis or a specimen basis.
- Methods used for processing the sputum specimen (including the minimum volume of sputum required and whether the specimen is expectorated or induced) or the method of isolating cultures may differ in various settings.

Generally studies were unblinded (mostly because they were retrospective analyses). Blinding, however, is probably not crucial to avoid bias in the assessment of smear microscopy as the same samples are used for smear and culture and are subject to standardised laboratory procedures and definitions. It was notable that none of the studies identified were performed in the UK.

▷ Diagnosing active respiratory TB if culture results are negative

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

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

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

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

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

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

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

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

▷ Diagnosing active non-respiratory TB if culture results are negative

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

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

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

5.2.3 Evidence statements: diagnosing active respiratory TB while awaiting culture results

▷ Sputum microscopy

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

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

The rates of smear positivity were calculated for specimens of expectorated sputum, induced sputum and bronchoalveolar lavage (BAL) specimens in a study in the USA.[43] Findings of smears of expectorated sputum specimens showed that 55% were culture positive for *M. tuberculosis* and were AFB smear positive. Smear positivity rates for induced sputum were

38% and for BAL were 26%. When the predictive value was calculated by including only the first smear-positive specimen from each patient the values were 87% for expectorated sputum, 70% for induced sputum and 71% for BAL. (**2**)

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

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

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

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

▷ Chest X-ray

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

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

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

In a US study[52] of TB culture-positive adults, 78% of HIV-negative patients' radiographs were consistent with post-primary pattern TB versus 26% of patients who were HIV positive ($p<0.001$). Only 11% of 18 significantly immunosuppressed HIV-positive patients (CD4 counts <200) had X-rays consistent with post-primary pattern TB, while all four patients with CD4

counts >200 had typical post-primary pattern chest radiographs ($p<0.005$). Of the 16 significantly immunosuppressed HIV positive patients the predominant chest X-ray finding was diffuse or multilobar infiltrates without an upper lobe predominance (N=8) followed by normal chest X-ray (N=3). (**3**)

▷ Gastric washings

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

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

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

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

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

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

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

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

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

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

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

▷ HIV-positive

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

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

5.2.6 From evidence to recommendations

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

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

▷ Testing for active respiratory TB while awaiting culture results

The yield of positive sputum microscopy is improved by an adequate sputum sample (5 ml or more), concentration of sputum, analysing multiple samples, and by fluorescence microscopy as the screening tool. Smear positive rates are higher for spontaneously induced sputum than for either induced sputum or BAL samples. The positive predictive value of positive sputum microscopy is 92% for spontaneously produced sputum, and 71% for both BAL and induced sputum. There appeared to be little difference in the results between HIV-positive and HIV-negative patients in terms of bacteriological results and sputum smear positivity. Microscopy on gastric washings has some utility in children, but a recent comparative study in children showed a single induced sputum (by hypertonic saline) to be superior to three gastric washings. Gastric washings are less likely to provide useful material in adults, because of acidic inhibition.

Chest X-ray changes are less specific in children and HIV-positive individuals, particularly if the CD4 count is under 200 cells/μl.

▷ Testing for active respiratory TB if culture results are negative

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

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

▷ Testing for active non-respiratory TB while awaiting culture results

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

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

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

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

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

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

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

RECOMMENDATIONS

R2 To diagnose active respiratory TB:

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

R3 To diagnose active non-respiratory TB:

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

Table 7 Suggested site-specific investigations in the diagnosis and assessment of non-respiratory TB

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

Cross-referring:
For details of rapid diagnostic tests, see sections 5.3 and 5.4.
For people with active TB, see treatment under chapters 6, 7 and 9.
For details of contact tracing, see section 12.2.
For details of notification and enhanced surveillance, see chapter 14.

5.3 Rapid diagnostic tests: molecular methods

5.3.1 Clinical introduction

▷ Molecular probes for diagnosis

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

▷ Molecular probes for species confirmation

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

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

▷ Molecular probes for rifampicin resistance

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

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

▷ Molecular typing of *M. tuberculosis* isolates

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

5.3.2 Methodological introduction

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

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

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

5.3.3 Evidence statements

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

5.3.4 From evidence to recommendations

▷ Molecular probes for diagnosis

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

▷ Molecular probes for species confirmation

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

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

▷ Molecular probes for rifampicin resistance

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

▷ Molecular typing of *M. tuberculosis* isolates

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

RECOMMENDATIONS

R4 Rapid diagnostic tests for *M. tuberculosis* complex *(M. tuberculosis, M. bovis, M. africanum)* on primary specimens should be used only if: **D(GPP)**

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

R5 Clinicians should still consider a diagnosis of non-respiratory TB if rapid diagnostic tests are negative, for example in pleural fluid, CSF and urine. **B(DS)**

R6 Clinical signs and other laboratory findings consistent with TB meningitis should lead to treatment (see section 7.1), even if a rapid diagnostic test is negative, because the potential consequences for the patient are severe. **D(GPP)**

R7 Before conducting a large contact-tracing initiative (for example, in a school or hospital), the species of *mycobacterium* should be confirmed to be *M. tuberculosis* complex by rapid diagnostic tests on microscopy- or culture-positive material. Clinical judgement should be used if tests are inconclusive or delayed. **D(GPP)**

R8 If a risk assessment suggests a patient has MDR TB (see section 7.1): **D(GPP)**

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

R9 Rapid diagnostic tests for *M. tuberculosis* complex identification should be conducted on biopsy material only if: **D(GPP)**

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

Cross-referring:
For details of managing drug-susceptible TB, see chapters 6 and 7.
For details of managing drug-resistant TB, see chapter 9.

5.4 Rapid diagnostic tests: automated liquid culture

5.4.1 Clinical introduction

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

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

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

5.4.2 Methodological introduction

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

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

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

5.4.3 From evidence to recommendations

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

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

RECOMMENDATIONS

R10 Clinical samples should ideally be sent for culture by automated liquid methods, bearing in mind that laboratories need a certain level of throughput to maintain quality control. **D(GPP)**

6 Management of respiratory tuberculosis

6.1 Drug treatment

6.1.1 Clinical introduction

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

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

▷ Duration of treatment

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

▷ Dosing schedule

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

▷ Combination medicines

Adherence with drug treatment is a major determinant of the outcome of treatment.[72] As an aid to adherence, combination tablets of three drugs (rifampicin, isoniazid and pyrazinamide) are available for use in the two-month initial phase of treatment, and of two drugs (rifampicin and isoniazid) in the four-month continuation phase of treatment. The dosages in combination tablets however are those set for a daily dosing schedule. The other potential advantage of

combination tablets is that they prevent accidental or inadvertent single drug therapy which can lead to acquired drug resistance within weeks in active TB disease. Care however is needed in the prescribing and dispensing of TB drugs in the UK, because of the similarities in names between several of the drugs (see Table 8).

Table 8 Commonly confused generic and brand names

Drug(s)	Brand name
Rifampicin (called rifampin in USA)	Rimactane, Rifadin
Rifabutin	Mycobutin
Rifampicin + isoniazid	Rifinah, Rimactazid
Rifampicin + isoniazid + pyrazinamide	Rifater
Isoniazid	Rimifon (not marketed in UK)
Ibuprofen	Rimafen

▷ Enlarged hilar lymph nodes in children

Children with enlarged hilar lymph nodes that cause bronchial compression and collapse with respiratory distress frequently benefit from additional glucocorticoid therapy, although the evidence is limited.[73]

6.1.2 Current services

▷ Dedicated TB clinics

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

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

▷ Nurse-led follow-up clinics

The review of current services found that outside London, 31% of TB service providers had nurse-led follow-up clinics. The majority of these conducted some follow up at the patient's home. In London, 55% of TB service providers had nurse-led follow-up clinics. None of these followed up patients at home. Variation in the provision of these nurse-led follow-up clinics did

not seem to be explained by the caseload (notifications), staffing levels or presence of specialist personnel. It is impossible to conclude from our data whether the variation is appropriate to local epidemiology, geography or service models, but these are all factors that ought to have been considered in the design of the TB service.

▷ Specialist TB+HIV clinics

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

▷ Specialist paediatric TB clinics

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

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

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

▷ Outreach work

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

6.1.3 Methodological introduction

▷ Duration of treatment

A Cochrane systematic review[74] assessed the effects of regimens lasting less than six months, compared to any longer regimens in the treatment of active TB (eg studies could compare two months *vs.* four months or five months *vs.* eight months). Seven trials were included (three trials in India,[75–77] two trials in Hong Kong,[78,79] one trial in Singapore[80] and one in Germany[81]) and five of these studies compared regimens of less than six months with regimens of six months or more.

An additional RCT[82] was identified which compared a five-month regimen with a twelve-month regimen. However, this was excluded due to methodological limitations.

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

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

▷ Dosing schedule

A Cochrane systematic review[83] compared the effectiveness of rifampicin-containing short-course treatment regimens, given twice or thrice weekly, with similar regimens given daily in adult patients with pulmonary TB. Only one RCT performed in Hong Kong was included within the review.[84] The review[83] was methodologically sound; however as it only included one study, this was reviewed separately. This RCT[84] was excluded due to limitations in its methodology.

The Cochrane review included studies where the intermittent arm was any rifampicin-containing multiple drug regimen with a maximum nine month duration, administered up to three times a week with an initial daily dosing phase which could not exceed one month (this was termed 'fully intermittent'). Three further RCTs[85–87] and a cohort study[88] were identified using similar inclusion criteria, except in terms of the initial daily dosing phase which was broadened to cover studies where this could be two months long, in line with the usual initial intensive treatment phase. Studies could also be intermittent during the intensive phase. The cohort study[88] and one RCT[87] were excluded due to methodological limitations.

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

None of the studies identified were blinded. Certainly this may have been problematic to achieve in terms of study participants, however those assessing outcomes could potentially have been blinded to treatment allocations.

Very few studies have compared intermittent regimens with daily regimens. Where studies have been conducted, apart from issues of methodology, there are a number of other variables which

should be considered when attempting to compare studies and ascertain whether intermittent and daily regimens have equivalent effectiveness. These include whether the intermittent treatment was received during the intensive or continuation treatment phases or during both, the drugs and dosing regimens used, whether treatment was directly observed or self-administered and the frequency of the intermittent regimen (ie whether once, twice or thrice weekly).

There is little high-quality evidence in this area and none of the studies identified were performed in the UK. In particular, no robust evidence is available in HIV-positive individuals or children.

▷ Combination medicines

Six RCTs compared fixed dose combination tablets with single-drug formulation regimens.[91–96] All of the studies except one used a fixed dose combination tablet containing isoniazid, rifampicin and pyrazinamide. The exception was an Indonesian study[96] which compared a four-drug, fixed-dose regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol with single-drug formulations.

Four of the studies were excluded due to methodological limitations.[91,92,94,95]

Two studies were included, one preliminary study from Indonesia[96] and one study from China,[93] which followed patients up for two years to assess relapse. In both of these studies treatment was directly observed in all patients, which is not a standard service model in the UK.

6.1.4 Evidence statements

▷ Duration of treatment

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

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

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

▷ Dosing schedule

In a RCT performed in Africa and Asia,[86] a significantly higher proportion of patients assigned a directly observed daily regimen in the two-month intensive phase rather than a directly observed three times weekly regimen, were culture negative at two months (85% *vs.* 77%, p=0.001). (1++)

In a Brazilian RCT[85] there was no significant difference between self-administered six-month treatment regimens, where treatment was daily for the first two months and then either daily or twice weekly during the continuation phase, in terms of the number of bacterial failures or deaths during treatment. (1+)

The same study[85] also found no significant difference between daily and twice-weekly regimens in the continuation phase of treatment in terms of adherence (measured by pill counts), relapse rates at 12 months follow up or adverse events. (1+)

▷ Combination medicines

An Indonesian study[96] compared a four-drug, fixed-dose combination (isoniazid, rifampin, pyrazinamide and ethambutol) with the same drugs in separate formulations and found there was no significant difference in terms of sputum conversion at two months or cure, failure or defaulter rates. The difference in frequency of complaints during the intensive phase between the separate and combined drugs groups was significant in terms of gastrointestinal complaints (56% *vs.* 41% respectively, p<0.01) and muscle joint complaints (46% *vs.* 32% respectively, p=0.01). (1+)

In a comparison in China[93] of a six-month, three-drug, fixed-dose combination tablets (isoniazid, rifampin, pyrazinamide) regimen with the same drugs in separate formulations, at the end of two and six months of treatment, the bacteriological status of patients did not differ significantly in the two treatment groups as determined by examination of both sputum smear and culture. Bacterial relapse in those who completed treatment at two years was not significantly different between the two groups. 11.8% of patients in the combined drug group, and 15.5% of patients in the separate drugs group, experienced adverse reactions, most of which were insignificant and temporary. Patients in the combined drug group actually took 99.9% of their treatment doses whilst in the separate drug group, 97% of doses were taken. (1+)

6.1.5 From evidence to recommendations

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

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

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

No studies compared twice- or thrice-weekly treatment with daily treatment throughout a six-month regimen, but nevertheless the GDG agreed that twice- and thrice-weekly regimens, with appropriate dosage adjustments, are effective in the treatment of tuberculosis. A single-arm, twice weekly regimen, using rifabutin in HIV-positive individuals with active tuberculosis in the USA (CDC TB Trials Consortium Trial Number 23), was stopped because of the development of acquired rifamycin resistance.[100] In addition to this concern, the twice-weekly regimen is the absolute minimum dosage strategy, and the penalty of missed doses may be increased relapse or treatment failure. For this reason the thrice-weekly regimen, which has a greater safety margin for a few missed doses, is recommended.

Whilst being easier to supervise twice- or thrice-weekly treatment, the large number of different pills (necessarily given as separate formulations), particularly in the initial four-drug phase, can cause nausea and adversely affect adherence. Vomiting as a side effect of rifampicin can be reduced at dosages of 600 mg or more by being taken after breakfast. Flu-like syndromes are more common with intermittent as opposed to daily rifampicin treatment.

The dosages of combination tablets are set for once-daily treatment.

The cost to the patient of prescription charges is lower for combination tablets.

Few studies in the evidence base for combination medicines are free from methodological limitations. Only one study used the three-drug combination available in the UK.[93] Virtually all the data are from adult patients not known to be HIV positive, but the GDG felt that the conclusions can be extrapolated to children and HIV-positive individuals.

Given the benefits of combination tablets, and the key aim of treatment completion and adherence, the GDG recommended them.

RECOMMENDATIONS

R11 Once a diagnosis of active TB is made, the clinician responsible for care should refer the person with TB to a physician with training in, and experience of, the specialised care of people with TB. The TB service should include specialised nurses and health visitors. TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised physician. If these arrangements are not possible, advice should be sought from more specialised colleagues throughout the treatment period. **C**

R12 A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in:

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

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

R13 Fixed-dose combination tablets should be used as part of any TB treatment regimen. **C**

R14 A thrice-weekly dosing regimen should be considered for patients receiving DOT (see section 8.2). **D(GPP)**

R15 A twice-weekly dosing regimen should not be used for the treatment of active TB. **D(GPP)**

Cross-referring:
For details of DOT, see section 8.2.
For details of approaches to improve adherence, see section 8.3.
For details of managing drug-resistant TB, see chapter 9.

6.2 Infection control

6.2.1 Clinical introduction

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

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

6.2.2 Methodological introduction

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

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

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

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

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

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

6.2.3 From evidence to recommendations

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

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

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

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

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

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

RECOMMENDATIONS

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

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

R16 All patients with TB should have risk assessments for drug resistance (see section 9.1) and for HIV. If risk factors for MDR TB are present, see section 9.3 for recommendations on infection control. **D(GPP)**

R17 Unless there is a clear clinical or socioeconomic need, such as homelessness, people with TB at any site of disease should not be admitted to hospital for diagnostic tests or for care. **D(GPP)**

R18 If admitted to hospital, patients with suspected respiratory TB should be given a single room. **D(GPP)**

R19 Patients with respiratory TB should be separated from immunocompromised patients, either by admission to a single room on a separate ward, or in a negative pressure room on the same ward. **D(GPP)**

R20 Any visitors to a child with TB in hospital should be screened as part of contact tracing, and kept separate from other patients until they have been excluded as the source of infection. **D(GPP)**

R21 Smear-positive TB patients without risk factors for MDR TB (see section 9.1) should be cared for in a single room, until: **D(GPP)**

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

R22 Aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment should be carried out in an appropriately engineered and ventilated area for: **D(GPP)**

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

R23 Healthcare workers caring for people with TB should not use masks, gowns or barrier nursing techniques unless: **D(GPP)**

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

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

R24 TB patients admitted to a setting where care is provided for HIV-positive or other immunocompromised patients should be considered infectious and, if sputum smear-positive at admission, should stay in a negative pressure room until: **D(GPP)**

1. the patient has had at least two weeks of appropriate multiple drug therapy, *and*
2. if moving to accommodation (inpatient or home) with HIV-positive or immunocompromised patients, the patient has had at least three negative microscopic smears on separate occasions over a 14-day period, *and*
3. the patient is showing tolerance to the prescribed treatment and an ability and agreement to adhere to treatment, *and either*
4. any cough has resolved completely, *or*
5. there is definite clinical improvement on treatment, for example remaining afebrile for a week.

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

R25 Inpatients with smear-positive respiratory TB should be asked (with explanation) to wear a surgical mask whenever they leave their room until they have had two weeks' drug treatment. **D(GPP)**

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

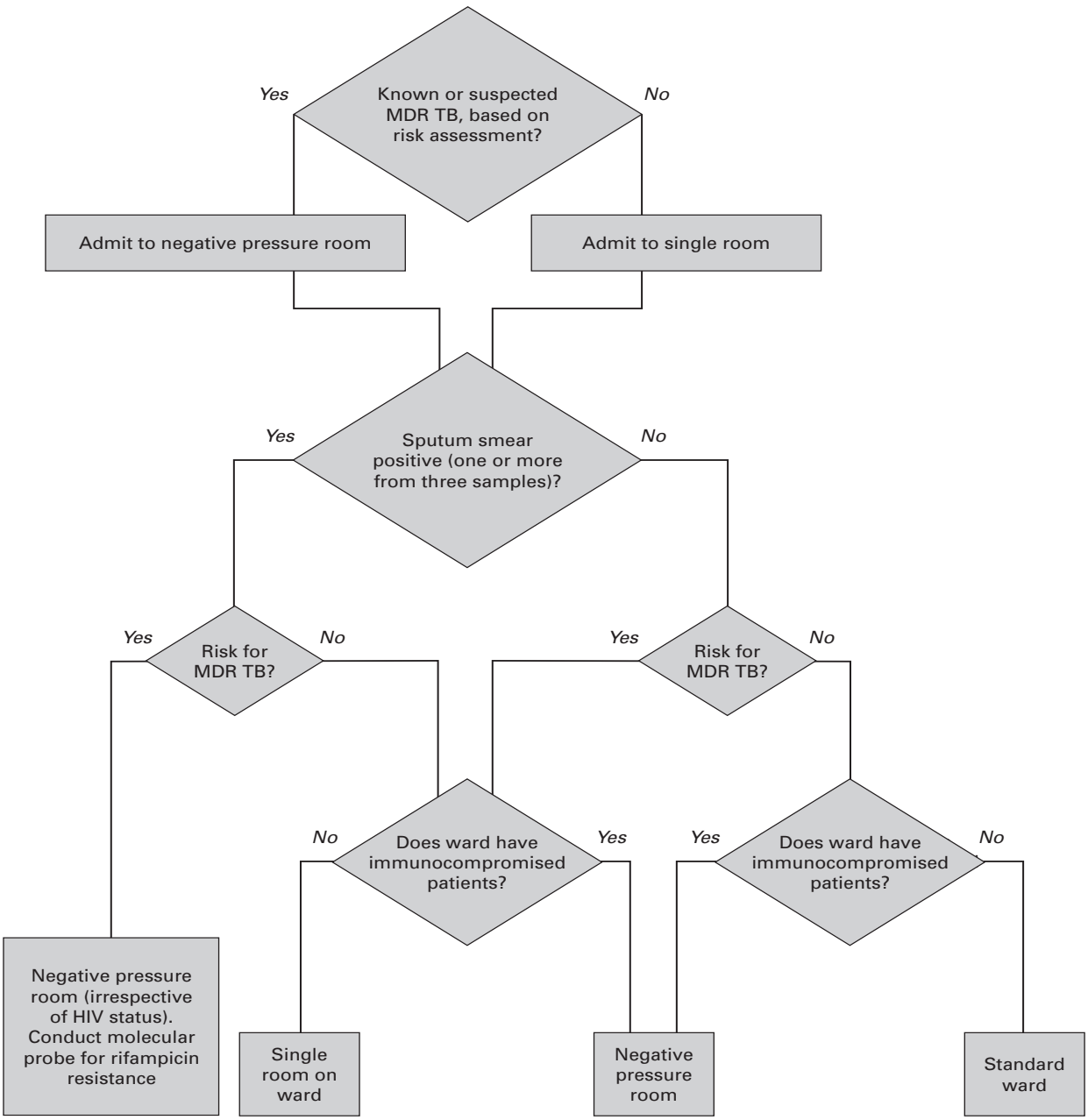

Figure 2: Algorithm showing isolation decisions for patients with suspected respiratory TB

7 Management of non-respiratory tuberculosis

7.1 Meningeal tuberculosis

7.1.1 Clinical introduction

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

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

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

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

7.1.2 Methodological introduction: duration of treatment in adults

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

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

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

7.1.3 Methodological introduction: duration of treatment in children

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

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

7.1.4 Methodological introduction: glucocorticoids as an adjunct to antituberculous drugs

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

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

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

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

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

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

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

7.1.5 Evidence statements

▷ Mortality and severe residual disability

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

▷ Disease severity and HIV status

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

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

▷ Adverse effects

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

7.1.6 From evidence to recommendations

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

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

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

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

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

RECOMMENDATIONS

R26 Patients with active meningeal TB should be offered:

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

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

R27 Clinicians prescribing treatment for active meningeal TB should consider as first choice:

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

Cross-referring:
For details of standard drug treatment, see section 6.1.
For details of managing drug-resistant TB, see chapter 9.

7.2 Peripheral lymph node tuberculosis

7.2.1 Clinical introduction

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

Trials by the BTS and its predecessors with regimens of 18 months,[134] nine months[134,135] and six months duration,[135–137] all showed a significant proportion of cases (up to 40%) to have residual nodes at the end of treatment, and up to 10% at 30 month follow-up. Sometimes new nodes and occasionally sinuses develop during treatment and/or during follow-up. Nearly all of these events are thought to be immunologically mediated responses to residual tuberculo-

proteins, and not failure to respond to treatment or relapses. When cultured there is seldom evidence of bacteriological activity.

7.2.2 Methodological introduction

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

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

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

7.2.3 Evidence statements

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

7.2.4 From evidence to recommendations

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

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

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

RECOMMENDATIONS

R28 For patients with active peripheral lymph node tuberculosis, the first choice of treatment should:

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

R29 Patients with active peripheral lymph node TB who have had an affected gland surgically removed should still be treated with the standard recommended regimen. **D(GPP)**

R30 Drug treatment of peripheral lymph node TB should normally be stopped after six months, regardless of the appearance of new nodes, residual nodes or sinuses draining during treatment. **D(GPP)**

Cross-referring:
For details of standard drug treatment, see section 6.1.
For details of managing drug-resistant TB, see chapter 9.

7.3 Bone and joint tuberculosis: drug treatment

7.3.1 Clinical introduction

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

7.3.2 Methodological introduction

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

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

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

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

7.3.3 Evidence statements

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

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

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

7.3.4 From evidence to recommendations

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

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

RECOMMENDATIONS

R31 The standard recommended regimen (see section 6.1 for details) should be planned and started in people with:

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

R32 Clinicians prescribing treatment for active bone and joint tuberculosis should consider as first choice:

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

See section 6.1 for details.

R33 CT or MR scan should be performed on patients with active spinal TB who have neurological signs or symptoms. If there is direct spinal cord involvement (for example, a spinal cord tuberculoma), management should be as for meningeal TB (see section 7.1). **D(GPP)**

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

7.4 Bone and joint tuberculosis: routine therapeutic surgery

7.4.1 Clinical introduction

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

7.4.2 Methodological introduction

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

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

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

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

7.4.3 Evidence statements

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

Whilst at ten years,[143] the surgery and six-months treatment regimen was less effective in terms of favourable status than the nine-month treatment regimen alone ($p=0.03$), the difference being due to surgical complications. However, patients in the surgery and anti-tuberculosis drug treatment group had a faster resolution of sinuses and/or clinically evident abscesses ($p<0.001$ at two months) and a lower incidence ($p=0.03$) than those in the anti-tuberculosis drug treatment only groups. There was no significant differences found between the groups in terms of occurrence of complete bony fusion or angle of kyphosis. There were four deaths associated with spinal tuberculosis (all within the first six months and all in the surgery and anti-tuberculosis drug treatment group). Three died in the postoperative period and the other had complications of postoperative paraplegia. (2++)

7.4.4 From evidence to recommendations

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

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

RECOMMENDATIONS

R34 In patients with spinal TB, anterior spinal fusion should not be performed routinely. **B**

R35 In patients with spinal TB, anterior spinal fusion should be considered if there is spinal instability or evidence of spinal cord compression. **D(GPP)**

7.5 Pericardial tuberculosis

7.5.1 Clinical introduction

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

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

7.5.2 Methodological introduction

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

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

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

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

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

7.5.3 Evidence statements

The results of RCTs performed in Transkei, South Africa, comparing prednisolone to placebo in pericardial effusion and pericardial constriction patients with or without drainage are presented in the table below.[158] Table 9 also includes the results of an RCT comparing prednisolone *vs.* placebo in HIV-positive pericardial effusion patients.[157]

Table 9 Summary of evidence for pericardial TB

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

7.5.4 From evidence to recommendations

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

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

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

RECOMMENDATIONS

R36 For patients with active pericardial TB, the first choice of treatment should:

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

R37 In addition to anti-TB treatment, patients with active pericardial TB should be offered:

- for adults, a glucocorticoid equivalent to prednisolone at 60 mg/day **A**
- for children, a glucocorticoid equivalent to prednisolone 1 mg/kg/day (maximum 40 mg/day), with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation. **D(GPP)**

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

7.6 Disseminated (including miliary) tuberculosis

7.6.1 Clinical introduction

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

These different labels for forms of what is essentially blood-borne spread of tuberculosis can cause confusion. Essentially, blood-borne spread may or may not be accompanied by chest X-ray or high-resolution CT changes. Such blood-borne spread often also causes significant liver function derangement because of diffuse liver involvement. This is a serious form of TB with a

significant morbidity and mortality, so the risks of treating the disease with drugs which have a low incidence of hepatic side effects (3%), are much less than those of leaving the patient inadequately treated. The meninges are also not infrequently involved as part of the blood-borne spread, with up to 30% having clinical or lumbar puncture evidence of such involvement.[140] The detection of CNS disease is important because of the longer duration of treatment required for CNS involvement.

7.6.2 Methodological introduction

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

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

7.6.3 From evidence to recommendations

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

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

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

RECOMMENDATIONS

R38 For patients with disseminated (including miliary) TB, the first choice of treatment should:

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

R39 Treatment of disseminated (including miliary) TB should be started even if initial liver function tests are abnormal. If the patient's liver function deteriorates significantly on drug treatment, advice on management options should be sought from clinicians with specialist experience of these circumstances. **D(GPP)**

R40 Patients with disseminated (including miliary) TB should be tested for CNS involvement by:

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

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

Cross-referring:

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

7.7 Other sites of infection

7.7.1 From evidence to recommendations

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

RECOMMENDATION

R41 For patients with:

- active genitourinary TB, or
- active TB of any site other than:
  - respiratory system
  - CNS (typically meninges)
  - peripheral lymph nodes
  - bones and joints
  - pericardium
  - disseminated (including miliary) disease

the first choice of treatment should:

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

Cross-referring:

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

8 Monitoring, adherence and treatment completion

8.1 Treatment completion and follow-up

8.1.1 Clinical introduction

In the UK, when the recommended regimen has been given to patients with fully susceptible organisms, the rate of relapse is low (0–3%) in both trial[69] and clinical practice conditions,[160] if there has been good adherence with treatment. Under these circumstances, it is important to know whether routine follow-up after treatment completion is cost-effective in detecting relapse.

8.1.2 Methodological introduction

No studies were identified which compared the detected relapse rates of previously treated TB patients who were subject to routine follow-up, with a group who did not receive routine follow-up.

However, there were five case series which reported the proportion of relapsing patients who were identified as a relapse case during routine follow-up appointments and the number of cases who self-referred outside routine follow-up due to onset of symptoms or who were referred by their general practitioner (GP) or detected after an admission for another initial diagnosis. Two studies were conducted in the UK,[161,162] two in the USA[163,164] and one in India.[165]

Many of the studies found were performed 20 to 30 years ago, prior to the advent of modern treatment regimens. These studies generally concluded that routine follow-up was unnecessary, which may explain the dearth of studies on routine follow-up for previously treated TB patients since this time. In addition, the definition of relapse varied across studies and in all the studies (apart from one where it is not clear[164]) only patients with pulmonary TB were included.

8.1.3 Evidence statements

▷ Detection by routine follow-up

In five case series studies of previously treated TB patients found to have relapsed, the percentage detected at routine follow-up clinic attendances were 27%,[165] 35%,[164] 40%,[163] 51%[161] and 58%[162] (one study[165] only included patients who had completed treatment). (**3**)

One study calculated that routine surveillance of 1,000 patients who had completed treatment would help to identify approximately six relapses in one year[165] whilst a yield of 0.6% of relapse cases detected from routine follow-up was calculated in another study.[164] (**3**)

▷ Rate of relapse

In a UK study the relapse rate at five years since the start of treatment was 3.5%.[162] In another study 4% of patients with active TB added to a TB register over a 7.5-year period had been diagnosed with reactivated disease[163] whilst in the Indian study the authors calculated a cumulative relapse rate of 11.6% at five years in patients who completed treatment.[165] (**3**)

▷ Risk factors for relapse

Of the patients who relapsed in a UK study, 82% discharged themselves prematurely from hospital and/or terminated their own treatment.[162] In another study 75% of relapsed patients over a 7.5-year period had a combined treatment regimen which was self-interrupted or self-discontinued and a further 14% received no treatment or streptomycin only.[163] An Indian study[165] found the main reason for prolongation of treatment was irregular drug taking during the course of treatment. Patients who completed their course of treatment in less than 24 months had an overall relapse rate of 4.09 % in five years; those who required 24 to 30 months had a cumulative relapse rate of 10.85% ($p<0.05$). (**3**)

In a group of relapsed chronic sputum-positive patients, 57% had inadequate duration of treatment regimen (less than 18 months) and a further 23% had adequate duration but irregular treatment.[161] In another study 61% of relapsed patients were not treated for the recommended treatment duration of 18 months.[162] Of a group of relapsed patients detected during routine follow-up, 49% had inadequate treatment (<1 year) with an effective regimen, or interruption of treatment serious enough to make the possibility of at least one year of continuous treatment unlikely.[164] Of these relapsed patients, 94% were found to have 'complicating factors' which included inadequate therapy, alcoholism or poor cooperation. (**3**)

In one study[162] the relapse rate in men was nearly twice that in women and was also higher in patients over 45 years. The relapse rate did not seem to be related to the extent of the disease. In another study of treatment completion patients the cumulative five-year relapse rate did not differ significantly between men and women or in terms of age or extent of initial disease, initial cavitary status or presence of drug-resistant bacilli.[165] (**3**)

The mean time between last positive sputum smear and relapse in patients treated after 1955 (when adequate therapy was employed) was 7.5±4.88 years.[161] (**3**)

8.1.4 From evidence to recommendations

All patients should receive 'inform and advise' information upon treatment completion. They should then inform other healthcare professionals, who may provide or organise their care in the future, of their history of latent TB or disease.

Routine follow-up was felt to be necessary for MDR TB, and worth considering for isoniazid-resistant TB, because these patients have received non-standard treatment with a potentially higher relapse rate.

The GDG felt that regular follow-up clinic visits were unnecessary. Patients should be advised to be alert to symptoms and to contact the TB service rapidly.

RECOMMENDATIONS

R42 Follow-up clinic visits should not be conducted routinely after treatment completion. **D**

R43 Patients should be told to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic. Key workers should ensure that patients at increased risk of relapse are particularly well informed about symptoms. **D(GPP)**

R44 Patients who have had drug-resistant TB should be considered for follow-up for 12 months after completing treatment. Patients who have had MDR TB should be considered for prolonged follow-up. **D(GPP)**

Cross-referring:
For examples of 'inform and advise' information, see Appendix F.

8.2 Improving adherence: directly observed therapy

8.2.1 Clinical introduction

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

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

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

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

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

8.2.2 Current practice

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

8.2.3 Methodological introduction

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

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

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

None of the studies identified were performed in the UK.

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

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

- a volunteering community member selected by a village leader who was interviewed and trained by a health worker, compared with observation by a health worker in the nearest health centre[185]

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

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

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

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

8.2.4 Evidence statements

▷ Efficacy of DOT

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

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

In illegal immigrants on prophylaxis for latent TB[174] in Italy, those on supervised (directly observed clinic-based) treatment were significantly less likely to complete treatment than did those on an unsupervised regimen (p=0.006, log rank test). Treatment completion rates were 7.3% in the supervised group and 26% in the unsupervised group. (**1++**)

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

▷ Observers for DOT

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

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

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

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

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

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

8.2.5 From evidence to recommendations

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

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

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

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

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

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

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

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

RECOMMENDATIONS

R45 Use of DOT is not usually necessary in the management of most cases of active TB. **A**
All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

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

R46 Clinicians who are planning to start a patient on a course of DOT should consider ways to mitigate the environmental, financial and psychosocial factors that may reduce adherence, including stability of accommodation, prescription charges and transport. The setting, observer and frequency of treatment should be arranged to be most practicable for the person with TB. The person with TB and his or her assigned key worker should be involved in deciding these arrangements. DOT should also be supported by frequent contact with the key worker (see 8.3). **D(GPP)**

8.3 Improving adherence: non-pharmacological strategies

8.3.1 Clinical introduction

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

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

8.3.2 Current practice

▷ Improving adherence

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

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

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

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

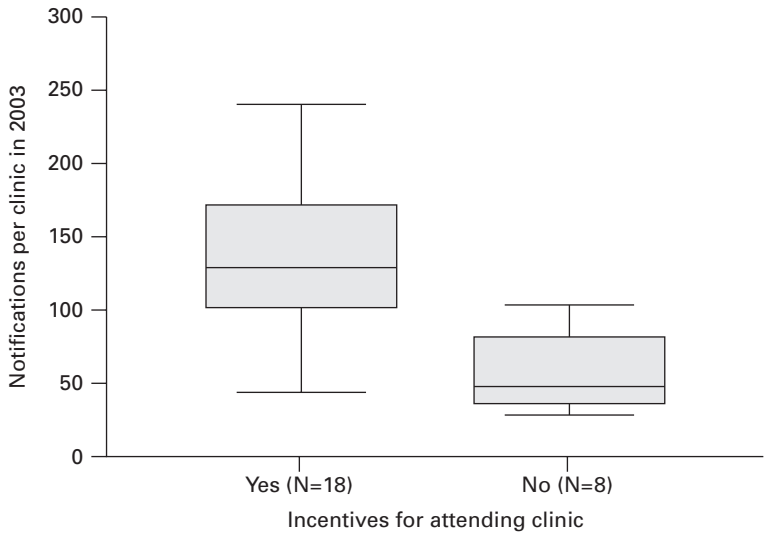

Figure 3: Box plot of notifications of TB per clinic in London, by use of incentives

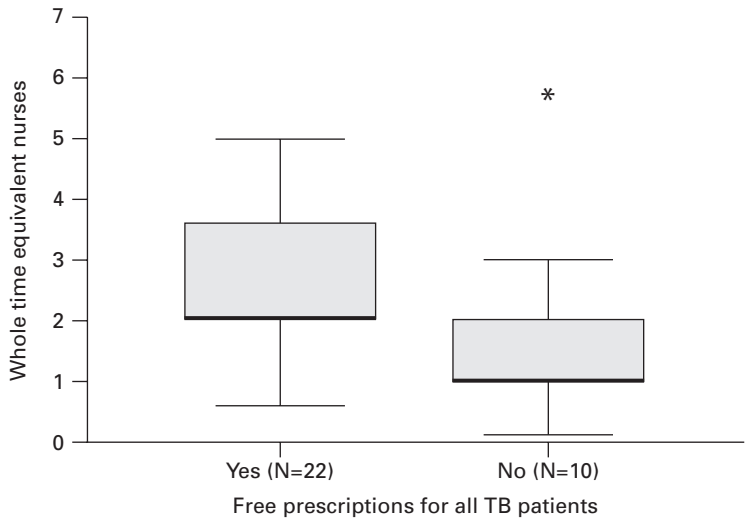

Figure 4: Box plot of notifications of TB per clinic in London, by use of free prescriptions

▷ Outreach work

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

8.3.3 Methodological introduction: adherence among patients on treatment for active TB

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

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

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

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

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

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

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

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

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

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

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

8.3.5 Evidence statements

▷ Active disease

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

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

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

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

▷ Latent infection

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

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

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

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

8.3.6 From evidence to recommendations

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

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

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

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

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

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

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

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

RECOMMENDATIONS

R47 To promote adherence, patients should be involved in treatment decisions at the outset of treatment for active or latent TB. The importance of adherence should be emphasised during discussion with the patient when agreeing the regimen. **D(GPP)**

R48 The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. **D(GPP)**

R49 TB services should consider the following interventions to improve adherence to treatment for active or latent TB if a patient defaults:

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

R50 Pharmacies should make liquid preparations of anti-TB drugs readily available to TB patients who may need them – for example children and people with swallowing difficulties. **D(GPP)**

R51 TB services should assess local language and other communication needs and, if there is a demonstrated need, provide patient information accordingly.* **D(GPP)**

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

9 Risk assessment and infection control in drug-resistant TB

9.1 Risk factors

9.1.1 Clinical introduction

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

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

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

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

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

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

9.1.2 Methodological introduction

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

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

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

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

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

9.1.3 Evidence statements

All evidence statements are graded level 2+.

Table 10 Risk factors

Study	Association
Age as a risk factor	
UK national surveillance study[213] (N=25,217)	A slightly higher proportion of isoniazid resistance (7.6%) was observed in those aged 15–44 years than in other age groups. This was significantly higher than in those aged >44 years for isoniazid resistance only and significantly higher than in those aged >65 years for MDR TB.
UK study based in one London hospital[214] (N=121)	Patients with drug-resistant TB were younger than those with drug-sensitive TB (OR 1.03, 95%CI 1.02 to 1.05, p<0.001). The mean age of those with resistance to more than one first-line drug was 40 years, resistance to only one first-line drug was 32 years and drug-sensitive TB was 47.4 years.
National US study[221] (N=67,340)	Those who were younger than 65 years were at increased risk of drug resistance to at least isoniazid with adjusted OR 1.7 (95%CI 1.4 to 2.2) for those aged 0–14 years, 2.0 (95%CI 1.8 to 2.2) for those aged 15–24 years, 1.8 (95%CI 1.6 to 1.9) for ages 25–44 years and 1.4 (95%CI 1.3 to 1.6) for those aged 45 to 64 years.

continued

Table 10 Risk factors – *continued*

Study	Association
Age as a risk factor – *continued*	
National surveillance study in Switzerland[224] (N=1,056)	An increased risk of resistance to any first-line drug was associated with being <65 years of age (adjusted OR 1.5, 95%CI 1.0 to 2.3).
National surveillance study in the Netherlands[223] (N=1,836), a surveillance study in Kenya[218] (N=491) and two South African studies[219,220] (N=7,266 and N=275 respectively)	No significant association was found between age and drug resistance.
Prior treatment history as a risk factor	
UK national surveillance study[213] (N=25,217)	Those reported to have had a previous episode of TB, exhibited a significantly higher proportion of resistance to at least isoniazid (15.5%) and MDR (9.4%) than either those patients who had never had TB (5.7% and 0.8% respectively), or those whose history regarding previous TB was not available (4.9% and 0.7%, respectively; p<0.001 (isoniazid resistance); p<0.001 (MDR)).
UK study of TB patients in England and Wales reported during two time periods (1993 to 1994 and 1998 to 2000)[216] (N=9,541)	There was a strong association between previous treatment and MDR TB (OR 9.1, 95%CI 6.3 to 13.2). This overall relationship was weaker for isoniazid resistance (OR 1.6, 95%CI 1.2 to 2.1).
UK study based in one London hospital[214] (N=121)	The highest risk for resistance to any drug was associated with previous treatment for TB (OR 22.85, 95%CI 5.1 to 102.5; p<0.001).
UK study in Leicestershire[215] (N=104)	Previous history of TB (OR 3.7, 95%CI 1.2 to 11.8, p=0.022) was significantly associated with resistance to at least one first line drug.
National US study[221] (N=67,340)	For resistance to any drugs and the combination of isoniazid and rifampin (MDR TB), the rate of resistance was higher among patients with prior TB compared with those without prior TB (p<0.05). Those with prior TB were at increased risk of resistance to at least isoniazid with an adjusted OR of 2.6 (95%CI 2.4 to 2.9).
French national surveillance study[222] (N=2,998)	An increased risk of resistance to any drug (OR 2.7, 95%CI 2.0 to 3.8) and MDR TB (OR 10.2, 95%CI 4.1 to 25.3) was associated with previous history of treatment. Similarly, unknown treatment history was associated with an increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.5) and MDR TB (OR 3.4, 95%CI 1.1 to 11.2).
National surveillance study in the Netherlands[223] (N=1,836)	Rates of acquired resistance (those who had been previously treated for TB) to isoniazid alone (11.4%) and isoniazid and rifampicin (MDR TB, 5.7%) were higher than rates of primary resistance (those who had never been diagnosed with TB before) to these drugs (5.2% and 0.7% respectively, p<0.05)
National surveillance study in Switzerland[224] (N=1,056)	An increased risk of resistance to any first-line drug was associated with previous history of treatment (adjusted OR 7.3, 95%CI 3.9 to 13.6).
Surveillance study of 26 districts in Kenya[218] (N=491)	Of 90.6% of patients with no history of previous treatment, 6.3% had a resistant strain while of 9.4% with a previous history of anti-tuberculosis drug treatment, 37% had a resistant strain (p<0.005).

continued

Table 10 Risk factors – *continued*

Study	Association
Prior treatment history as a risk factor – *continued*	
South African study analysing rates of drug resistance in the West Cape region[219] (N=7,266)	Patients with a history of TB treatment were found to be at an increased risk of developing drug resistance (RR 2.6).
South African study based in one hospital[220] (N=275)	No significant association was found between previous treatment history and drug resistance.
Previous TB status in addition to other risk factors	
In a UK study of TB patients reported during two time periods (1993 to 1994 and 1998 to 2000)[216] (N=9,541)	In those with previous TB, significant risk factors for isoniazid resistance were smear positive status (OR 3.2, 95%CI 1.1 to 9.2) and being of non-UK origin but arriving in the UK in the past 10 years (OR 3.2, 95%CI 1.4 to 7.0). This was similar for MDR TB where the most significant risk factors were smear positive disease (OR 5.9, 95%CI 1.8 to 19.0) and non-UK origin – particularly those who had arrived in the last five years in whom the risk compared with UK-born was approximately sixfold (OR=0.58, 95%CI 1.8 to 18.5). In those without previous TB, significant risk factors for isoniazid resistance were London residence (OR 1.4, 95%CI 1.1 to 1.7), being HIV positive (OR 2.4, 95%CI 1.1 to 5.2) although this was only significant in 1993 to 1994 (OR 2.4, 95%CI 1.1 to 5.2), and ethnicity. Compared with the white ethnic group, adjusted odds ratios were similar in people of Indian (subcontinent) origin (OR 1.6, 95%CI 1.2 to 2.1), people of black African origin (OR 1.7, 95%CI 1.2 to 2.4) and other ethnic groups combined (OR 1.9, 95%CI 1.3 to 2.8). For MDR TB the most significant risk factors were being HIV positive (OR 2.5, 95%CI 1.2 to 5.2) and London residence (OR 2.0, 95%CI 1.2 to 3.3). Birth outside the UK was also important, with the risk of MDR TB higher for those arriving in the last five years (OR 3.2, 95%CI 1.4 to 7.3).
Ethnicity as a risk factor	
UK national surveillance study[213] (N=25,217)	Among the three ethnic groups from whom substantial numbers of isolates were received, the highest proportion of resistance to at least isoniazid and MDR TB was reported in isolates from people of black African origin (10.1% and 2.0% respectively) with 7.2% and 1.4% in those originating from the Indian subcontinent, and 4.1% and 1.4% in those of white ethnic origin. Resistance to at least isoniazid was significantly different between all three ethnic groups ($p<0.001$).
UK study based in one London hospital[214] (N=7,266), Kenyan study[218] (N=491), South African study[219] (N=7,266)	No significant association was found between Caucasian and non-Caucasian ethnicity and drug resistance[214] and in the other two studies similarly no association was found between drug resistance and ethnic group.
Gender as a risk factor	
UK national surveillance study[213] (N=25,217)	The proportion of those resistant to at least isoniazid was higher in men (5.9%) than in women (5.4%), although the difference was not significant. However, men were significantly more likely to have MDR TB (1.4% *vs*. 0.9%, $p<0.001$).
National surveillance study in Switzerland[224] (N=1,056)	Increased risk of resistance to any first-line drug was associated with male sex (adjusted OR 1.4, 95%CI 1.1 to 2.0).

continued

Table 10 Risk factors – *continued*

Study	Association
Gender as a risk factor – *continued*	
UK study based in one London hospital[214] (N=121), national surveillance study in the Netherlands[223] (N=1,836), Kenyan study[218] (N=419), two South African studies[219,220] (N=7,266 and N=275 respectively)	No association was found between drug resistance and gender.
Place of birth as a risk factor	
UK national surveillance study[213] (N=25,217)	People born outside the UK were significantly more likely to have resistance to at least isoniazid than those born in the UK (9.1% *vs*. 4.2%, OR 2.27, p<0.001). Similarly, 2.0% of people born outside the UK had an MDR isolate compared with 1.0% of those born in the UK (OR 1.97, p<0.001).
National US study[221] (N=67,340)	Foreign-born cases had significantly higher rates of resistance to isoniazid (12.4% *vs*. 6.4%, p<0.05) and streptomycin (10.0% *vs*. 4.3%, p<0.05) than US-born case patients but similar rates of rifampin resistance (3.1% *vs*. 2.9%) and MDR TB (2.4% *vs*. 2.0%). Those who were foreign born were at increased risk of resistance to at least isoniazid with an adjusted OR 1.5, 95%CI 1.4 to 1.6.
French national surveillance study[222] (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.3 to 2.2) and MDR TB (OR 2.7, 95%CI 1.1 to 6.2) was associated with foreign birth.
National surveillance study in the Netherlands[223] (N=1,836)	Drug resistance was reported in 9% of patients born in the Netherlands and in 18% of foreign-born TB patients (p<0.001).
National surveillance study in Switzerland[224] (N=1,056)	Foreign-born patients showed a slightly but not significantly elevated risk of resistance (adjusted OR 1.5, 95%CI 0.8 to2.8).
Two UK studies, (N=121)[214] (N=104)[215] and a Kenyan study [218] (N=491)	Drug resistance was not associated with foreign birth.
Place of diagnosis as a risk factor	
UK national surveillance study[213] (N=25,217)	Compared with other English NHS regions and Scotland, Northern Ireland and Wales, patients diagnosed in London were more likely to have isolates resistant to at least isoniazid (7.6% *vs*. 4.6%, p<0.001). Similarly, patients from London were more likely to have MDR isolates (1.7% *vs*. 0.9%, p<0.0001).
HIV status as a risk factor	
UK national surveillance study[213] (N=25,217)	Those known to be co-infected with HIV were more likely to be either resistant to at least isoniazid (11.6% *vs*. 5.5%) or be MDR (4.6% *vs*. 1.1%) than those from people of unknown or negative HIV infection status (p<0.001 (isoniazid resistance); p=<0.001 (MDR)).
National US study[221] (N=67,340)	For all drugs, resistance was significantly higher (p<0.05) in HIV-positive *vs.* HIV-negative patients and HIV-positive *vs*. those with unknown status, except for patients with isolates resistant to ethambutol. Those who were HIV positive were at increased risk of resistance to at least isoniazid with an adjusted OR 1.6 (95%CI 1.4 to 1.8).

continued

Table 10 Risk factors – *continued*

Study	Association
HIV status as a risk factor – *continued*	
French national surveillance study[222] (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.4) was associated with HIV positive status however an association was not found for MDR TB.
National surveillance study in the Netherlands[223] (N=1,836)	HIV positivity was more frequently reported in the drug-resistant group than in the drug-susceptible group (7.7% *vs*. 4.9%) but this difference was not significant.
South African study based in one hospital[220] (N=275)	No significant association was found between HIV status and drug resistance.
History of poor treatment adherence as a risk factor	
UK study in Leicestershire[215] (N=104)	Poor adherence (OR 4.8, 95%CI 1.4 to 14.4, p=0.005) was significantly associated with resistance to at least one first-line drug.
Other risk factors	
UK study based in one London hospital[214] (N=121)	Bilateral disease at presentation was associated with drug resistance (OR 8.5, 95%CI 2.1 to 35.0, p<0.005) but not with recent entry to the UK for foreign-born patients, alcoholism, psychological disturbances, homelessness, living in care homes or poor understanding of the English language (although for many of these risk factors patient numbers identified were very small).
UK study in Leicestershire[215] (N=104)	No significant associations were found between site of TB, foreign travel or recent immigration and resistance to at least one first-line drug (although it should be noted that only a small number of participants had these risk factors).
In a national surveillance study in the Netherlands[223] (N=1,836)	Asylum seekers diagnosed on arrival in the Netherlands showed an increased risk of resistance to any drug with 4.8% of cases in the drug-susceptible group and 10.4% in the drug-resistant group (p<0.001). With regard to site of disease and other clinical features (diabetes, malignancy and pregnancy) and a number of other risk groups (sailors, travellers, illegal immigrants, the homeless, alcohol users, drug users, prisoners and healthcare workers), no differences were observed between the groups.

9.1.4 From evidence to recommendations

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

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

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

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

3. HIV infection.
4. Residence in London.
5. Age profile, with highest rates between the ages of 25 and 44 years.
6. Male gender.

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

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

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

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

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

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

RECOMMENDATIONS

R52 A risk assessment for drug resistance should be made for each patient with TB, based on the risk factors listed below: **C**

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

R53 The TB service should consider the risk assessment for drug resistance and, if the risk is regarded as significant, urgent molecular tests for rifampicin resistance should be performed on smear-positive material or on positive cultures when they become available (see section 5.2). **D(GPP)**

R54 Response to treatment should be closely monitored in patients at increased risk of drug resistance. If there is no clinical improvement, or if cultures remain positive after the fourth month of treatment ('treatment failure'), drug resistance should be suspected and treatment reviewed with a clinician experienced in the treatment of MDR TB. **D(GPP)**

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

* Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

9.2 Referral

9.2.1 Clinical introduction

MDR TB comprises some 0.8–0.9% of culture-confirmed TB cases in the UK, mainly in England and Wales.[140] As such they represent only 30–40 cases per year in number, but they have disproportionate importance because of:

- a prolonged infectious potential in pulmonary disease
- the need for higher levels of infection control, with negative pressure ventilated side wards, because of this and the potential adverse effects of acquiring the organism
- a much greater cost to treat, a minimum of £50–70,000 per case[211]
- prolonged treatment, often requiring multiple second-line drugs with an increased toxicity profile
- worse cure and survival rates, in both HIV-negative and HIV-positive individuals[226–230]
- the risk to healthcare workers and other contacts if they become infected.

Because treatment is complex, time consuming and demanding on both the patient and the physician, practice to date, based on BTS guidelines for treatment,[68] has been that treatment is only carried out:

- by physicians with substantial experience in drug-resistant TB
- in hospitals with appropriate isolation facilities (a negative pressure room)
- in close conjunction with the HPA and HPA regional centres for mycobacteriology.

Clinical management of these cases is not addressed by this guideline, as it is a rare, highly specialised and highly individualised activity, which may include second-line drugs, close monitoring, full supervision of treatment and surgical options. It is therefore the concern of this guideline to promote transfer of patients to an appropriate unit.

9.2.2 Methodological introduction

A retrospective cohort study[231] performed in the USA was identified, which examined the treatment experience of patients diagnosed with MDR TB who were managed for at least part of their time on treatment in a specialist TB hospital. This study was excluded due to limitations in the methodology.

No studies of sufficient quality were found pertaining to whom (or where) MDR TB patients should be referred in order for them to achieve the most favourable treatment outcomes. Therefore, no evidence statements have been made in this section.

9.2.3 From evidence to recommendations

The GDG were aware that there are still relatively few cases of MDR TB in the UK each year, but noted that this represents a vitally important area in TB control and a unique challenge for treatment. The GDG felt that treatment failure (non-concordance) is a significant risk factor for drug resistance.

People with MDR TB are not always treated under the care of an MDR TB specialist. It was felt that there had been no evidence to support change in current practice in MDR TB referral since the BTS's code of practice.[6]

Patient acceptability and shared care arrangements need to be considered when arranging referral, and hence this section gives recommendations for discussing and consulting with specialist colleagues.

RECOMMENDATION

R55 The options for organising care for people with MDR TB should be discussed with clinicians who specialise in this. The views of the patient should be sought and taken into account, and shared care should be considered. **D(GPP)**

9.3 Infection control

9.3.1 Clinical introduction

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

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

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

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

9.3.2 Current practice

The review of current services collected the number of negative pressure units in service providers and aggregated these within HPU areas. There appears to be a positive relationship between the number of negative pressure units and number of notifications (see Figure 5).

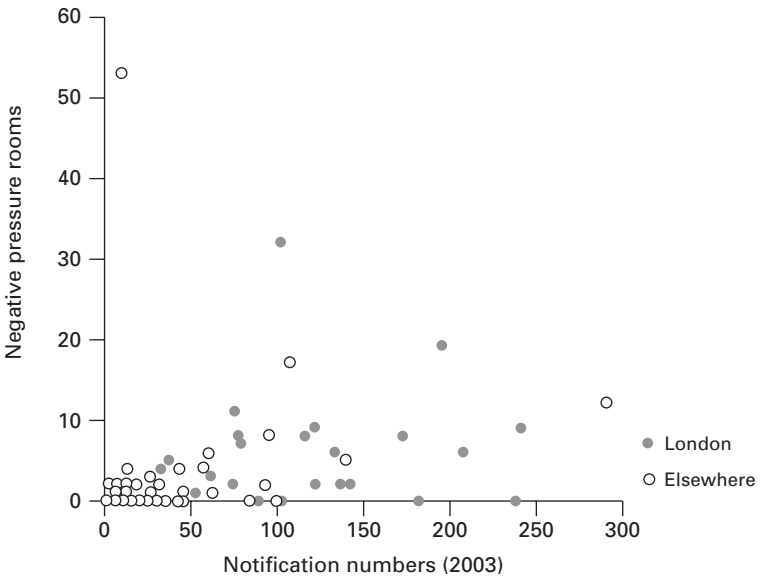

Figure 5: Negative pressure rooms *vs.* notified cases of TB per service provider

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

9.3.3 Methodological introduction

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

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

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

9.3.4 Evidence statements

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

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

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

9.3.5 From evidence to recommendations

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

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

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

RECOMMENDATIONS

R56 Patients with suspected or known infectious MDR TB who are admitted to hospital should be admitted to a negative pressure room. If none are available locally, the patient should be transferred to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases. Care should be carried out in the negative pressure room until the patient is found to be non-infectious or non-resistant, and ideally until cultures are negative. **D(GPP)**

R57 Staff and visitors should wear FFP3 masks,* during contact with a patient with suspected or known MDR TB while the patient is considered infectious. **D(GPP)**

* European standard EN149:2001; masks should meet the standards in the Health and Safety Executive's *Respiratory protective equipment at work: a practical guide HSG53.*[385]

R58 Before the decision is made to discharge a patient with suspected or known MDR TB from hospital, secure arrangements for the supervision and administration of all anti-TB therapy should have been agreed with the patient and carers. **D(GPP)**

R59 The decision to discharge a patient with suspected or known MDR TB should be discussed with the infection control team, the local microbiologist, the local TB service, and the consultant in communicable disease control. **D(GPP)**

R60 Negative pressure rooms used for infection control in MDR TB should meet the standards of the Interdepartmental Working Group on Tuberculosis,[386] and should be clearly identified for staff, for example by a standard sign. Such labelling should be kept up to date. **D(GPP)**

Cross-referring:
For details of contact tracing in hospital in-patients, see section 12.7.
Also see the algorithm in section 6.2.

9.4 Treatment of non-MDR TB resistance

9.4.1 Clinical introduction

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

▷ Isolated streptomycin resistance

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

▷ Isolated isoniazid resistance

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

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

▷ Isolated pyrazinamide resistance

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

▷ Isolated ethambutol resistance

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

▷ Isolated rifampicin resistance

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

▷ Combined streptomycin and isoniazid resistance

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

▷ Other non-MDR TB combinations

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

RECOMMENDATION

R61 Patients with drug-resistant TB, other than MDR, should be under the care of a specialist physician with appropriate experience in managing such cases. First-choice drug treatment is set out in Table 11.

Table 11 Recommended regimens for non-MDR drug-resistant TB

Drug resistance	Initial phase	Continuation phase
S	2RHZE	4RH
H known prior to treatment	2RZSE	7RE
H found after starting treatment	2RZE	10RE
Z	2RHE	7RH
E	2RHZ	4RH
R (only if confirmed isolated resistance)	2HZE	16HE
S+H	2RZE	10RE
Other	Individualised	

See Appendix B for details of the system of drug regimen abbreviations

10 Management of latent tuberculosis

10.1 Treatment regimens for latent tuberculosis infection

10.1.1 Clinical introduction

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

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

10.1.2 Current practice

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

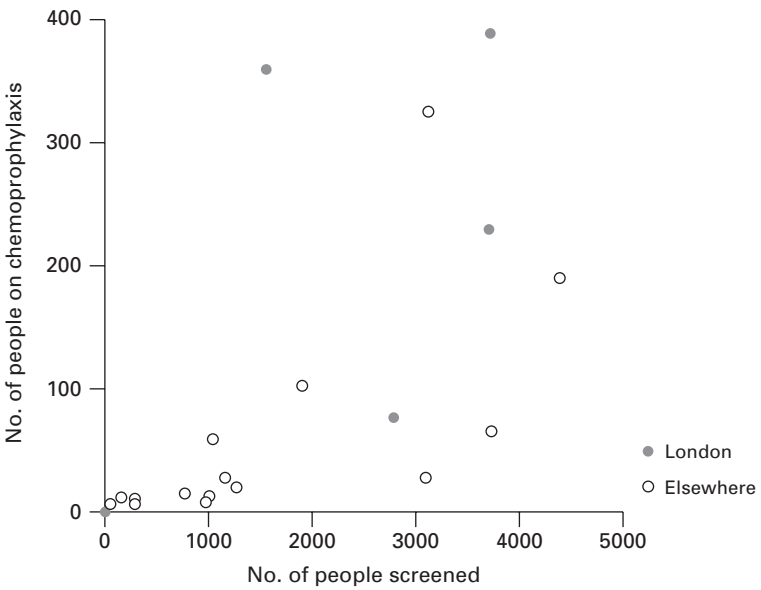

Figure 6: Correlation of people screened against people given treatment for latent TB infection (chemoprophylaxis)

10.1.3 Methodological introduction

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

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

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

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

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

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

10.1.4 Evidence statements

▷ Efficacy

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

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

▷ Treatment completion

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

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

▷ Adverse events

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

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

▷ Children

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

▷ People with HIV: development of active TB

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

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

▷ People with HIV: all-cause mortality

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

▷ People with HIV: incidence of adverse drug reactions

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

10.1.5 From evidence to recommendations

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

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

In 2000 a regimen of rifampicin and pyrazinamide for two months (2RZ) was recommended for treatment for latent TB infection in the USA.[248] In the UK, although this 2RZ regimen was

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

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

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

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

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

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

RECOMMENDATIONS

R62 Treatment of latent TB infection should be considered for people in the following groups, once active TB has been excluded by chest X-ray and examination: **D(GPP)**

- people identified through screening who are:
  - younger than 36 years (because of increasing risk of hepatotoxicity with age)
  - any age with HIV
  - any age and a healthcare worker

  and are either:
  - Mantoux positive (6 mm or greater), and without prior BCG vaccination, *or*
  - strongly Mantoux positive (15 mm or greater), interferon-gamma positive, and with prior BCG vaccination
- children aged 1–15 years identified through opportunistic screening, to be:
  - strongly Mantoux positive (15 mm or greater), *and*
  - interferon-gamma positive (if this test has been performed), *and*
  - without prior BCG vaccination

- people with evidence of TB scars on chest X-ray, and without a history of adequate treatment.

R63 People with HIV who are in close contact with people with sputum smear-positive respiratory TB should have active disease excluded and then be given treatment for latent TB infection. Mantoux testing may be unreliable in people with HIV. **D(GPP)**

R64 Treatment for latent TB infection should not be started in close contacts* of people with sputum smear-positive MDR TB who are strongly Mantoux positive (15 mm or greater), as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease. Long-term monitoring should be undertaken for active disease. **D(GPP)**

R65 People who have agreed to receive treatment for latent TB infection should be started on one of the following regimens: **C**

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

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

R66 Neonates who have been in close contact with people with sputum smear-positive TB who have not received at least two weeks' anti-tuberculosis drug treatment should be treated as follows. **D(GPP)**

- ❑ The baby should be started on isoniazid 5 mg/kg for three months and then a Mantoux test performed after three months' treatment.
- ❑ If the Mantoux test is positive (6 mm or greater) the baby should be assessed for active TB (see section 5.2). If this assessment is negative, then isoniazid should be continued for a total of six months.
- ❑ If the test is negative (less than 6 mm), then isoniazid should be stopped and a BCG vaccination performed (see chapter 11).

R67 Children older than four weeks but younger than two years who have not had BCG vaccination and are in close contact with people with sputum smear-positive TB should be treated as follows. **D(GPP)**

- ❑ The child should be started on isoniazid 5 mg/kg and a Mantoux test performed.
- ❑ If the Mantoux test is positive (6 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is ruled out, full treatment for latent TB infection should be given (see R69).

* Close contacts may include a boyfriend or girlfriend and frequent visitors to the home of the index case, in addition to household contacts.

- ❑ If the test is negative (less than 6 mm), then isoniazid should be continued and the Mantoux test repeated after six weeks.
- ❑ If the repeat test is negative, isoniazid may be stopped and BCG vaccination performed (see chapter 11).
- ❑ If the repeat test is positive (6 mm or greater), an interferon-gamma test should be conducted, if available. If this is positive, full treatment for latent TB infection should be given. If the test is not available, the child should be started on treatment for latent TB infection after a positive repeat Mantoux test result.

Contact tracing for children younger than two years when the index case is sputum smear positive is summarised in an algorithm (section 12.2).

R68 BCG-vaccinated children aged older than four weeks but younger than two years, in close contact with people with sputum smear-positive respiratory TB, should be treated as follows. **D(GPP)**

- ❑ The child should have a Mantoux test. If this is positive (15 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is excluded, then treatment for latent TB infection should be given (see R69).
- ❑ If the result of the test is as expected for prior BCG (less than 15 mm), it should be repeated after six weeks.
- ❑ If the repeat test is also less than 15 mm, no further action is needed.
- ❑ If the repeat test becomes more strongly positive (15 mm or greater and an increase of 5 mm or more over the previous test), an interferon-gamma test should be conducted, if available. If this is positive, the child should be assessed for active TB (see section 5.2). If the interferon-gamma test is not available, the child should be assessed for active TB after a positive repeat Mantoux test result. If active TB is excluded, treatment for latent TB infection should be given.

R69 For children requiring treatment for latent TB infection, a regimen of either three months of rifampicin and isoniazid (3RH) or six months of isoniazid (6H) should be planned and started, unless the child is known to be HIV positive, when 6H should be given (see R69). **D(GPP)**

R70 Healthcare workers should be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: **D(GPP)**

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

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

Cross-referring:
For details of excluding active TB, see section 5.2.
For details of DOT, see section 8.2.
For details of approaches to improving adherence, see section 8.3.
For details of active case finding, including contact tracing, see chapter 12.
For examples of 'inform and advise' information, see Appendix F.

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

10.2.1 Clinical introduction

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

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

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

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

10.2.2 Current practice

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

The review of current services followed-up respondents reporting more than five people screened for latent tuberculosis in 2003, and sought a breakdown between those who were new entrants and those who were contacts of people with infectious TB. Although all the clinics that

were followed-up were able to provide some response, in the majority they reported that they could not derive such detail from the data that they had collected locally. Many reported ongoing work to improve their local collection of data on screening.

10.2.3 Methodological introduction

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

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

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

10.2.4 From evidence to recommendations

The GDG discussed the issues and agreed that, rather than attempting to synthesise all the evidence in this area, it would be more useful to provide tables of risk factor data. These tables, modified from the American Thoracic Society official statement of 'targeted tuberculin testing and treatment of latent infection'[248] are shown below. Table 12 (overleaf) ranks a range of active TB incidence rates in tuberculin-positive persons with certain risk factors/medical conditions. Table 13 (overleaf) ranks a range of relative risks of active tuberculosis, in populations with certain risk/factors/medical conditions, independent of TST status.

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

RECOMMENDATIONS

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

Table 12 Incidence of active TB in persons with a positive tuberculin test by selected risk factors

Risk factor		TB cases/1,000 person-years
HIV infection[254]		35.0–162
Injecting drug use[255]	HIV seropositive	76.0
	HIV seronegative or unknown	10.0
Silicosis[237]		68.0
Recent latent tuberculosis[256]	Infection <1 year past	12.9
	Infection 1–7 years past	1.6
Radiographic findings consistent with prior TB[257–259]		2.0–13.6
Weight deviation from standard[260]	Underweight by >15%	2.6
	Underweight by 10–14%	2.0
	Underweight by 5–9%	2.2
	Weight within 5% of standard	1.1
	Overweight by >5%	0.7

Table 13 Relative risk for developing active TB by selected clinical conditions

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

THE GUIDELINE: PREVENTION AND CONTROL

11 BCG vaccination

11.1 Overview

11.1.1 Overall introduction

Bacille Calmette-Guerin (BCG) was developed by Calmette and Guèrin, at the Pasteur Institute (Lille) using *in vitro* attenuation by repeated passage of an isolate of *M. bovis* from 1908 onwards; it was finally tested in humans in 1921. Since BCG has never been cloned and has been grown under different conditions and in different laboratories, genetic differences have developed between the various commercially used strains,[279] so called 'antigenic drift'. Genome research has since shown that in the passaging of the organism, but before its distribution from the Pasteur Institute, a section of the genome, the RD1 region, was deleted. This deleted region common to all BCG strains contains antigens such as ESAT6 and CFP10 which are now used in interferon-gamma based blood tests, and hence these blood tests are not affected by prior BCG vaccination (see section 5.1 for further details).

The efficacy of a vaccine is a measure of its activity on individuals given the vaccine and can be defined as the proportion of those vaccinated who gain protective immunity from the vaccination.[280] Huge variations in estimates of efficacy against pulmonary TB, ranging from 0% to >80%, have been shown for different BCG vaccines in various geographical settings.

While a number of explanations have been put forward for this, geographical latitude seems to have a particularly important effect, accounting for over 40% of the variability in efficacy.[281] Thus nearly zero efficacy against tuberculosis in India,[282] is contrasted with a 64% protective efficacy in people of Indian origin with the same vaccine in a higher, more temperate, latitude.[283] Though the effect of climate on environmental mycobacteria has been suggested as the cause of the latitude effect, this has not been proven.

A further conundrum in BCG efficacy is that even in parts of the world where there is little reported efficacy against tuberculosis, efficacies of 50–60% are reported against leprosy and Buruli ulcer, caused by other mycobacteria.[280] Yet another problem with interpreting the data is that although it was assumed that the tuberculin sensitivity induced by BCG vaccination correlated with protective efficacy, this is not so. In a large UK study there was no correlation between tuberculin sensitivity induced by BCG and protective efficacy; those individuals tuberculin negative after BCG vaccination derived just as much protection as those who became tuberculin positive.[284]

Many controlled trials have followed efficacy for 10–15 years and have shown some decline over time, but the total duration of any benefit was not known and could only be expressed as an efficacy lasting up to 15 years.[285] The only truly long-term follow-up of BCG vaccination, in a North American aboriginal population, reported in 2004, showed 50% protective efficacy lasting for at least 50 years.[286]

BCG is a live vaccine and as such is contraindicated[3] in a number of situations where the immune system may be compromised, particularly if the person is known or suspected to be HIV positive, because of the risk of generalised BCG infection. HIV testing, after appropriate

counselling, is also an important consideration, but lies outside the scope of this guideline. Readers should be aware of the British HIV Association guidelines on TB/HIV co-infection[8] and those forthcoming on testing from the British Association for Sexual Health and HIV.

Current practice in vaccination is led by the advice of the Joint Committee on Vaccination and Immunisation, principally through the 'Green Book'.[3,21]

OVERALL RECOMMENDATIONS

R71 When BCG is being recommended, the benefits and risks of vaccination and remaining unvaccinated should be discussed with the person (or, if a child, with the parents), so that they can make an informed decision. This discussion should be tailored to the person, be in an appropriate language, and take into account cultural sensitivities and stigma. **D(GPP)**

R72 People identified for BCG vaccination through occupational health, contact tracing or new entrant screening who are also considered to be at increased risk of being HIV positive, should be offered HIV testing before BCG vaccination. **D(GPP)**
(See section 10.1 for details of further action in HIV-positive patients.)

11.2 For neonates

11.2.1 Clinical introduction

Neonatal BCG (up to age three months) is given in countries, or in subgroups defined by ethnicity and/or deprivation, with high rates of TB disease. Efficacy studies on neonatal BCG have used different end points which have contributed to some confusion about its efficacy in various settings. These have included the end points of pulmonary disease, death, TB meningitis, disseminated (miliary) disease, and laboratory-confirmed cases.

In England and Wales, which has had a selective neonatal BCG programme for over 20 years, assessments of coverage of appropriate infants have shown substantial variation in, and deficiencies in, both BCG policy and implementation.[287] These deficiencies and system problems were particularly in medium and low TB incidence districts which often had no system for identifying those neonates for whom BCG was recommended.

11.2.2 Current practice

The DH advises BCG vaccination for all neonates at higher risk of TB, with opportunistic vaccination of older children as necessary, according to criteria set out below in the recommendations.

The review of current services, conducted in the year prior to the introduction of neonatal vaccination and abolition of school-based vaccination, found that outside London, only two of 62 clinics (3%) (in the same HPU, an area of high notifications) reported universal neonatal BCG vaccination. In London, 12 of 31 clinics (39%) reported universal coverage. There was no consistency in the risk groups used for selected neonatal BCG. Many respondents did not name any explicit risk groups, but those who gave details mostly cited ethnicity, immigration and family history as the means for identifying neonates at higher risk.

11.2.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination administered in neonates and infants in preventing the development of TB infection or disease were sought. This was compared to unvaccinated groups in relevant populations. One meta-analysis, one cohort study and one case control study were found.

One meta-analysis conducted in the USA[288] included five RCTs and 11 case control studies in the analysis. The scope was international, but all RCTs were conducted in the northern hemisphere and were situated far from the equator relative to case controls, which were distributed across both temperate and equatorial regions. The analysis combined RCT and case control studies separately and did not use cross-design analysis since there were too few RCTs relative to case control studies. It was therefore appropriate to grade the evidence statements according to whether they were derived from the RCT (level 1) or case control results (level 2).

Factors for consideration raised by the meta-analysis included the following:

- The duration of BCG vaccination protection administered in infancy was inadequately established despite information on this issue being available from six studies. This was due to the small numbers of TB cases when data was analysed separately by year of occurrence.
- The impact of BCG strain on efficacy of immunisation was not associated with variation in the protection afforded by the vaccine in the studies reviewed.
- Differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score.
- Study quality validity scores accounted for 15.3% of the heterogeneity in the results of the nine case control studies, while RCTs were homogeneous.
- Distance from the equator did not appear to be an important correlate of BCG efficacy reported by case control studies, while RCTs displayed homogeneity in terms of distance from the equator.

One cohort study conducted jointly in the Federal Republic of Germany (FRG) and the German Democratic Republic (GDR),[289] was published prior to the meta-analysis, but not cited in it. The study retrospectively focused on BCG vaccination administered to an entire population of neonates in the GDR over a three and a half year period compared to no vaccination in the FRG over the same time period to investigate the efficacy of the vaccine in preventing cases of TB meningitis.

A case control study conducted in Spain,[290] which was not cited in the meta-analysis was excluded due to methodological limitations presented in Appendix G.

11.2.4 Evidence statements

Evidence was found for the efficacy of BCG vaccination in infancy for preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- laboratory-confirmed TB cases
- disseminated TB.

Evidence for these five outcomes is presented in Table 14 overleaf.

Table 14 Summary of evidence: neonatal BCG vaccination

Outcomes	Intervention: BCG vaccinated *vs.* unvaccinated infants	Results	Association/ statistical significance	Ref and NICE grade
Pulmonary TB disease	Four RCTs	Protective effect 0.74	Combined RR 0.26 (95%CI 0.17 to 0.38, p<0.05)	[288] 1+
	Nine case control studies	Protective effect 0.52	Combined OR 0.48 (95%CI 0.37 to 0.62, p<0.05)	[288] 2+
TB deaths	Five RCTs	Protective effect 0.65	Combined RR 0.35 (95%CI 0.14 to 0.88, p<0.05)	[288] 1+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95%CI 0.18 to 0.70, p<0.05)	[288] 2+
	One cohort study	0/770,000 intervention *vs.* 57/2,100,000 (0.0048%) control cases developed TB disease	Not reported	[289] 2+
Laboratory-confirmed TB cases	Three case control studies	Protective effect 0.83 (based on results of 108 TB cases confirmed by either histology or culture)	Combined OR 0.17 (95%CI 0.07 to 0.42, p<0.05)	[288] 2+
Disseminated TB	Three case control studies	Protective effect 0.78	Combined 0.22 (95%CI 0.12 to 0.42, p<0.05)	[288] 2+

11.2.5 Health economics

The GDG considered the interactions between neonatal and school-age BCG vaccination programmes required population dynamic economic modelling, which is, at the time of writing, being commissioned by the DH. With this in mind, recommendations on neonatal BCG are presented purely on the basis of clinical evidence, pending the findings of the model.

11.2.6 From evidence to recommendations

Neonatal BCG is significantly better than no vaccine using the end points of pulmonary disease, death, meningitis, laboratory-confirmed TB and disseminated TB.

There is difficulty ensuring thorough vaccination coverage in primary care, where babies are not registered until the first appointment, compared to vaccination by midwives, for example, where coverage can be assured.

The GDG supported the explicit criteria set out by the WHO for discontinuing universal vaccination, but wished TB clinicians and service planners to be aware of possible future

changes to the criteria in response to changing global epidemiology. The aim of this section is to guide clinicians in vaccinating those who are most at risk.

Given the conclusions of the health economics for school-based BCG vaccination in section 11.3, the recommendations seek to provide guidance for a neonatal BCG programme that will offer protection to all who are at risk. In a high-incidence area, this may be most easily provided by a universal programme.

The largest group of neonates who are at increased risk of TB are those whose families have immigrated from high-incidence countries. Neonates continue to be at risk even if their parents were also UK born because of continuing migration, home visits and exposure to increased levels of TB within communities. The recommendations therefore advise selection on the basis of a parent or a grandparent being born in a high-incidence country. GDG members were aware of selection being practised on the basis of skin colour or surname, and aimed to provide clear-cut recommendations to replace these practices.

In accordance with the Green Book,[3] tuberculin skin testing is not routinely recommended prior to BCG vaccination for children under six years of age.

RECOMMENDATIONS

R73 Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. **D(GPP)**

R74 Primary care organisations with a high incidence of TB* should consider vaccinating all neonates soon after birth. **D(GPP)**

R75 In areas with a low incidence of TB,* primary care organisations should offer BCG vaccination to selected neonates who: **D(GPP)**

- were born in an area with a high incidence of TB,* or
- have one or more parents or grandparents who were born in a high-incidence country,† or
- have a family history of TB in the past five years.

R76 Mantoux testing should not be done routinely before BCG vaccination in children younger than six years. **D(GPP)**

Cross-referring:
For details of identifying the Mycobacterium species prior to large-scale contact tracing, see section 5.3

* As defined by the HPA; go to **www.hpa.org.uk** and search for 'tuberculosis rate bands'.
† Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

11.3 For infants and older children

11.3.1 Clinical introduction

Following clinical trials in the early 1950s, BCG vaccination was introduced for previously unvaccinated adolescents aged 10–14.[284] Age 10–14 was selected for vaccination in 1953 because at that time, in what was nearly entirely a white UK-born population, TB was most common in those aged 15–29 (with a second peak in older people). This cohort, now aged over 70, have the highest TB rates among white UK-born people (see Appendix E). The rationale therefore was to give vaccination at this age to try to prevent acquisition of pulmonary disease before this peak, and it became known as the 'Schools BCG Programme'. During the writing of this guideline, the DH abolished the programme, replacing it with neonatal vaccination based on the criteria given above.

Tuberculosis rates fell through the 1950s and early 1960s by almost 10% per annum, and continued to fall at a lower rate until 1987 (approximately), since when there has been an increase. However, over this time, both the proportion of cases and rates of disease in the white UK-born ethnic group have continued to fall. The proportion of cases in this ethnic group was 85% in 1985, 43% in 1993, 37% in 1998, and is now under 30%.[140] Rates of TB in white UK-born children aged 10–14 years, the cohort of previously unvaccinated children to whom the schools programme applies, are between one and two cases per 100,000 for both sexes (see Appendix E).

▷ International criteria for discontinuation of unselective BCG vaccination

The International Union against Tuberculosis and Lung Disease published their criteria for discontinuation of BCG programmes in countries of low prevalence in 1993.[291] This set out general considerations and criteria. The general criteria to be met in a country before stopping or modifying BCG programmes were:

- there is a well functioning TB control programme
- there has been a reliable monitoring system over the previous five years or more enabling the estimation of the annual incidence of TB by age and risk groups, with particular emphasis on TB meningitis and sputum smear-positive pulmonary TB
- due consideration has been given to the possibility of an increase in the incidence of TB resulting from HIV infection.

The criteria for discontinuing a BCG vaccination programme in a country with a low prevalence of TB were:

- the average annual notification rate of sputum smear-positive pulmonary TB should be five cases/100,000 population or less during the previous three years, *or*
- the average annual notification rate of TB meningitis in children under age five years of age should be less than 1 case per 10 million general population over the previous five years, *or*
- the average annual risk of TB infection should be 0.1% or less.

Additional considerations were also suggested.

❑ **Cost:** with it being advisable, but not essential, to calculate the number of cases which would be prevented by continuing BCG vaccination, so that the saving can be expressed in terms of preventing human suffering and also in saving of cost of treatment.

- **Adverse reactions to BCG:** documentation of the rate of adverse reactions to BCG vaccination in a country are helpful. A low incidence rate of active tuberculosis, coupled with a high rate of adverse reaction tends to reinforce a decision to stop or modify the BCG vaccination programme. The reported rates of serious adverse reactions varies from country to country, with vaccination technique used, the preparation of BCG vaccination used, and doctors' awareness of reactions being factors influencing the reported rates.
- **Risk groups:** in the event of discontinuation of the BCG vaccination programme for the general population, it may be advisable to continue vaccination in certain well-defined population groups with a known high notification rate of active tuberculosis.

11.3.2 Current practice

The Department of Health no longer recommends BCG vaccination for school children between ages 10–14 years.

11.3.3 Methodological introduction

The focus was on studies investigating the effectiveness of BCG vaccination administered in a school-aged population in preventing TB infection or disease. One RCT and two cohort studies were found that addressed the topic.

One RCT conducted in the UK[285] reported on the protective efficacy of BCG vaccination against tuberculosis (TB) disease in vaccinated and unvaccinated groups of school-aged subjects in England over a 20-year follow-up period. Two cohort studies, both conducted in the UK,[292,293] retrospectively identified notified cases of TB disease who had been eligible for BCG vaccination within the schools vaccination scheme when aged 13.[292,293] These studies estimate the protective efficacy of the BCG vaccine in this general population and in the white ethnic group. Sutherland and Springett[292,293] estimate the numbers of additional TB notifications that would be expected among young white adults annually, if the schools BCG scheme were to be discontinued at specific dates. Both cohort studies incorporated data from the RCT cited above.

11.3.4 Evidence statements

▷ Efficacy of BCG vaccination for preventing TB disease

One RCT[285] and one cohort study[292] found that BCG given in school-aged children led to a reduction in the annual incidence of TB disease in vaccinated compared to unvaccinated individuals. Evidence is presented in Table 15.

Table 15 Summary of evidence: vaccinated and unvaccinated children of school-going age

BCG vaccinated *vs.* unvaccinated results	Statistical significance	Ref and NICE grade
Protective efficacy 0.77; average annual incidence 0.23 per 1,000 versus 0.98 per 1,000 (20 years follow-up)	Not reported	[285] 1+
1949–1981: Protective efficacy 0.80 (ages 15–19), 0.75 (ages 20–24)	Not reported	[292] 2+
1983: Protective efficacy 0.75 (ages 15–24); notification rate 3.3 per 100,000 versus 13.2 per 100,000	Not reported	[292] 2+

▷ BCG vaccination in school-aged children and longitudinal trends in TB prevention

Evidence was found on BCG vaccination use in school-aged children in England and Wales and the following longitudinal trends:

- decrease in the efficacy of BCG and the incidence of TB notifications
- the estimated risk of notified TB in the white ethnic population eligible for the school's BCG vaccination scheme
- TB notifications prevented by BCG vaccination in the white school-aged population
- TB notifications as a consequence of discontinuing the BCG schools vaccination scheme for the white ethnic population
- the estimated risk of notified TB in the white ethnic group if the school's BCG vaccination scheme were discontinued.

The evidence is presented in Table 16.

11.3.5 Health economics

A decision analytic model was used to estimate the cost-effectiveness of the current school BCG programme. The model distinguished between a 'high-risk' group of children who should have already been offered BCG before the school programme (through neonatal or new entrant schemes) and a 'low-risk' group, which is the remainder of the 10–14-year-old cohort. The school BCG programme is potentially beneficial for low-risk children and as a catch-up for previously unvaccinated high-risk children. The model relies on the assumption that there is negligible transmission between the high-risk and low-risk groups.[294]

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. The effectiveness of school BCG for the low-risk group and the number of secondary cases per primary case were taken from Saeed *et al* (2002),[295] updating the work of Sutherland and Springett in 1989.[293] The benefits for unvaccinated high-risk children were then estimated. It is important to note that this method can only give approximate results for an infectious disease such as TB. A population dynamic model would be expected to provide more reliable results.

Whenever possible, the input parameters and assumptions for the model were based on best available empirical evidence. However, we could not find evidence to inform all of the important parameters. In such cases, estimates are based on judgement by the guideline economist and the GDG. There is some 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 estimated QALY loss due to TB, and the estimated cost of treating a case of TB.

▷ Cost-effectiveness of school BCG for the low-risk group

The economic model suggests that the schools programme is not cost-effective for the low-risk group alone – with 0% in the high-risk group, the incremental cost per QALY gained (incremental cost-effectiveness ratio, ICER) is over £150,000 if we assume 15-year protection from BCG, and over £750,000 if we assume only 10-year protection. School BCG appears to be

Table 16 Summary of evidence: vaccination and longitudinal trends in TB among children of school-going age

BCG use and longitudinal trend	Results Vaccinated *vs.* unvaccinated groups/BCG discontinued *vs.* continued	Statistical significance	Ref and NICE grade
Progressive decrease in protective efficacy in successive five-year follow-up periods	0.40, 0.33, 0.10, 0.09 *vs.* 2.50, 1.06, 0.26, 0.08 per 1000	p=0.01	[285] 1+
Annual decrease in TB notification rates in three cohorts covering a 29-year period	Ages 15–19: 5% *vs.* 10%	Not reported	[292] 2+
	Ages 20–24: 7% *vs.* 11%		
Estimated risk of notified TB between ages 15 and 30 in white UK-born people eligible for BCG schools programme	1984: 1/6,500 (BCG administered at age 13) *vs.* 1/700 (TST negative)	Not reported	[293] 2+
	1994: 1/17,000 (BCG administered at age 13) *vs.* 1/4,300 (TST negative)		
Estimated TB notifications prevented by BCG vaccination in the white school-aged population	1983: 557 at ages 15–29 due to 7.65 million vaccinations in previous 15 years	Not reported	[293] 2+
	1988: 370 at ages 15–29 due to 7.65 million vaccinations in previous 15 years		
Additional TB notifications due to discontinuing BCG schools vaccination in the white ethnic population	Discontinuation in 1986: 129 in 2,003 (ages 15–29)*	Not reported	[293] 2+
	Discontinuation in 1996: 51 in 2,013 (ages 15–29)		
Estimated risk of notified TB in the white ethnic population if BCG schools vaccination were discontinued	Discontinuation in 1986: 1/2,200 between ages 15 and 30 (first wholly unvaccinated five-year cohort aged 13 in 1987–91) *vs.* 1/2,700	Not reported	[293] 2+
	Discontinuation in 1996: 1/5,400 between ages 15 and 30 (five-year cohort aged 13 in 1997–2001) *vs.* 1/6,900		

*Some of these would be secondary additional notifications outside the age group 15–29 years of age.

cost-effective for the 'low-risk' population only if their 10–15-year risk is very high: approximately 0.13–0.15%. This compares with current estimates of 0.03% (age 15–24) or 0.05% (age 15–29) (see Table 17 overleaf).

▷ Cost-effectiveness of school BCG as a catch-up for unvaccinated high-risk children

Based on the assumptions that 64% of high-risk children have been previously vaccinated, that they have a relative risk of 40 (compared with the low-risk group), and that BCG offers protection for 10 years, the schools programme appears to be cost-effective for areas with around 25–30% or more children in the high-risk group. If we assume 15-year BCG protection, school BCG appears cost-effective with around 10–15% or more in the high-risk group (see Table 18 overleaf).

Table 17 Cost-effectivensss of school BCG for low-risk group only by baseline risk of TB

	10-year protection			15-year protection		
Risk of TB over period of BCG protection (%)	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0.03	718	1	767,800	720	1	696,100
0.05	671	3	193,500	674	4	185,300
0.07	625	6	104,100	629	6	100,700
0.09	578	9	67,700	583	9	65,900
0.11	532	11	48,000	538	11	46,900
0.13	485	14	35,700	492	14	35,000
0.15	439	16	27,200	447	17	26,800
0.17	392	19	21,000	401	19	20,800
0.19	346	21	16,300	355	22	16,300

Table 18 Cost-effectiveness of school BCG by percentage of cohort in high-risk group

	10-year protection			15-year protection		
'High-risk' as % of cohort	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0	718	1	767,800	674	4	185,300
5	646	4	180,700	573	8	70,800
10	574	6	92,400	471	13	37,600
15	502	9	56,700	370	17	21,700
20	430	11	37,400	268	21	12,500
25	358	14	25,300	167	26	6,400
30	286	17	17,100	65	30	2,200

These results are sensitive to the estimated mean cost of treatment and QALY loss per case of TB age 15–24/29.

11.3.6 From evidence to recommendations

The GDG noted that the schools BCG programme was for those at low risk of TB and previously unvaccinated, whilst those at higher risk of TB (see section 10.2) receive BCG vaccination either at birth or on entry to the UK.

Whilst BCG in school-age children has a protective efficacy of 75–80% lasting 10–15 years, the incidence of active TB in those at low risk is now in the order of 1 case per 100,000, with a continuing downward trend.

England and Wales meet the accepted international criteria for the cessation of universal BCG vaccination in a low-prevalence country,[291] and have done so at least since 2000.

Economic modelling shows that the schools programme is not cost effective, and extremely expensive with an incremental cost-effectiveness ratio between £696,000 and £767,000 for low-risk individuals.

The schools programme becomes cost-effective only if 15% or more of the children included are at higher risk and previously unvaccinated.

For these reasons, it was felt that routine BCG vaccination of children aged 10 to 15 in schools should not continue. Those children at risk will either have been vaccinated neonatally (see section 11.2) or on entry to the UK (see section 11.4). Where universal childhood screening and vaccination is thought appropriate for an area because of very high local incidence, then this would be better achieved by a local universal neonatal BCG policy.

RECOMMENDATIONS

R77 Routine BCG vaccination is not recommended for children aged 10–14.

- Healthcare professionals should opportunistically identify unvaccinated children older than four weeks and younger than two years at increased risk of TB (see section 10.2) who would have qualified for neonatal BCG and provide Mantoux testing and BCG (if Mantoux negative). **C**
- This opportunistic vaccination should be in line with the Chief Medical Officer's advice* on vaccinating this age group following the end of the school-based programme. **D(GPP)**

R78 Mantoux testing should not be done routinely before BCG vaccination in children younger than six years unless they have a history of residence or prolonged stay (more than one month) in a country with a high incidence of TB. **D(GPP)**

11.4 For new entrants from high-incidence countries

11.4.1 Clinical introduction

The incidence of tuberculosis in new entrants from countries of high incidence (40/100,000 per year or greater) is high, peaking 2–3 years after first entry, and falling significantly after 10 years, but remaining well above general UK population rates (see Appendix E). Up to 30% of such recent arrivals from the Indian subcontinent are tuberculin negative.[296,297] Since they will be living in communities with a rate of TB some 25 times that of the white UK-born community, they may benefit from BCG vaccination to reduce the risk of acquiring TB disease. Such a BCG policy would however have to take into account the possibility of false negative TST from HIV co-infection.

* **www.dh.gov.uk/assetRoot/04/11/81/35/04118135.pdf**

11.4.2 Current practice

In the Department of Health's *Immunisation against infectious diseases* (the Green Book) 1996,[3] the following recommendation is made for new entrants from countries with a high prevalence of tuberculosis, their children and infants wherever born.

> '*New entrants to the UK,* including students, from countries with a high prevalence of tuberculosis, and all refugees and asylum seekers, should be tuberculin tested as part of the initial screening procedure unless there is **definite** evidence of a BCG scar. Those with positive reactions should be referred for investigation as they may require chemo-prophylaxis or treatment. BCG immunisation should be offered immediately to those who are tuberculin negative.'

Under section 32.4.1d of the same document HIV-positive individuals are listed as one of the contraindicated groups to whom BCG vaccine should not be given with the following comment:

> 'BCG is absolutely contraindicated in symptomatic HIV positive individuals. In countries such as the UK where the risk of tuberculosis is low, it is recommended that BCG is withheld from **all** subjects known or suspected to be HIV positive, including infants born to HIV positive mothers. There is no need to screen mothers for HIV before giving BCG as part of a selective neonatal immunisation programme (see 32.3.2(e))'.

The newly updated chapter of the draft 2006 Green Book[21] states:

> 'BCG immunisation should be offered to... previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater.'

Readers should also be aware of the recommendations made for neonates (see section 11.2).

11.4.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination in new entrants from high-risk countries in preventing TB infection or disease were targeted. No systematic reviews, randomised controlled trials, cohort or case control studies were found that directly addressed the area.

One meta-analysis conducted in the USA[298]demonstrated that BCG vaccine had protective efficacy across a wide range of study conditions, BCG strains, populations, age ranges and vaccine preparation methods. BCG efficacy in new entrants from countries with a high TB incidence was not addressed.

Since the meta-analysis did not use cross-design analysis, it was appropriate to grade evidence statements according to whether they were derived from the RCT (level 1), clinically controlled trial (level 2) or case control study (level 2) results.

Factors for consideration raised by the meta-analysis included:

- differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score

- among 13 prospective trials, study validity explained 30% of the between-study variance in the trials, and geographical latitude accounted for 41% of the variance
- among the 10 case-control studies, data validity score was the only variable to explain a substantial amount (36%) of the heterogeneity
- different strains of BCG were not associated with more or less favourable results in the 13 trials, as differing BCG strains administered in the same populations provided similar levels of protection.

One non-analytic study from the UK[299] was excluded due to methodological limitations presented in Appendix G.

11.4.4 Evidence statements

Evidence was found for the efficacy of BCG vaccination in preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- disseminated TB.

Evidence for these four outcomes is presented in Table 19.

Table 19 Summary of evidence: BCG vaccination for new entrants

Outcomes	Intervention: BCG vaccinated *vs.* unvaccinated infants	Results	Association/ statistical significance	Ref and NICE grade
Pulmonary TB disease	Seven RCTs	Protective effect 0.63	Combined RR 0.37 (95%CI 0.18 to 0.74)	[298] 1+
	Six clinically controlled trials	Protective effect 0.51	Combined RR 0.49 (95%CI 0.34 to 0.70)	[298] 2+
	Ten case control studies	Protective effect 0.50	Combined OR 0.50 (95%CI 0.39 to 0.64)	[298] 2+
TB deaths	Three RCTs and four clinically controlled trials	Protective effect 0.71	Combined RR 0.29 (95%CI 0.16 to 0.53)	[298] 2+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95%CI 0.18 to 0.70)	[298] 2+
Disseminated TB	Three case control studies	Protective effect 0.78	Combined OR 0.22 (95%CI 0.12 to 0.42)	[298] 2+

11.4.5 From evidence to recommendations

The GDG noted that there was little data in this field. The high rates of tuberculosis in recently arrived new immigrants from high incidence countries was also noted from epidemiological data over the last 25 years.

Although there is no direct evidence in this group in the UK, the meta-analysis cited above was regarded as applicable.

Analysis of the evidence on BCG efficacy has shown no evidence for persons aged over 35. The GDG felt that for this pragmatic reason, BCG vaccination should be limited to those under 36, unless they have occupational risk factors.

RECOMMENDATIONS

Readers should also be aware of the recommendations under new entrant screening (section 12.8). This process should include Mantoux tests on appropriate new entrants and risk assessment for HIV prior to vaccination.

R79 BCG vaccination should be offered to Mantoux-negative new entrants who:

- are from high-incidence countries,* *and* **B**
- are previously unvaccinated (that is, without adequate documentation or a characteristic scar), *and* **B**
- are aged 35 or younger.† **D(GPP)**

11.5 For healthcare workers

11.5.1 Clinical introduction

Although earlier studies had not shown an association, in the 1990s healthcare workers were shown to have twice the expected incidence of TB, allowing for age, sex and ethnic factors.[300] Because of the risk of exposure, it became standard practice to recommend BCG vaccination to people commencing healthcare work who would have contact with patients or clinical material, if they had not had prior BCG vaccination, and were TST negative.

11.5.2 Current practice

In *Immunisation against infectious disease* (the Green Book),[3] the Department of Health recommended BCG vaccination for all those at *higher risk of tuberculosis.* Under section 32.3.2a this included:

> '**Health service staff** who may have contact with infectious patients or their specimens. These comprise doctors, nurses, physiotherapists, radiographers, occupational therapists, technical staff in microbiology and pathology departments including attendants in autopsy rooms, students in all these disciplines, and any others considered to be at high risk. It is particularly important to test and immunise staff working within maternity and paediatric departments, and departments in which patients are likely to be immunocompromised, eg transplant, oncology and HIV units.'

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* Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

† The draft 2006 Green Book recommends BCG for new entrants only up to the age of 16. However in this guideline BCG is recommended for those up to 35 years who come from the countries with the very highest rates of TB because there is some evidence of cost-effectiveness.

The newly updated chapter of the draft 2006 'Green book'[21] states:

'People in the following occupational groups are more likely than the general population to come into contact with someone with TB:

- healthcare workers who will have contact with patients or clinical materials
- laboratory staff who will have contact with patients, clinical materials or derived isolates...'

11.5.3 Methodological introduction

Studies investigating the efficacy of BCG vaccination in health care workers for preventing the development of TB infection or disease in comparison to unvaccinated healthcare workers were targeted. One systematic review was found that addressed the topic.

One systematic review conducted in the USA[301] included two randomised controlled trials, two prospective cohort studies, one historically controlled study, one retrospective cohort study and six non-analytic studies. Information on the study methods and results was reported for only four of the six non-analytic studies. The scope was international, but all 12 studies were conducted in the northern hemisphere, 10 in temperate zones situated far from the equator, the eleventh in California, and for the twelfth, the specific setting was unknown.

The systematic review was methodologically sound, and hence it could technically be given a grading of 1+. However, the review did not conduct a meta-analysis due to the heterogeneity of study designs and methodological limitations in each of the studies. The methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements for this area. The review authors noted that despite methodological limitations, all six controlled studies reported a protective effect for BCG vaccination.

11.5.4 From evidence to recommendations

Whilst the systematic review was sound, all of the studies had multiple methodological flaws. There was however a consistent trend to benefit in the six controlled studies. Also, given the weight of evidence for the efficacy of BCG in other settings, it seemed unlikely that BCG would not be effective in this population. The GDG also noted that potential TB exposure continues throughout a career in individuals with patient or clinical material contact, and is not age limited.

There is not sufficient age-specific evidence to make recommendations on BCG vaccination for people over 35 but vaccination is recommended for healthcare workers of all ages because of the increased risk to them – and consequently the patients they care for – if they remain unvaccinated.

RECOMMENDATIONS

R80 BCG vaccination should be offered to healthcare workers, irrespective of age, who: **D(GPP)**

- are previously unvaccinated (that is, without adequate documentation or a characteristic scar), *and*

- will have contact with patients or clinical materials, *and*
- are Mantoux (or interferon-gamma) negative.

Cross-referring:
For details of occupational health screening, see sections 13.1 and 13.2

11.6 BCG vaccination for contacts of people with active tuberculosis

11.6.1 Clinical introduction

Contacts of cases of pulmonary tuberculosis are at risk of contracting TB. This is particularly the case with household or close contacts of sputum smear-positive disease, where up to 10% become infected (see section 12.2). It may take several weeks to develop an immune response to infection, as judged by a positive tuberculin skin test. A second TST has to be performed in those whose initial test is negative, six weeks after the initial negative one and a decision made with the second result.[6] Those with serial negative skin tests are deemed not to have been infected, but BCG vaccination up to and including the age of 35 years is recommended. The index case should be rendered non-infectious within a few weeks by anti-tuberculosis drug treatment, but tuberculin-negative contacts remain at risk if there are secondary cases.

11.6.2 Current practice

The Department of Health's *Immunisation against infectious disease* (the Green Book) 1996[3] recommended BCG vaccination for all those at *higher risk of tuberculosis*.[3] Under section 32.2d this included:

> '**Contacts** of cases known to be suffering from active pulmonary tuberculosis. Contacts of a sputum smear positive index case may have a negative tuberculin skin test when first seen but be in the early stages of infection before tuberculin sensitivity has developed. A further skin test should be performed six weeks later and immunisation only carried out if this second test is negative. (If the second skin test is positive, the patient has converted and must be referred for consideration of chemoprophylaxis). However, if for some reason a further test is impossible, vaccine may be given after the first test. Newly born babies should be given prophylactic isoniazid chemotherapy and tuberculin tested after three to six months. If the skin test is positive, chemoprophylaxis is continued; if negative, BCG vaccine is given provided the infant is no longer in contact with infectious tuberculosis. Newly born contacts of other cases should be immunised immediately.'

The newly updated chapter of the draft 2006 Green Book[21] states:

> 'BCG immunisation should be offered to... previously unvaccinated tuberculin-negative contacts of cases of respiratory TB (following recommended contact management advice – currently Joint Tuberculosis Committee of the British Thoracic Society 2000 [6] and National Institute for Health and Clinical Excellence 2006 [this document]...'

11.6.3 Methodological introduction

The focus was on studies investigating the efficacy of BCG vaccination in contacts of those with diagnosed active tuberculosis disease in comparison to unvaccinated contacts from the same population. One cohort study and five non-analytic studies were identified. All studies addressed BCG vaccination of contacts prior to their exposure to the index case.

One prospective cohort study conducted in South Korea[302] over a period of approximately two and a half years reported on the protective efficacy of BCG vaccination against TB disease in child contacts. Four studies[278,303,304,305] reported contact tracing results that included stratification of contacts by BCG vaccination status. BCG vaccination status was not the primary variable used to generate group allocation or to stratify the analysis of the results, and for this reason the studies were classified as non-analytic. One study was conducted in the UK (England, Wales and Scotland) and two studies in Scotland. A fourth study conducted in Brazil dealt with contacts of index cases diagnosed with MDR TB. Although the latitude effect could have influenced the study findings, the study was included since it focused on BCG vaccination in a contact population at risk of acquiring MDR TB disease. MDR TB is not addressed in the three UK-based studies.

A fifth non-analytic study was excluded due to methodological limitations, which are presented in the appendix.

11.6.4 Evidence statements

Evidence on the efficacy of BCG vaccination in preventing TB disease was found for contacts:

- of index cases
- of index cases diagnosed with MDR TB
- belonging to different ethnic groups

The evidence is presented in Table 20.

11.6.5 From evidence to recommendations

The appraised evidence shows some protective efficacy for BCG vaccination given before contact with tuberculosis, but none of the studies addressed the efficacy of BCG administered to tuberculin-negative contacts after exposure to TB. However, such individuals may be at increased risk from secondary TB cases if not vaccinated. As for new entrants, the potential benefit of BCG vaccination is reduced with age, and there is no reason to change the upper age limit of 35 years, which is currently widely used.

RECOMMENDATION

R81 BCG vaccination should be offered to Mantoux-negative contacts of people with respiratory TB (see section 12.2 for details of contact tracing) if they are previously unvaccinated (that is, without adequate documentation or a characteristic scar) and are: **D(GPP)**

- aged 35 or younger
- aged 36 and older and a healthcare or laboratory worker who has contact with patients or clinical materials (see section 11.5).

Cross-referring:
For details of contact tracing, see sections 12.2–12.6.

Table 20 Summary of evidence: BCG vaccination for contacts of people with TB

Population	Results N (%) TB disease cases in BCG-vaccinated versus unvaccinated persons	Association/ statistical significance	Ref and NICE grade
Contacts of index cases	Child contacts aged 0–5: protective effect 0.70; 46/806 (5.7) *vs.* 80/417 (19.2) scored six or higher, indicating TB disease	Not reported	[302] 2+
	Stratification by age: protective effect 0.74	Summary RR 0.26 (95%CI 0.62 to 0.82)	[302] 2+
	Close contacts: 14/1081 (1.3) *vs*. 149/3587 (4.2)	Not reported	[278] 3+
	Contacts: 16/1821 (0.88) *vs.* 62/3595 (1.72)	Not reported	[303,304] 3+
	Contacts with new TB (active TB disease plus those on treatment for latent TB infection): protective effect 0.62; (1.15) *vs.* (3.06)	p<0.001	[303,304] 3+
	Contacts: 14/1605 (0.87) *vs*. 34/1761 (1.93)	Not reported	[303,304] 3+
	Contacts received chemotherapy/ treatment for latent TB infection for TB disease/infection: protective effect 0.59; 23/1605 (1.4) *vs.* 60/1761 (3.4)	Not reported	[303,304] 3+
Contacts of index cases diagnosed with MDR TB	Protective effect 0.69 (excluding three contact TB cases with drug-susceptible isolates); 8/153 (5) *vs.* 9/65 (14)	RR 0.35 (95%CI 0.13 to 0.99, p< 0.05)	[305] 3+
	TB disease found significantly more in unvaccinated MDR TB contacts	RR 3.1 (95%CI 1.2 to 8.1)	[305] 3+
Contacts belonging to different ethnic groups	Asian contacts: 7/425 (1.6) *vs.* 57/1479 (3.9)	Not reported	[278] 3+
	Non-Asian (mainly white) contacts: 7/656 (1.1) *vs.* 92/2108 (4.4)	Not reported	[278] 3+
	Asian contacts: 0/86 *vs.* 5/228 (2.19)	Not reported	[303,304] 3+
	Non-Asian (mainly white) contacts: 16/1735 (0.92) *vs.* 57/3367 (1.69)	Not reported	[303,304] 3+
	Incidence of TB in black African *vs.* white contacts: 2.2 versus 0.4 per 1,000 person-years	p<0.001*	[305] 3+

* Using Cox's regression test, ethnicity was no longer associated with incidence of TB disease.

11.7 Other groups

The Department of Health currently recommends BCG vaccination for a range of other people who may be at risk from TB.[21] This guideline concentrated on the groups given individually above but for completeness this section addresses the other groups at risk, who stand to benefit from BCG vaccination. For veterinary surgeons, abattoir workers and other people working with animals, there are a number of possible sources of infection, but no standard occupational health screening. Workplace screening is likely to be provided by private sector firms, and is therefore outside the remit of NICE. However, a number of regulations apply:

- the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995, which require employers to notify the Health and Safety Executive
- the Management of Health and Safety at Work Regulations 1999, which require general standards of risk assessment
- the Control of Substances Hazardous to Health Regulations 2002, which require employers to assess infection risk and prevent or control exposure.

RECOMMENDATION

R82 BCG vaccination should be offered to previously unvaccinated, Mantoux-negative people under 35 in the following groups at increased risk of exposure to TB, in accordance with the 'Green Book':[21] **D(GPP)**

- veterinary and other staff such as abattoir workers who handle animal species known to be susceptible to TB, such as simians
- prison staff working directly with prisoners
- staff of care homes for elderly people
- staff of hostels for homeless people and facilities accommodating refugees and asylum seekers
- people going to live or work with local people for more than 1 month in a high-incidence country.*

See section 11.5 for advice on healthcare workers.

* Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

12 Active case finding

12.1 Overview

12.1.1 Clinical introduction

Active case finding is looking systematically for cases of active tuberculosis and latent infection in groups known, or thought to be, at higher risk of tuberculosis, rather than waiting for people to develop symptoms/signs of active disease and present themselves for medical attention (passive case finding). Active case finding is informed by a knowledge of the general epidemiology of TB in the country, and in population subgroups. The current incidence of active TB in England and Wales is 12.9 cases per 100,000 population per year, with individual ethnic groups having rates of 4 per 100,000 (white), 104 per 100,000 (Indian), 145 per 100,000 (Pakistani), and 211 per 100,000 (black African).[140] Data are not available on latent tuberculosis rates in the general population. Active case finding, if targeted on appropriate groups, or subgroups, should have a yield substantially above that that would be found by chance screening. The Chief Medical Officer's TB Action Plan[2] set improvements in case finding as one of the essential activities to improve TB care in England and Wales, and to reverse the trend of increasing incidence.

12.1.2 Current practice

The review of current services included service provision and organisation for active case finding in terms of contact tracing (sections 12.2 and 12.3), new entrant screening (section 11.7), and screening other risk groups

Outside London, 25% of service providers had some screening for high-risk groups, whereas within London, 39% had such screening. Examples of high-risk groups were drug users, the homeless and alcoholics.

12.2 Contact tracing: human-to-human transmission

12.2.1 Clinical introduction:

Contact tracing and examination have traditionally been undertaken to find associated cases, to detect people infected but without evidence of disease (latent infection) and to identify those not infected and for whom BCG vaccination may be appropriate. Where recent infection has occurred (eg clinical disease in children), contact tracing is done to find a source of infection, and any co-primary cases. In people with latent tuberculosis, BCG vaccination does not prevent its development into active disease. BCG vaccination is addressed in chapter 10 of this guideline.

Five contact studies in England and Wales,[306–310] reporting 22,971 contacts in the early 1990s, showed that up to 10% of new TB cases were diagnosed through contact tracing, that disease occurred in about 1% of contacts, and that disease was usually found on the first visit in unvaccinated contacts of sputum smear-positive disease. Three smaller studies reported in the

late 1990s in England and Wales,[311–313] largely confined to close contacts, showed a mean number of contacts examined at 6.5 per index case, and confirmed a secondary case yield of 1% (1,000/100,000).

Smear-negative pulmonary tuberculosis is significantly less infectious than smear-positive, but some transmission does occur. Studies in San Francisco[314] and Western Canada[315] using DNA fingerprinting estimated this transmission risk (as a proportion of smear-positive transmission risk) at between 0.22 and 0.18–0.35 respectively, similar to estimates (0.28) using 'conventional' methods.[316] DNA fingerprinting studies may also identify clusters not identified by 'conventional' contact tracing and in some cases assumed to be recently linked.[314,315]

12.2.2 Current practice

The review of current services found that outside London, 70% of service providers had contact clinics and 16% saw patients at home. Within London, 91% had a contact tracing clinic, and no service providers saw patients at home other than in exceptional cases.

An assessment of the extent of current contact tracing practice can be made by comparing the number of notified cases with the number of contacts screened. The graph below, where each dot represents a service provider, and clinics which only do tracing have been removed, shows that there is considerable variation in the number of contacts traced per index case. (Perfect consistency, which is an unreasonable expectation, would be demonstrated in a straight line.)

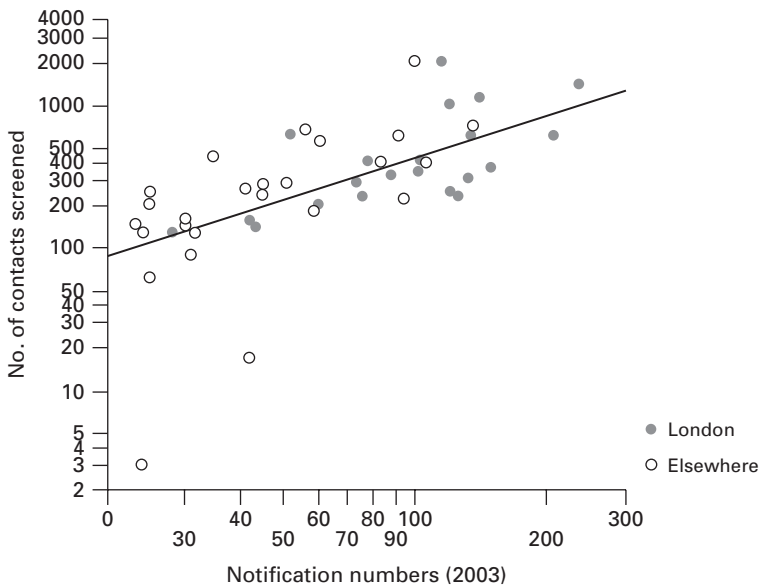


Figure 7: Correlation of contacts screened with cases notified (logarithmic scale)

A similar comparison has been made between the number of contacts traced and the number of treatments for latent TB infection cases, and is reported under section 10.1.

12.2.3 Methodological introduction

Two clinical questions were drawn up to search the evidence base for this topic. The results of the searches and the critical appraisal are discussed below for each in turn.

▷ Are contact tracing procedures effective in identifying cases of tuberculosis disease or infection (excluding contacts of cattle with TB)?

No systematic reviews or randomised controlled trials were found that met the inclusion criteria for this question.

The literature search identified 10 studies conducted in England and Wales that reported epidemiological descriptions of specific contact tracing exercises. These studies did not include comparative case yield data from other contact tracing or case finding exercises in similar populations and settings, and so were not considered for appraisal. Without comparative data, these studies could not evaluate the effectiveness of the specific contact tracing intervention method used. Nevertheless these studies contribute towards an epidemiological overview of contact tracing in England and Wales, and the main results of these studies are collated in Table 21 below in order to provide local background information on this aspect of active case finding.

Table 21 Descriptive studies of contact tracing carried out in England and Wales

Reference	Description	Results
Ruddy MC, Davies AP, Yates MD, Yates S *et al*. Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004;**59(4)**:279–285.	Study type: descriptive. Population: contact tracing of isoniazid resistant TB outbreak in North London, including prisons. Study period: retrospective analysis 1995–2001.	• At least 440 named close contacts of confirmed or probable TB cases to date. • Screening of 269 close contacts yielded 13 confirmed or probable TB cases, 13 clinical cases, and three linked cases. • This represents a transmission rate of 11% among close contacts screened to date. • 27 infected contacts were placed on treatment for latent TB infection.
Corless JA, Stockton PA, Davies PD. Mycobacterial culture results of smear-positive patients with suspected pulmonary tuberculosis in Liverpool. *European Respiratory Journal* 2000;**16**:976–979.	Study type: descriptive. Population: contact tracing of suspected pulmonary TB from two hospitals in Liverpool. Study period: retrospective analysis 1996–1999.	• A total of 937 contacts were identified from 57 index patients with cultured *M. tuberculosis*. • No contact in the study developed tuberculosis while under surveillance.

continued

Table 21 Descriptive studies of contact tracing carried out in England and Wales – *continued*

Reference	Description	Results
Ansari S, Thomas S, Campbell IA, Furness L, Evans MR. Refined tuberculosis contact tracing in a low incidence area. *Respiratory Medicine* 1998;**92(9)**:1127–1131.	Study type: descriptive. Population: patients with TB and their contacts in South Glamorgan. Study period: retrospective analysis 1992–1994.	• A total of 726 contacts were identified from 103 index patients, with 707 contacts receiving full screening. • TB disease was found in 7 (1%) close contacts, all identified at the initial screening (one with smear-positive index case; five with two overseas index cases with unknown smear status; one with child index case with unknown smear status). • TB disease was found later in a further five contacts initially screened and cleared (in two cases the protocol was not followed correctly and three cases developed extra-pulmonary TB. • Treatment for latent TB infection was given to 21 (2.9%) of close contacts.
Irish C, Jolly E, Baker T. Contact tracing smear positive and non-pulmonary tuberculosis in a high incidence area. *Thorax* 1997;**52**:A34.	Study type: descriptive epidemiological study. Population: contacts of non-pulmonary (NP), sputum smear-positive (POS), and negative (NEG) cases of tuberculosis disease in Tower Hamlets. Study period: 1995.	• One of 158 (0.5%) contacts of POS cases, four of 196 (2%) contacts of NEG cases, and none of 57 contacts of NP cases were treated for tuberculosis disease. • Twenty-two of 158 (14%) POS contacts, 21 of 196 (11%) NEG contacts, and five of 57 (9%) NP contacts received treatment for latent TB infection. • Differences in proportions of POS, NEG, and NP contacts requiring one or more repeat X-ray, further clinic follow-up, treatment for latent TB infection or full tuberculosis treatment were not significant.
Stoddart H, Noah N. Usefulness of screening large numbers of contacts for tuberculosis: questionnaire-based review. *British Medical Journal* 1997;**315**:651.	Study type: cross-sectional survey Population: 155 districts in England and Wales where in the preceding three years more than 100 contacts were screened in response to specific incidents. Study period: April 1994.	• Forty-four cases of tuberculosis disease were found in 18 of the 56 investigations, giving a detection rate of 0.375%. • A further 106 (0.9%) contacts received treatment for latent TB infection. • The development of tuberculosis in 39 investigations with details available was significantly correlated with the proportion of contacts who had tuberculin skin test positive results (P=0.008).
Harding MJ, Pilkington P, Thomas J. Tuberculosis epidemiology in Croydon. *Public Health* 1995;**109**:251–7.	Study type: descriptive. Population: contact tracing in response to tuberculosis incidents in Croydon. Study period: retrospective analysis 1988–1991.	• A total of 522 close contacts were identified from 172 index cases. • Three cases of tuberculosis were identified from the contacts (0.6%). • Forty-eight contacts (9.2%) had either a positive Heaf test or chest X-ray indicative of past primary infection. • 19.6% of contacts of index patients with smear-positive disease were 'positive' *vs.* 9.8% of contacts of non-smear positive index patients, *vs.* 5.2% of patients with non-pulmonary disease (P=0.0002).

continued

Table 21 Descriptive studies of contact tracing carried out in England and Wales – *continued*

Reference	Description	Results
Hardinge FM, Black M, Chamberlain P. TB contact tracing in South Buckinghamshire from 1994 to mid 1998. *Am J Respir Crit Care Med* 1999;**159**:A303.	Study type: descriptive. Population: all patients with TB and their contacts in South Buckinghamshire. Study period: retrospective analysis 1994 to mid 1998.	• 369 contacts were identified from 72 index cases. • Eight cases of TB were identified among contacts, four at initial screening (1%) – all were close contacts of smear-positive pulmonary disease index cases. • Three contacts were given treatment for latent TB infection (0.8%), and 143 (38%) were given BCG vaccination.
Ormerod LP. Results of tuberculosis contact tracing: Blackburn 1982–90. *Respiratory Medicine.* 1993;**87**:127–131.	Study type: descriptive. Population. contact tracing in Blackburn using methods 'virtually identical' to procedures recommended in 1983 by the JTC. Study period: retrospective analysis 1982–1990.	• 7,017 close contacts were identified from 649 index cases. • 50 cases of TB (0.7% of all contacts) were identified, 13 in the white ethnic group, and 37 in the Asian ethnic group. • 38% of cases in the Indian subcontinent ethnic group were contacts of smear-positive pulmonary disease, and 46% were contacts of other forms of respiratory disease. • All cases of TB were in white contacts of index cases with smear-positive pulmonary disease.
Kumar S, Innes JA, Skinner C. Yield from tuberculosis contact tracing in Birmingham. *Thorax* 1992;**47**:875.	Study type: descriptive. Population: yield from contact tracing of notified TB cases at the Birmingham chest clinic using a contact tracing procedure 'broadly similar' to 1990 BTS guidelines. Study period: retrospective analysis 1987–1989.	• 7,960 contacts were identified from 788 index cases. • 75 new cases of TB were identified from contacts (1% of all contacts), 46 of Indian subcontinent origin, 15 white, and 14 black Caribbean. • 254 contacts were given treatment for latent TB infection (3% of all contacts). • All contacts with TB disease were contacts of index cases with pulmonary smear-positive TB except for six (8% of total) Indian contacts of index cases with non-respiratory disease.
Hussain SF, Watura R, Cashman B, Campbell IA, Evans MR. Audit of a tuberculosis contact tracing clinic. *BMJ.* 1992;**304**:1213–15.	Study type: descriptive. Population: TB contact tracing in South Glamorgan. All patients with a diagnosis of active TB disease who appeared in the contact tracing records and laboratory data from the Public Health Laboratory Service (PHLS) *Mycobacterium* Reference Unit within this period were included in the study, as were all recorded contacts of these patients. Study period: retrospective analysis 1987–89.	• 611 contacts were identified from 101 index patients. • Active TB disease was diagnosed in five contacts (two of Indian subcontinent origin, three of other origins), all made on initial screening. All were close contacts and none were known to have been vaccinated. • Four contacts who received treatment for latent TB infection were also close contacts of patients with smear-positive pulmonary TB and had not been vaccinated.

continued

Table 21 Descriptive studies of contact tracing carried out in England and Wales – *continued*

Reference	Description	Results
Teale C, Cundall DB, Pearson SB. Time of development of tuberculosis in contacts. *Respiratory Medicine* 1991;**85**:475–7.	Study type: descriptive. Population: contact tracing procedures at the Leeds chest clinic Study period: retrospective analysis 1983–1987.	• 6,602 contacts were identified from 555 notified index cases. • 42 (8%) contacts had TB disease (10 cases smear or culture positive, five contacts of Asian origin, five contacts of non-family members; four cases diagnosed more than one year after first clinic attendance). • 35 (6%) previously unimmunized child contacts with Heaf grade 2 or more results received treatment for latent TB infection.

Of the 17 studies appraised, 11 were excluded due to methodological limitations, which are presented in Appendix G. Six non-analytic studies were included as evidence in two main areas:

- non-homeless and homeless populations
- contact tracing and DNA fingerprinting analysis.

▷ Are contact tracing procedures which identify casual contacts in addition to close contacts effective in identifying cases of tuberculosis disease or infection?

Studies were included that compared the number of cases of latent tuberculosis infection and/or active tuberculosis disease identified during contact tracing in groups of close and casual contacts. No systematic reviews, randomised controlled trials, cohort or case control studies were found that met the inclusion criteria for this question.

Seven studies on contact tracing in close and casual contacts were identified, but six of these[316–321] were excluded due to methodological limitations presented in Appendix G. One prospective non-analytic study [322] was included as level 3 evidence for this question.

12.2.4 Evidence statements

▷ Contact tracing compared in non-homeless and homeless populations

A study carried out in the USA[323] found that contact tracing identified significantly more contacts in non-homeless compared to homeless tuberculosis cases. The evidence is presented in Table 22.

Table 22 Summary of evidence: contact tracing in homeless and non-homeless people

Outcome	Results Homeless *vs.* non-homeless TB index cases	Statistical significance	NICE grade
Mean number contacts identified	2.7 *vs.* 4.8	p<0.001	3+
Four plus contacts identified	40 (26) *vs.* 1419 (50)	p<0.0001	3+
No contacts identified N (%)	70 (46) *vs.* 304 (11)	p<0.0001	3+

▷ Contact tracing and DNA fingerprint analysis

Five non-analytic studies compared DNA fingerprint analysis of transmission links between cases of tuberculosis with the number of epidemiological links established through contact tracing for the same set of cases. These studies did not have a control group. Factors for consideration within this topic are used below.

- ❑ DNA fingerprint analysis can only be carried out on culture-positive cases of *M. tuberculosis*. Contact tracing includes culture-positive and-negative cases, and identifies cases of latent infection. Contact tracing therefore covers a wider population of at-risk contacts than DNA fingerprinting analysis, so the procedures are not equivalent comparators.
- ❑ Reliance on *M. tuberculosis* isolates means that molecular typing usually occurs some time after contact tracing has commenced, and so cannot complement in real time the epidemiological links established by the latter.
- ❑ None of the studies were carried out in the United Kingdom.
- ❑ Contact tracing was generally poorly reported and differed within each study setting.

Four studies[324–327] found that when contact tracing and DNA fingerprint analysis were carried out on the same group of contacts, tracing found fewer transmission links between identified cases of active tuberculosis than DNA fingerprint analysis. The evidence from the studies is presented in Table 23 below.

Table 23 Summary of evidence: DNA fingerprinting

Results: DNA fingerprint analysis	Results: Contact tracing	Ref and NICE grade
155 clustered TB cases	Identified links in 37/155 (24%) clustered cases; missed detectable links in 10/155 (6%) clustered cases; non-detectable (by contact tracing) links in 106/155 (68%) clustered cases.	[324] 3+
Four clusters of TB cases with transmission links identified	Identified links in 3/4 (75%) clusters.	[325] 3+
84 TB cases in 26 clusters	Identified links in 20/84 (24%) linked TB cases.	[326] 3+
96 TB cases in eight clusters	Two TB cases identified an unspecified number of cases in the same cluster as 'contacts'.	[327] 3+

One study[328] found that DNA fingerprint analysis identified erroneous transmission links inferred by contact tracing to exist between cases of tuberculosis disease.

Eight of 13 epidemiological transmission links (61.5%) identified by contact tracing were verified by DNA fingerprint analysis, but the remaining five (38.5%) cases linked by contact tracing did not acquire their infection from the putative source. (3+)

▷ Close contacts compared to casual contacts in detecting latent tuberculosis infection

One study[322] found that both latent tuberculous infection and active tuberculous case yields were significantly higher for close compared to casual contacts of 302 index cases diagnosed at a single non-hospital practice. The evidence is summarised in Table 24 below.

Table 24 Summary of evidence: contact tracing in close and casual contacts

Outcomes	Close contacts N (%)	Casual contacts N (%)	Association/statistical significance (OR)	NICE grade
Latent TB infection	488 (55.9)	94 (26.4)	OR 3.54 (95%CI 2.68 to 4.69 p<0.00001)	3+
Active TB disease	40 (4.6)	2 (0.6)	OR 8.51 (95%CI 2.18 to 73 p<0.001)	3+

12.2.5 From evidence to recommendations:

▷ General issues

Contact tracing procedures should be carried out on a patient-centred basis. The GDG felt it was important to consider the lifestyle of an index/source case carefully as it may reveal places of close contact other than domestic or occupational such as homeless shelters, cinemas, bars, clubs, prisons or aircraft.[329]

Contact tracing is usually conducted according to the 'stone in the pond' principle,[330] and it is with this in mind that the recommendations below are set out. Closest contacts (those with most exposure, typically household contacts) are found and assessed first. If sufficient TB is found to raise clinical suspicion of further infection, another tier of contacts are traced, and so on. This helps to limit the effort put into such exercises.

▷ Definition of close contacts

Descriptive studies from the UK which were considered by the GDG do not give a clear definition of close contacts and it is therefore difficult to give guidance on whom to trace.

It would be useful to give TB nurses an objective definition of close contacts, but there is insufficient evidence to make a recommendation on factors such as length of time spent in the same room without ventilation before 'close contact' is deemed to have occurred.

▷ DNA fingerprint analysis

DNA 'fingerprint' analysis has been used to identify clusters that have not been identified by contact tracing. It can support the presumed links between cases.

Only one study checked the effectiveness of molecular typing through follow-up, and the GDG did not feel that the evidence base was sufficient to inform clinical recommendations.

Molecular typing will underestimate the epidemiological linkages relevant to contact tracing, because it relies exclusively on analysis of culture-positive TB isolates.

▷ Who to include in contact tracing?

Whilst the highest pick-up will be in the contacts of pulmonary smear-positive cases, there is a significant yield from screening household contacts even of non-respiratory index cases, as this is assessing and screening a local population with a high incidence of TB.

Contacts with a cumulative total exposure to a smear positive case of TB exceeding eight hours within a restricted area equivalent to a domestic room are equivalent to domestic contacts; the guideline recommends tracing these contacts in addition to the domestic ones.

'Inform and advise' information is an important minimum level of TB education for all contacts once they are traced. However, for close contacts, this should not pre-empt screening and discussion with a healthcare professional (as a normal part of contact tracing), because of patient confidentiality.

RECOMMENDATIONS

R83 Once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. **D(GPP)**

R84 Screening should be offered to the household contacts of any person with active TB, irrespective of the site of infection. Household contacts are defined as those who share a bedroom, kitchen, bathroom or sitting room with the index case. Screening should comprise: **D(GPP)**

- standard testing for latent TB for those aged 35 or younger, and consideration of BCG or treatment for latent TB infection once active TB has been ruled out
- interferon-gamma test six weeks after the Mantoux test, and consideration of BCG or treatment for latent TB infection once active TB has been ruled out, for those who:
  - are previously unvaccinated *and*
  - are household contacts of a person with sputum smear-positive TB *and*
  - are Mantoux negative (<6 mm)
- chest X-ray (if there are no contraindications) for those older than 35, possibly leading to further investigation for active TB.

R85 For people with sputum smear-positive TB, other close contacts should be assessed. These may include boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts, and should be assessed in the same way. **D(GPP)**

R86 Casual contacts of people with TB, who will include the great majority of workplace contacts, should not normally be assessed. **C**

R87 The need for tracing casual contacts of people with TB should be assessed if: **D(GPP)**

- the index case is judged to be particularly infectious (for example, evidenced by transmission to close contacts), *or*
- any casual contacts are known to possess features that put them at special risk of infection (See section 10.1).

R88 'Inform and advise' information should be offered to all contacts of people with smear-positive TB. **D(GPP)**

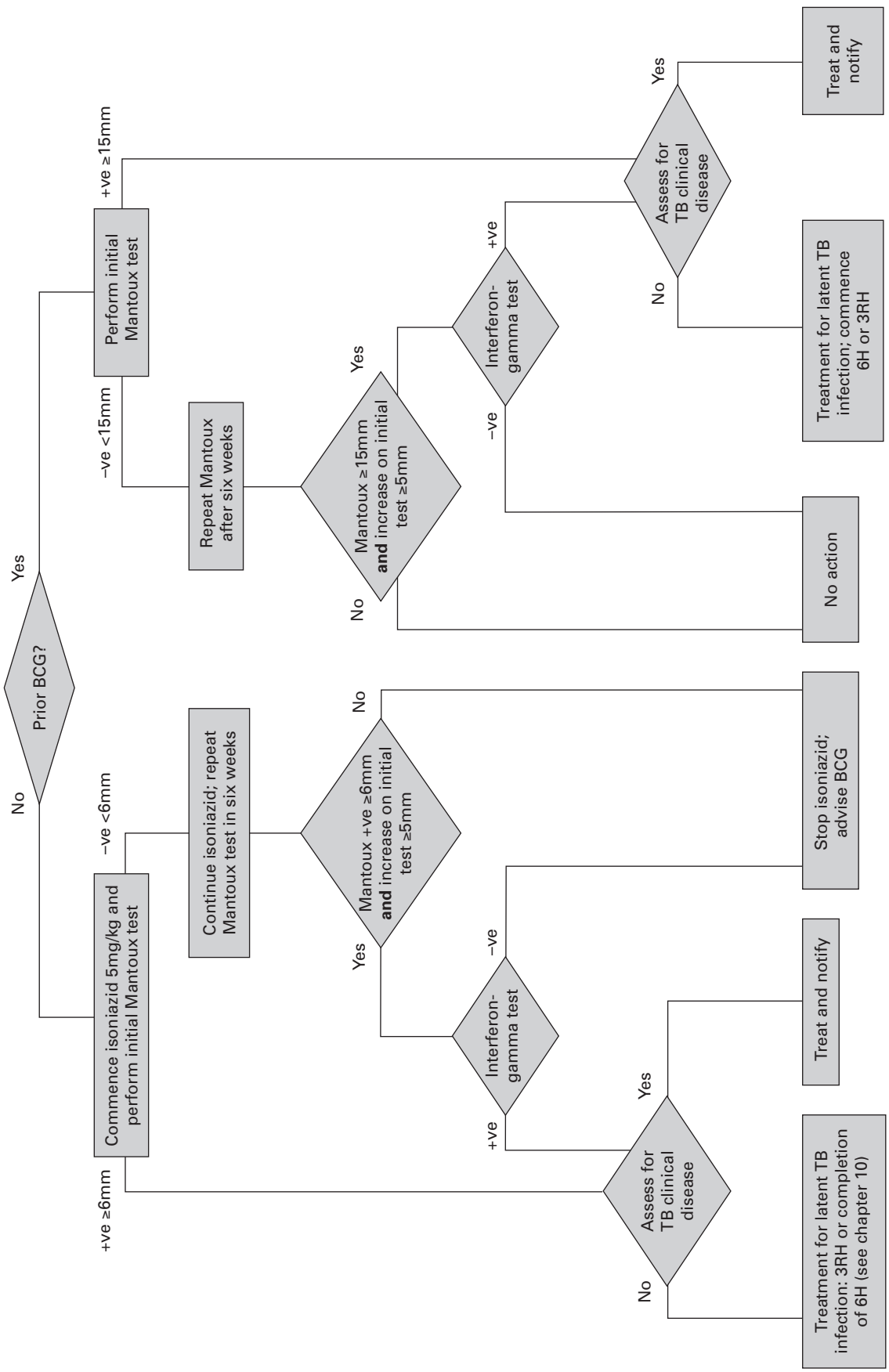
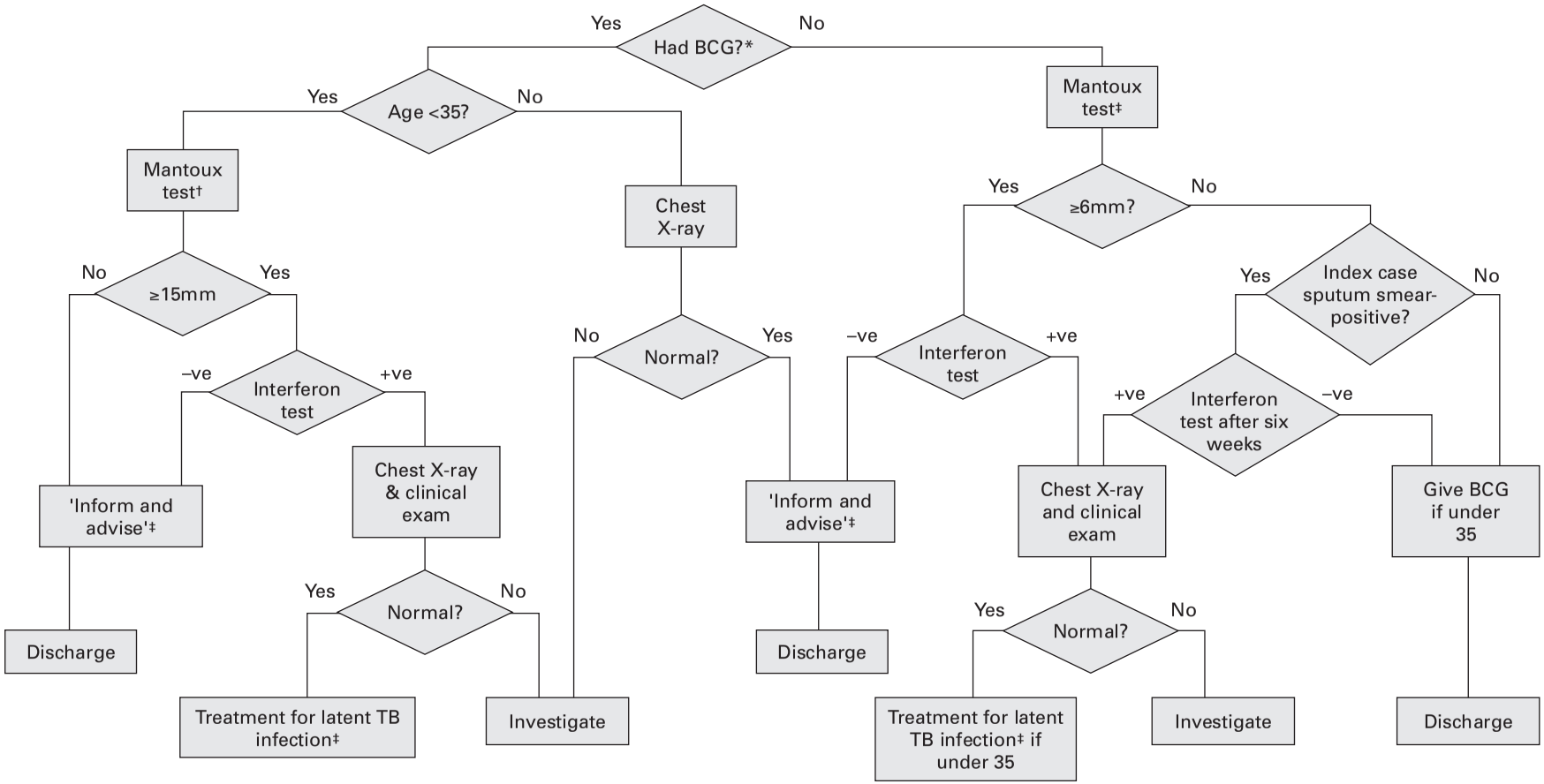


Figure 8: Algorithm for testing and treating asymptomatic children aged between 4 weeks and 2 years old who are contacts of people with sputum smear-positive TB



* Previous BCG vaccination cannot be accepted as evidence of immunity in HIV-infected patients.
† A negative test in immunocompromised people does not exclude TB infection.
‡ People advised to have treatment for latent TB infection, but who decline, should have 'inform and advise' information reinforced and chest X-ray follow-up at three and 12 months.
For children aged between four weeks and two years old who are contacts of people with sputum smear-positive TB, use the algorithm in Figure 8.

Figure 9: Algorithm for asymptomatic household and other close contacts of all cases of active TB

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of dealing with children aged less than 2 years who are close contacts of people with sputum smear-positive TB, see section 10.1.
For details of BCG vaccination, see section 11.6.
For examples of 'inform and advise' information, see Appendix F.

12.3 Contact tracing: cattle-to-human transmission

12.3.1 Clinical introduction

Tuberculosis in cattle, as judged by postmortem studies and tuberculin reactors, has become more common in England and Wales over the last 20 years. The highest rates in cattle are in the south west of England, parts of Wales and the West Midlands. Bovine tuberculosis is almost entirely caused by *M. bovis*, which can be differentiated from *M. tuberculosis* in the laboratory after culture. Following the increase in cattle TB, surveillance for human *M. bovis* infection was enhanced. However the reporting system of the PHLS (MycobNet, see chapter 13) reported only 210 humans with isolates of *M. bovis* between 1993–1997, approximately 1% of reported human *M. tuberculosis* complex isolates.[331] People with *M. bovis* isolates were very different from those with other *M. tuberculosis* complex isolates. Of the 210, 200 were of white ethnic origin, with over three quarters aged 50 years or more, findings suggesting reactivation of disease acquired earlier in life.

The overwhelming majority of the UK population is at negligible risk from *M. bovis* infection because of milk pasteurisation. Continuing data from MycobNet since 1997[140] shows no increase in the numbers of human *M. bovis* isolates.

Readers should be aware of the Department of Health's advice on the public health implications of bovine TB.[332]

12.3.2 Current practice

The review of current services did not specifically ask for details, but some respondents supplied information on their work with bovine TB. It was regarded as being responsible for a significant workload in three HPU areas. Three clinics reported 28 cases of *M. bovis* infection, for which they had traced an average of six contacts per case. This would be a not insignificant workload for contact tracing services in a dispersed rural population.

12.3.3 Methodological introduction

No systematic reviews, randomised controlled trials, case control studies or non-analytic studies were found that met the inclusion criteria for this question. One cohort study[333] conducted in the USA was excluded due to methodological limitations listed in Appendix G. Two Canadian papers investigated human contacts of diseased elk, and one UK paper was purely descriptive of case yield but did not evaluate contact tracing as an intervention. There are therefore no evidence statements for this question.

12.3.4 From evidence to recommendations

Since there is little evidence of cattle–human or human–human transmission of *M. bovis* from national epidemiology or the limited UK data, the group considered that tuberculin skin testing and interferon-gamma testing should be limited to previously unvaccinated children and adolescents (age <16) who have regularly drunk unpasteurised milk from animals with udder lesions, with treatment for latent TB infection being offered to those with a positive result.

RECOMMENDATION

R89 'Inform and advise' information should be given to people in contact with TB-diseased animals. Diagnostic tests for latent TB should be considered only for children younger than 16 who have not had BCG vaccination and have regularly drunk unpasteurised milk from animals with TB udder lesions. **D(GPP)**

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.6.
For examples of 'inform and advise' information, see Appendix F.

12.4 Contact tracing: cases on aircraft

12.4.1 Clinical introduction

The evidence base upon which assessments can be made of the risks of transmission of TB in aircraft is relatively slim. The confined space and the recirculation of air clearly give rise to potential hazards. Whether or not these are greater for an individual on a single flight than, say, regular travel on the same commuter bus or train as an infectious case of TB cannot be established.

Aircraft passengers are, in theory at least, more readily identifiable than passengers of other kinds. Identifiability and traceability are not, however, synonymous and characteristically, aircraft passengers do not make multiple repeat journeys and are widely dispersed once they reach their destination. Further, airlines (who hold the passenger lists) may prove reluctant to disseminate information about the hazards of having travelled with them.

Recommendations about contact tracing where an aircraft passenger has been identified as having infectious TB must therefore be guided by the practicalities of the process.

12.4.2 Methodological introduction

Studies were targeted that attempted to establish whether latent tuberculosis infection and active tuberculosis disease identified by contact tracing in passenger and crew contacts was due to recent transmission from an index case of tuberculosis on an aircraft. No systematic reviews, randomised controlled trials, or case control studies were found that met the inclusion criteria.

One cohort study conducted in the USA[334] compared case yields for latent tuberculosis infection identified by contact tracing in flight crew exposed to an index case of tuberculosis with flight crew with no prior exposure to infectious tuberculosis. Five non-analytic studies[335–339] were identified that investigated whether latent tuberculosis infection identified in passenger and crew contacts was due to prior risk factors for tuberculosis or recent exposure to an index case of tuberculosis on an aircraft. Methodologically, all six studies differed with regard to:

- varying geographical locations
- varying countries of residence of contacts
- differing exposure periods
- variation in prior BCG vaccination of contacts depending on country of residence
- sample sizes ranging from 100 to 760.

Prior risk factors for latent tuberculosis infection and contamination of tuberculin skin test results identified in the study populations included:

- high BCG vaccination rates
- prior exposure to family members or close friends with tuberculosis
- born or resident in a country with a high incidence of tuberculosis
- extensive travel in settings with a high incidence of tuberculosis
- having old, inactive tuberculosis
- exposure to tuberculosis in the workplace (excludes flight crew)
- exposure to other mycobacterial infection.

12.4.3 Evidence statements

▷ Recent transmission of latent tuberculosis infection

One study[334] found significantly more cases of recent transmission of tuberculosis infection in aircraft crew exposed to an index case of tuberculosis than in a control group of non-exposed crew. Two studies[336,337] found evidence of recent transmission of TB infection in airplane contacts of cases with tuberculosis disease, while three other studies[335,338,339] found no conclusive evidence of recent transmission in airplane contacts of active TB disease cases. None of the studies reported symptoms of active tuberculosis in contacts. The evidence is presented in Tables 25 and 26 below.

Table 25 Exposed and non-exposed aircraft crew

N (%) exposure group TST positive	N (%) control group TST positive	Association/statistical significance	Ref and NICE grade
May–July 1993: 10/169; 5.9	**May–July 1993:** 13/247; 5.3	NS	[334] 2++
August–October 1993: 13/43; 30 (TST positive rates ≥5 mm induration)	**August–October 1993:** 13/247; 5.3 (TST positive rates ≥5 mm induration)	RR 5.74 (95%CI 2.86 to 11.54, p<0.01)	
11/43; 25.6 (TST positive of 10 mm induration)	4/247; 1.6 TST positive (rates of 10 mm induration)	RR 15.8 (95%CI rates 5.27 to 47.34, p<0.01)	

Table 26 Aircraft contacts with latent TB infection attributed to prior risk factors *vs.* aircraft-mediated transmission

N (%) TST positive contacts with prior risk factors for TB	N (%) TST positive contacts attributed to aircraft transmission	Ref and NICE grade
6/9 (66.6)	3/9 (33.3) Flight exposure-related conversion rate for latent TB infection was 1.3% (3/225 contacts)	[336] 3+
14/20 (70%)	6/20 (30) Flight exposure related conversion rate for latent TB infection was 0.8% (6/760 contacts)	[337] 3+
24/24 (100%)	0	[335] 3+
32/34 (94%)	2/34 (5.8) Impossible to determine whether two US-born TST positive reactors were due to aircraft transmission, since estimated 4–6% of the US population are TST positive	[338] 3+
5/5 (100%)	0	[339] 3+

▷ Duration of exposure

One study[334] found that duration of exposure to the index case was the factor most strongly associated with latent tuberculosis infection among exposed aircraft crew contacts.

Over three months 49 (96%) crew contacts all had at least 14.5 total hours of exposure to the index case. Total time exposed to the index case during this period was the variable most strongly associated with the probability of having a TST positive result ($p<0.001$) for all variables and interactions considered. (**2++**)

▷ Seating proximity of infected contacts to the index case

One study (N=760)[337] found a statistically significant relationship between TST-positive contacts with no prior risk factors for tuberculosis, and seating proximity to an index patient with MDR TB on an aircraft (RR 8.5, 95%CI 1.7 to 41.3, p=0.01). (**3+**)

Three studies (N=120,[338] N=100,[339] and N=225)[336] found no evidence that TST-positive contacts without prior risk factors for tuberculosis were more likely to be seated in closer proximity to an index case with tuberculosis on an aircraft than TST-positive contacts with prior risk factors. (**3+**)

12.4.4 From evidence to recommendations

The evidence base for this topic is prone to publication bias, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.

One of the studies[334] had a crew member as an index case and assessed transmission to other crew. This is therefore a workplace study and not directly applicable to passenger-to-passenger transmission.

The evidence base indicates low yield from aircraft-based contact tracing, but proximity to the index case was seen to be a risk factor. However, identifying proximity is costly and difficult. Seating records, or even passenger lists, are not always available, and the onus of contacting passengers lies with the airline. Similar possibilities for transmission arise in other forms of long-haul transport, but seating plans are not generally available in these situations.

'Inform and advise' information is of limited utility in such situations, where risk of infection is extremely low, neither the TB service nor the airline know which passengers are more susceptible to infection, and the passengers receiving such information will not be in contact with a TB service from whom they can seek further advice face to face.

It was therefore felt that it was not an effective use of resources to conduct contact tracing among aircraft passengers or similar transport scenarios, unless a seating plan was available, or where exceptional circumstances exist.

Such exceptional circumstances were identified as including: an index case with MDR TB, frequent coughing, and a flight of over eight hours' duration. The eight hours threshold was recognised as fairly arbitrary, but is drawn from what little evidence exists. It is impossible to define 'frequent coughing' given a subjective assessment which may take place weeks after the flight. Clinical judgement will have to be used in any such case to identify how many passengers to advise the airline to send information to.

Where the index case is a crew member, contact tracing of individual passengers is not necessary as passengers will have had minimal exposure.

RECOMMENDATIONS

R90 Following diagnosis of TB in an aircraft traveller, contact tracing of fellow passengers should not routinely be undertaken.

R91 The notifying clinician should inform the relevant consultant in communicable disease control (CCDC) if: **D(GPP)**

- less than three months has elapsed since the flight and the flight was longer than eight hours, *and* **D(GPP)**
- the index case is sputum smear positive, *and* **D(GPP)**
- the index case has MDR TB, *or* **C**
- the index case coughed frequently during the flight. **D(GPP)**

The CCDC should provide the airline with 'inform and advise' information to send to passengers seated in the same part* of the aircraft as the index case. **D(GPP)**

R92 If the TB index case is an aircraft crew member, contact tracing of passengers should not routinely take place. **D(GPP)**

R93 If the TB index case is an aircraft crew member, contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues (see section 12.4). **B**

* Published evidence does not allow for a precise definition, but such contact tracing on aircraft has often only included people within three rows on either side of the index case.

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see chapter 11.
For details of contact tracing in general, see section 12.2.

12.5 Contact tracing: cases in schools

12.5.1 Clinical introduction

TB in school pupils or staff requires particular attention because of the potential for spread of infection and also because of the anxiety that may arise among pupils, parents, staff and others. They should all be subject to individual risk assessment following discussion with the consultant in communicable disease control.

If the index case of TB is an adult member of staff, the purpose is to detect secondary cases elsewhere in the school, while if it is a pupil, the purpose is not only to detect secondary cases but also to find the source case, if it is not already thought to be known.

12.5.2 Methodological introduction

Studies were included that attempted to establish whether contact tracing was effective in identifying latent and active tuberculosis in school contacts exposed to an index case of tuberculosis in the school setting.

Six cohort studies and four non-analytic studies were found. None of the cohort studies were conducted in the UK, and only one non-analytic study took place in the UK. One cohort study[11] and one non-analytic study[340] were excluded due to methodological limitations, which are presented in Appendix G. Despite limited reporting of participant baseline characteristics, five cohort studies[341–345] and three non-analytic studies[346–348] were included.

12.5.3 Evidence statements

▷ Case yields of latent tuberculous infection

Six studies[341–343,345,347,348] investigated case yields of latent TB infection in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Latent TB infection yield was reported for the following four exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases
- school pupils with different levels of classroom contact to index cases of TB disease
- school pupils with direct classroom contact to index cases of TB disease in comparison to pupils with no classroom exposure to index cases.

The evidence for latent TB infection is presented in Table 27 overleaf.

Table 27 Detection of latent TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils TST+	Association/ statistical significance	Study location	Ref and NICE grade
1. Schools with pupil index cases *vs.* control schools	Four secondary schools *vs.* 10 secondary schools	277/3188 (8.7) *vs.* 123/3321 (3.7) ¶ *	$p<10^{-7}$	Italy	[343] 2+
	Two primary schools *vs.* three primary schools	51/722 (7.1) *vs.* 19/702 (2.7) **	NS	Canada	[344] 2+
2. Exposed *vs.* non-exposed school pupils (pupil index cases)	All current high school pupils *vs.* non-exposed new school entrants	120/333 (36) *vs.* 39/248 (16)	RR 2.3 (95%CI 1.7 to 3.2, p<0.05)	USA	[342] 2+
	All high school graduates *vs.* non-exposed new school entrants	35/138 (25) *vs.* 39/248 (16)	RR 1.6 (95%CI 1.1 to 2.4, p<0.05)	USA	[342] 2+
	US-born current high school pupils *vs.* US-born new school entrants	27/145 (19) *vs.* 4/132 (3)	RR 6.1 (95%CI 2.2 to 17.9, p<0.05)	USA	[342] 2+
	US-born high school graduates *vs.* non-exposed US-born new school entrants	6/66 (9) *vs.* 4/132 (3)	RR 3.0 (95%CI 0.9 to 10.3)	USA	[342] 2+
3. Different levels of classroom exposure to pupil index cases	Junior high school pupils sharing one plus class *vs.* pupils entering a class recently vacated by index case	95/118 (81) *vs.* 30/88 (34)	Not reported	USA	[345] 2+
	Junior high school pupils sharing three *vs.* two *vs.* one class with index case	9/9 (100) *vs.* 32/35 (91) *vs.* 55/74 (74)	Not reported	USA	[345] 2+
	High school pupils sharing three plus *vs.* one plus (normally ventilated) *vs.* one plus (normal or enhanced ventilation) classrooms with index case	7/13 (54) *vs.* 21/66 (32) *vs.* 25/106 (24)	RR 5.7 (95%CI 3.26 to 10.13) *vs.* RR 4.2 (95%CI 2.6 to 6.75) *vs.* RR 3.2 (95%CI 2.0 to 5.18)	USA	[341] 2+
4a. Pupils with *vs.* pupils without classroom exposure to pupil index cases	High school pupils sharing a classroom *vs.* pupils without classroom exposure	22/110 (20) *vs.* 54/616 (9)	RR 2.3 (95%CI 1.4 to 3.8)	USA	[342] 2+
	Secondary school pupils sharing a classroom *vs.* pupils without classroom exposure	76% tine test positive, nearly 11 times higher than pupils without classroom exposure	RR 10.9 (95%CI 8.7 to 13.4)	Italy	[343] 2+
	Primary school pupils sharing classrooms *vs.* pupils without classroom exposure	No significant difference in TST positive rates reported	Not reported	Canada	[344] 2+

continued

Table 27 Detection of latent TB in schools contact tracing – *continued*

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils TST positive	Association/ statistical significance	Study location	Ref and NICE grade
4b. Pupils with *vs.* pupils without classroom exposure to teacher index cases	Primary school pupils sharing a classroom *vs.* pupils without classroom exposure	12/28 (43) *vs.* 3/27 (11)	Not reported	Ireland	[342,343,347,348] 3+

¶ Tine Test positive
** BCG vaccination was discontinued in Italy before the present research cohort were born, so tine test positivity could not be attributed to the booster effect.*
*** Prior BCG vaccination and foreign-born status were both significantly associated with TST positive outcome in all schools.*

▷ Case yields of active tuberculous disease

Three studies[343,344,347,348] investigated case yields of active TB disease in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Active disease in contacts was variably defined as

- abnormal chest X-ray[342,343,347,348]
- not specified by test result or site of disease[344]
- presence/absence of positive AFB sputum smear or X-ray findings compatible with cavitary disease.[343]

Active TB disease case yield was reported for the following two exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases.

The evidence for active TB disease is presented in Table 28.

Table 28 Summary of evidence: detection of active TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils with TB disease	Statistical significance	Study location	Ref and NICE grade
Schools with index cases *vs.* control schools	Four secondary schools *vs.* 10 secondary schools	14/3188 (0.4) *vs.* 1/ 3321 (0.03)	Not reported	Italy	[343] 2+
	Two primary schools *vs.* three primary schools	1/722 (0.1) *vs*. 0/702	Not reported	Canada	[344] 2+
Pupils with *vs.* pupils without classroom exposure to teacher index cases	Primary school pupils sharing a classroom *vs.* pupils without classroom exposure	8/28 (29) *vs.* 0/27	Not reported	Ireland	[342,343,347,348] 3+

▷ Case yields for a general TB outcome

One study conducted in the UK[342,343,347,348] reported a general TB outcome (combined latent TB infection and active TB disease yield) for primary schools pupils with *vs.* those without classroom exposure to a teacher with sputum smear- and culture-positive tuberculous disease who developed symptoms over a three-month period prior to the outbreak.

31/46 (67%) pupils from two classrooms shared with the index case *vs.* 15/46 (33%) pupils from five non-exposed classrooms were diagnosed with TB infection or disease. No statistical significance testing was reported. (**3+**)

▷ Transmission of tuberculosis disease from an index case to exposed school contacts verified by DNA fingerprint analysis

A study conducted in New Zealand[346] found that cases of active tuberculosis identified by contact tracing in secondary school pupils were confirmed by DNA fingerprint analysis to be due to direct transmission from school index cases. (**3+**)

12.5.4 From evidence to recommendations

There are the following potential difficulties in making recommendations from the evidence base.

- There is a possibility of publication bias in the evidence base, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.
- The evidence base does not take into account the country of birth or ethnicity of pupils, which is likely to be a confounding factor. In schools with a large proportion of pupils drawn from populations with high rates of TB, latent infection and active disease in some of those screened might erroneously be concluded as being due to transmission from the index case.
- Many of the studies conducted outside the UK were carried out in non-BCG vaccinated populations.
- Rates of disease are calculated on small denominators and are therefore imprecise.

The aim of contact tracing is different across age groups. In younger children a source is being sought, while in adolescents and adult staff members contact tracing is usually (but not invariably) the sole reason for the exercise.

The GDG were keen to limit the resources that might be consumed by these large and mainly unproductive exercises, and agreed that initially, only children in the same class as the index case need to be assessed. School registers may help in identifying the pupils at highest risk.

After-school, sports and religious activities should also be kept in mind where the degree of contact might be equivalent to classroom contact. The GDG agreed that outdoor activities would not normally pose a risk of TB transmission, unless this involved confined spaces for prolonged time periods, for example camping. Such obvious exceptions were not felt to require a recommendation.

RECOMMENDATIONS

R94 Following diagnosis of TB in a school pupil or member of staff, the CCDC should be prepared to explain the prevention and control procedures to staff, parents and the press. Advice on managing these incidents and their public relations is available from the HPU. **D(GPP)**

R95 If a school pupil is diagnosed with sputum smear-positive TB, the rest of his or her class (if there is a single class group), or the rest of the year group who share classes, should be assessed as part of contact tracing. **B**

R96 If a teacher has sputum smear-positive TB, the pupils in his or her classes during the preceding three months should be assessed as part of contact tracing. **C**

R97 Clinicians conducting contact tracing in a school should consider extending it to include children and teachers involved in extracurricular activities, and non-teaching staff, on the basis of: **D(GPP)**

- the degree of infectivity of the index case
- the length of time the index case was in contact with others
- whether contacts are unusually susceptible to infection
- the proximity of contact.

R98 Secondary cases of sputum smear-positive TB should be treated as index cases for contact tracing (see R94–R97 above for class of recommendation).

R99 If the index case of a school pupil's TB infection is not found, and the child is not in a high-risk group for TB, contact tracing and screening (by either symptom enquiry or chest X-ray) should be considered for all relevant members of staff at the school. **D(GPP)**

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.6.
For details of contact tracing in general, see section 12.2.
If smear-positive TB is diagnosed in an adult working in community childcare, see section 12.6.
For examples of 'inform and advise' information, see Appendix F.

12.6 Contact tracing: community childcare

12.6.1 Clinical introduction

Children, particularly of pre-school age, are more likely to acquire TB infection, and progress to TB disease, than older children and adults if they are exposed to infectious tuberculosis – usually from adults. Each year in England and Wales there are a number of incidents where children in nurseries and other childcare facilities are screened for tuberculosis after exposure to an adult staff member. Government policy and social changes mean that more children will be found in childcare settings. An increasing number of adults will therefore be in contact with children up to age 16 years.

12.6.2 Methodological introduction

Studies investigating whether there were specific management strategies that were effective in preventing and controlling the transmission of TB infection and disease in childcare settings were sought. One cohort study was found that addressed the question.

The study, conducted in a hospital nursery setting in the USA[349] focused on screening for tuberculosis in infants and healthcare workers exposed to an index case of TB disease. Selection of infants to different TB screening procedures was based on level of TB exposure. TST conversion rates in healthcare workers who worked in the nursery unit when the index case was present were compared with healthcare workers in the hospital who had not worked in the unit.

12.6.3 Evidence statements

▷ Latent TB infection in infants and healthcare workers with high versus low risk of exposure to an index case of TB

No difference between high and low exposure groups in the number of tuberculin-positive reactions was identified.[349] The evidence is summarised in Table 29.

Table 29 Summary of evidence: detection of latent TB in community childcare

Patient group and exposure status	N (%) TST positive reactors in participants with low exposure to the index case	N (%) TST positive reactors in participants with high exposure to the index case	Statistical significance	NICE grade
Infants Low/high exposure shared unit with index case 8–12/0–8 weeks prior to diagnosis	1/259 (7 mm reaction at age 11 weeks, received BCG vaccination at age three days)	0/139 (including 30 aged more than 56 days)	Not reported	2+
Healthcare workers Low/high exposure never worked in unit/worked in unit during index case stay	14/619 (2.26) converted	4/130 (3.08) converted	NS p<0.6	2+

▷ Completion rate for isoniazid prophylaxis among high-exposure infants

132/139 (95%) infants with high exposure to an index case of TB disease completed a three month course of isoniazid prophylaxis.[349] (2+)

12.6.4 From evidence to recommendations

There is no relevant evidence on which to base recommendations. Because of the lack of an infrastructure to provide screening for this very diverse setting, which includes informal care arrangements, recommendations deal only with contact tracing.

RECOMMENDATION

R100 When an adult who works in childcare is diagnosed with sputum smear-positive TB, management is as for contact tracing (see section 12.2). **D(GPP)**

12.7 Contact tracing: cases in hospital inpatients

12.7.1 Clinical introduction

With the increasing numbers of clinical cases of tuberculosis, some of whom are admitted to hospital, there are incidents where patients with tuberculosis are not appropriately isolated, leading to potential exposure of other patients, some of whom may have reduced immunity. Such incidents are not strictly outbreaks, but may consume considerable resources identifying exposed patients, many of whom are at minimal risk.

A further type of incident is where a healthcare worker is found to have active tuberculosis, with patients being exposed to possible infection risks. This latter type of incident often involves staff recruited from overseas, who may only have been screened to healthcare worker level and not to the higher level advised for new entrants from high-incidence settings (see section 12.1).

Finally, there have been true outbreaks where patients, usually but not exclusively HIV co-infected, have acquired active tuberculosis disease from other inpatients, often due to failure to use appropriate infection control measures, or because facilities thought to be negative pressure were not actually so.[232] Such outbreaks, particularly when of MDR TB transmission, can have a high mortality and morbidity, as well as major medicolegal implications for NHS trusts.[232]

12.7.2 Methodological introduction

Studies that investigated whether contact tracing was effective in identifying latent tuberculosis infection and active tuberculosis disease in patient and staff contacts exposed to an index case of tuberculosis in the hospital setting were targeted.

One case control study and four non-analytic studies were identified. The case control study from the USA[350] evaluated a contact tracing investigation of hospital staff conducted in relation to an index patient diagnosed with tuberculosis disease from an extrapulmonary site. Despite limited reporting of baseline characteristics, and no significance testing for the outcome of TST converters in exposed cases and non-exposed controls, the study was included. Two non-analytic studies from the UK[351] and the USA[352] were included.

Three non-analytic studies from the USA[353] and the UK[232,354] were excluded due to methodological limitations, which are presented in Appendix G.

12.7.3 Evidence statements

▷ Case yields of latent tuberculous infection

Two studies[350,352] investigated latent TB infection in staff with different levels of exposure to index cases of active TB disease in hospital settings. Neither of the studies was conducted in the UK.

The evidence for latent TB infection is presented in Table 30.

Table 30 Detection of latent TB in contact tracing among health care workers (HCWs)

Exposure category	Exposure content	Results Healthcare workers with TST conversions, N (%)	Association/ statistical significance	Ref and NICE grade
Exposed *vs.* non-exposed healthcare workers (non-pulmonary patient index case)	Nurses exposed to index case after surgery *vs.* nurses and students exposed prior to surgery *vs.* non-exposed historical control nurses	12/95 (13) *vs.* 2/1435 (0.14) *vs*. 0/23	Not reported	[350] 2+
Exposed *vs.* non-exposed healthcare workers (healthcare workers index case)	Healthcare workers on two wards (A and B) *vs.* healthcare workers on non-exposed wards	Ward A 21/70 (30) *vs*. 10/76 (13.2) non-exposed wards	RR 2.3 (95%CI 1.2 to 4.5, p=0.02)	[352] 3+
		Ward B 29/61 (47.5) *vs.* 10/76 (13.2) non-exposed wards	RR 3.6 (95%CI 1.9 to 6.8, p<0.001)	[352] 3+
		Controlling for exposure to infectious TB patients (N=25): risk of TST conversion remained higher for healthcare workers on wards A and B	Weighted RR 3.0 (95%CI 1.9 to 4.5, p<0.001)	[352] 3+

▷ Case yields of active tuberculous disease

Two studies[351,352] investigated case yields of active TB disease in patients and staff in hospitals where index cases of active TB disease had been identified. One of the studies was conducted in the UK. Active TB disease case yields were reported for the following:

- staff with and without exposure to TB index cases
- hospital staff, surgical patients and renal patients exposed to a TB index case.

The evidence for active TB disease is presented in Table 31 below.

Table 31 Detection of active TB in contact tracing among healthcare workers

Population	Exposure to healthcare workers index cases	Results Healthcare workers with TB disease, N (%)	Statistical significance	Ref and NICE grade
Exposed *vs.* non-exposed healthcare workers	HCWs exposed on two wards (A and B) *vs.* Healthcare workers on non-exposed wards	8/51 (16) wards A and B *vs*. 0/76 non-exposed wards	Not reported	[352] 3+
Healthcare workers *vs.* renal patients *vs.* surgical patients	All groups exposed in a hospital	0/135 *vs.* 1/220 (0.45%) *vs.* 0/57	Not reported	[351] 3+

▷ Type of exposure to the index case

One study[350] found that exposure to the surgical wounds of an index case of non-pulmonary TB was significantly associated with latent TB among previously TST-negative nurses.

Irrigation or packing of the wound was the only statistically significant risk factor for a positive TST (OR 9, 95%CI 1.2 to 67, p=0.03), with nurses involved in these activities having nine times the risk of TST conversion compared to nurses not involved in substantial wound care. (**2+**)

▷ Duration of exposure

Hospital staff TST converters and index cases worked more total shifts on two wards with infectious TB cases than staff who were TST negative (Ward A median 80 *vs.* four shifts, p=0.004; Ward B median 124 *vs.* five shifts, p<0.001).[352] (**3+**)

12.7.4 From evidence to recommendations

The wide variety of settings and possibilities mean that narrowly drawn guidelines are not appropriate. The pick-up from contact tracing exercises is very low so it is important to avoid unnecessary screening. Evidence from North America may show levels of potential transmission, but is not particularly relevant for the effectiveness of service models in the UK. The GDG's considerations were otherwise constrained by the paucity of evidence relevant to the UK.

Awareness of tuberculosis and transmission risks needs to be maintained in healthcare workers who work with immunocompromised patients – for example surgeons who work with transplant patients, and oncologists. A rigorous risk assessment was regarded as useful before any action is taken.

The GDG recognised the need to limit contact tracing exercises to instances where there is a genuine risk of TB transmission, and chose eight hours as a time threshold for exposure. There is no evidence to support this, but it is in line with the threshold given elsewhere for contact tracing.

RECOMMENDATIONS

R101 Following diagnosis of TB in a hospital inpatient, a risk assessment should be undertaken. This should take in to account:

- the degree of infectivity of the index case
- the length of time before the infectious patient was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact.

Contact tracing and testing should be carried out only for patients for whom the risk is regarded as significant. **D(GPP)**

R102 Patients should be regarded as at risk of infection if they spent more than eight hours in the same bay as an inpatient with sputum smear-positive TB who had a cough. The risk should be documented in the contact's clinical notes, for the attention of the contact's consultant. The contact should be given 'inform and advise' information, and their general practitioner should be informed. **D(GPP)**

R103 If patients were exposed to a patient with sputum smear-positive TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, they should be managed as equivalent to household contacts (see section 12.2). **D(GPP)**

R104 If an inpatient with sputum smear-positive TB is found to have MDR TB, or if exposed patients are HIV positive, contact tracing should be in line with the Interdepartmental Working Group on Tuberculosis guidelines.[386] **D(GPP)**

R105 In cases of doubt when planning contact tracing after diagnosing sputum smear-positive TB in an inpatient, further advice should be sought from the regional or national Health Protection Agency and/or people experienced in the field. **D(GPP)**

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.6.
For details of contact tracing in general, see section 12.2.
For examples of 'inform and advise' information, see Appendix F.

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

12.8.1 Clinical introduction

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

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

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

12.8.2 Current practice

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

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

12.8.3 Methodological introduction

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

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

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

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

12.8.4 Evidence statements: service models

▷ Proportions of new immigrants identified by different service models

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

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

The evidence for the proportions of new entrants identified by the different models is presented in Table 32 overleaf.

Table 32 Summary of evidence: models of new entrant screening

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

▷ Proportions of new immigrants identified with latent tuberculosis

In one study[356] the POA service model identified more new immigrants with weak tuberculin-positive reactions, but fewer with strongly positive TST reactions in comparison to targeted screening of homeless new immigrants and new immigrants screened in GP settings. The evidence is presented in Table 33.

Table 33 Detection of latent TB in contact tracing among new entrants

POA model, N (%) Heaf tested, Heaf grade	Primary care model, N (%) Heaf tested, Heaf grade	Homeless screening model, N (%) Heaf tested, Heaf grade	Statistical significance	NICE grade
100/181 (55) grade 2	14/39 (35) grade 2	84/172 (49) grade 2	Not reported	2+
9/181 (5) grade 3 or 4	8/39 (21) grade 3 or 4	13/172 (8) grade 3 or 4	Not reported	2+

▷ Proportions of new immigrants identified with active tuberculosis

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

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

The evidence is presented in Tables 34 and 35 below.

Table 34 Detection of latent TB in contact tracing among new entrants

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

Table 35 Detection of active TB disease in new entrants detected within the same five-year time period, N (%)

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

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

One study[357] found that active TB cases detected by new immigrant screening had on average shorter duration of symptoms and fewer hospital admissions compared to TB patients detected by passive case finding. The evidence is presented Table 36.

Table 36 Symptoms and hospital admissions in new entrants identified with active TB

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

12.8.5 Evidence statements: screening methods

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

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

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

▷ Effectiveness of TST in comparison to chest X-ray for predicting a diagnosis of active tuberculosis

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

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

12.8.6 Health economic modelling

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

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

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

12.8.7 Cost-effectiveness of prophylaxis for suspected latent infection

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

▷ Cost-effectiveness of BCG for TST-negative new entrants

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

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

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

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

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

▷ Cost-effectiveness of new entrant screening

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

12.8.8 From evidence to recommendations

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

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

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

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

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

2. To detect those with tuberculosis infection, particularly children, for whom treatment for latent TB infection is appropriate.
3. To identify those with no evidence of tuberculosis infection who, if previously unvaccinated, may benefit from BCG vaccination.

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

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

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

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

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

RECOMMENDATIONS

R106 Healthcare professionals, including primary care staff, responsible for screening new entrants* should maintain a coordinated programme to:

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

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

R107 New entrant screening for tuberculosis should be incorporated within larger health screening programmes for new entrants, linked to local services. **D(GPP)**

R108 Assessment for, and management of, TB in new entrants should consist of the following. **D(GPP)**

- ❑ A chest X-ray for those who have not had one recently taken, unless they are younger than 11 or are possibly pregnant.
- ❑ Clinical assessment for those with an abnormal chest X-ray.
- ❑ Risk assessment for HIV, including HIV prevalence rates in the country of origin, which is then taken into account for Mantoux testing and BCG vaccination.
- ❑ A Mantoux test for people with normal recent chest X-ray who are:
  - younger than 16, *or*
  - aged 16–35, from sub-Saharan Africa or a country with a TB incidence greater than 500 per 100,000.
- ❑ A Mantoux test for:
  - children younger than 11 years
  - pregnant women.
- ❑ Interferon-gamma test (if available) if Mantoux test positive (6 mm or greater) in someone who has not had BCG vaccination, or strongly positive (15 mm or greater) in someone who has been vaccinated.
- ❑ Assessment for active TB if interferon-gamma test is positive; interpret chest X-ray first if it is not contraindicated.
- ❑ Treatment for latent TB infection for people aged 35 or younger in whom active TB has been excluded, with a positive Mantoux test inconsistent with their BCG history, and a positive interferon-gamma test (if this test was available), and who are:
  - younger than 16, *or*
  - aged 16–35, from sub-Saharan Africa or a country with a TB incidence greater than 500/100,000.
- ❑ Consideration of BCG for unvaccinated people who are Mantoux negative (see section 11.4).
- ❑ 'Inform and advise' information for people who do not have active TB and are not being offered BCG or treatment for latent TB infection.

See the algorithm in Figure 10 for further detail.

R109 New entrants should be identified for TB screening from the following information:

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

R110 Any healthcare professional working with new entrants should encourage them to register with a GP. **D(GPP)**

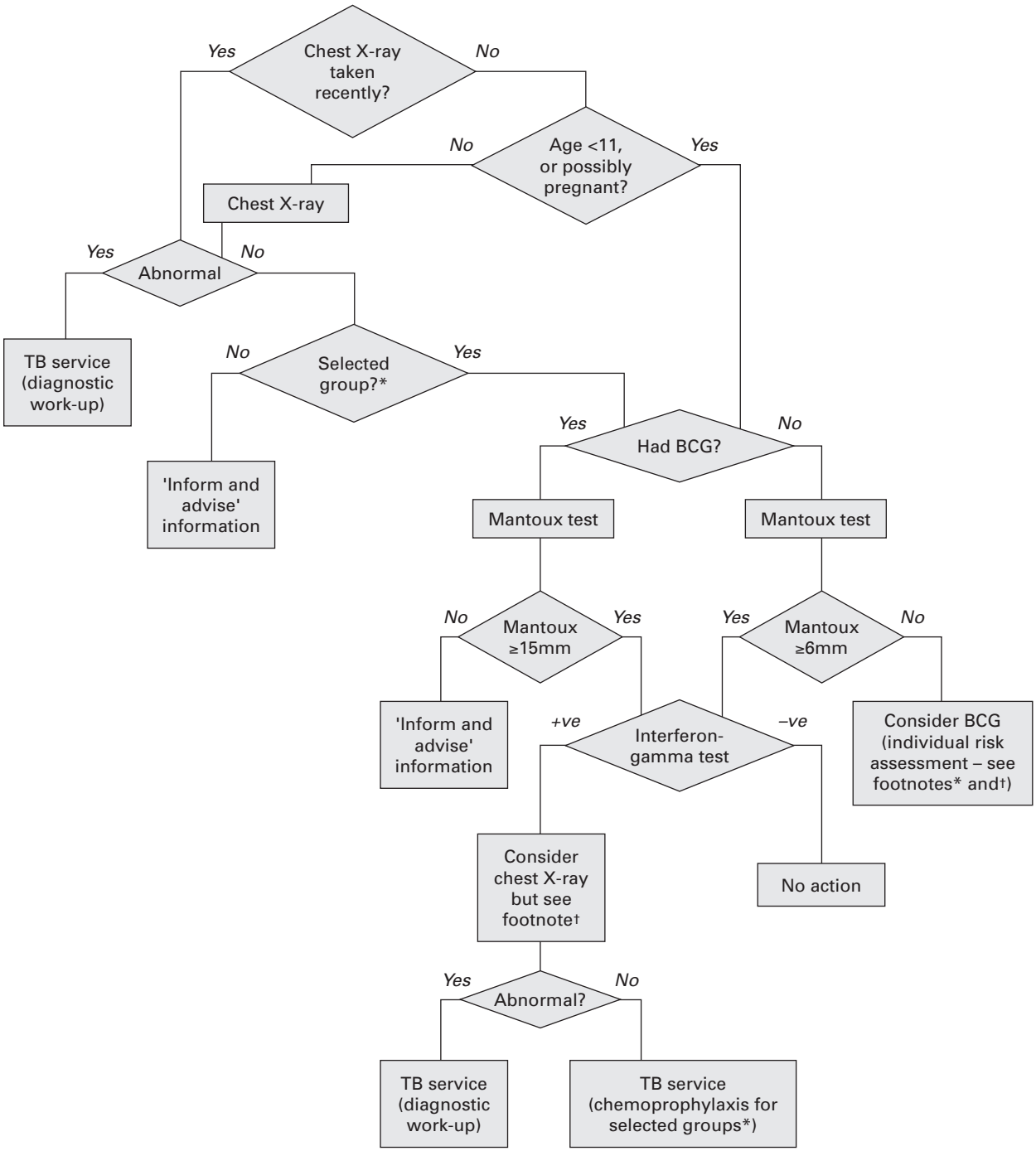
Cross-referring:

For details of diagnosing latent TB, see section 5.1.

For details of diagnosing active TB, see section 5.2.

For details of BCG vaccination, see section 11.4

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



This algorithm sets out the actions for screening new entrants (or people returning after a prolonged stay) to England or Wales from a country with a high incidence of TB (as defined by the HPA; go to **www.hpa.org.uk** and search for 'WHO country data TB'). It does **not** apply to people who are known to be HIV-positive, who should be referred to an HIV team. People coming to the UK to work in healthcare with either patient or clinical material contact should be screened in line with the 'new NHS employees' algorithm. It applies to dedicated new entrant screening services, and therefore does not detail the systems for detecting new entrants, nor the clinic activities that follow. Service providers with a different service model may need to adapt this to their individual processes.

* Select new entrants for further screening/action if they are any one of the following:
  - age <16
  - age 16–35 from sub-Saharan Africa or a country with incidence >500/100,000

† Timing of chest X-ray and/or BCG may be dependent on pregnancy status. Interpret existing chest X-ray if one has been taken recently.

Figure 10: Algorithm for new entrant screening

12.9 Street homeless people

12.9.1 Clinical introduction

Deprivation has long been associated with tuberculosis. Much higher rates of tuberculosis disease in street homeless people and hostel dwellers have been recognised for many years[362,363]. Chest X-ray screening of homeless people attending a soup kitchen in London in 1993[364] showed 4.3% with X-ray changes suspicious of active tuberculosis of which 1.5% (1,500/100,000) were confirmed as having bacteriologically confirmed active disease. The great majority of such street homeless people in the UK up to the late 1990s were men of white ethnicity, whose rate of tuberculosis from national data would normally be expected to be in the range of 5/100,000 per annum.[26,140]

12.9.2 Methodological introduction

Studies that compared different methods of screening for latent tuberculosis infection and active tuberculosis disease in homeless people in order to evaluate which method was most effective were targeted.

Six non-analytic studies focused on different tuberculosis screening methods applied to homeless participants. None of the studies reported the results of interferon-gamma immunological testing in homeless people. Four studies[308,328,365,366] did not make comparisons between the different screening methods they reported and were excluded.

Two studies[367,368] conducted in the UK and the USA compared homeless people diagnosed with active tuberculosis with their prior test results on symptom questionnaire, tuberculin skin test, and chest X-ray. The studies were included despite having the following methodological limitations.

- ❑ The number of people approached for screening and resultant screening uptake was not clearly reported.
- ❑ Not all tests were read and no explanation for this was provided.
- ❑ Some studies offered incentives to attend for screening, while others did not.
- ❑ Those involved in collecting prospective data via interviews were aware of retrospective findings that categorised subjects by clinical outcome.
- ❑ It was not reported how screening tests were conducted and read and by whom.
- ❑ Screening methods used did not show a combination of good sensitivity and specificity.
- ❑ Uptake of screening varied between 40–90% at different sites.
- ❑ Investigators did not state whether tests were performed blindly or independently.
- ❑ Statistical significance testing was not done.

12.9.3 Evidence statements

▷ Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting latent tuberculous infection

One retrospective study[367] found that tuberculin skin testing was more effective in detecting latent tuberculosis and eligibility for treatment for latent TB infection in homeless people than either symptom questionnaire or chest X-ray. The evidence is presented in Table 37.

Table 37 Summary of evidence: detection methods for latent TB

People with abnormal symptom questionnaire scores	People with positive tuberculin skin test results, Heaf grade 4	People with abnormal chest X-ray results	Statistical significance	NICE grade
0/5 with Heaf grade 4 (0% sensitivity)	5/5 prescribed treatment for latent TB infection (100% sensitivity)	0/5 with Heaf grade 4 (0% sensitivity)	Not reported	3+

▷ Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting active tuberculous disease

Two retrospective studies,[367,368] did not find consistent evidence that any of the three screening methods compared were more effective than the others in detecting signs and symptoms of TB in homeless people subsequently diagnosed with active tuberculosis. Evidence is summarised in Table 38 below.

Table 38 Summary of evidence: detection methods for active TB

N (%) TB disease cases with abnormal symptom questionnaire scores	N (%) TB disease cases with tuberculin skin test positive scores	N (%) TB disease cases with abnormal chest X-ray results	Statistical significance	Ref and NICE grade
2/10 (20) reported haemoptysis	1/10 (10) (7/10 cases did not have TST)	8/10 (80)	Not reported	[367,368] 3+
13/16 (81), sensitivity 81%, specificity 51%, PPV 23%, NPV 94%	11/16 (69), sensitivity 69%, specificity 83%, PPV 42%, NPV 94%	5/16 (31), sensitivity 31%, specificity 94%, PPV 50%, NPV 88%	Not reported	[367;368] 3+

PPV = Positive predictive value; NPV = Negative predictive value.

12.9.4 From evidence to recommendations

The rate of TB in street homeless people is still high. This group is difficult to reach. Emphasis should therefore be on active case finding, which may have to be done on an opportunist and/or symptomatic basis. In urban settings, digital chest X-ray provides fast results for likely active disease.

Simple incentives for attending screening, such as hot drinks or snacks, may be useful. Because of the mobility of this group, tuberculin skin testing and interferon-gamma testing were felt to be less useful generally, because people may move before test reading and are also not likely to complete treatment for latent TB infection. The important role of the TB service was recognised in promoting awareness of TB, and who to contact, among those working with homeless people, including primary care professionals, and the social and voluntary sectors.

The GDG were unable to make a service configuration recommendation on the frequency of screening in this group, given the lack of any evidence to guide them.

RECOMMENDATIONS

R111 Active case finding should be carried out among street homeless people (including those using direct access hostels for the homeless) by chest X-ray screening on an opportunistic and/or symptomatic basis. Simple incentives for attending, such as hot drinks and snacks, should be considered. **D(GPP)**

R112 Healthcare professionals working with people with TB should reinforce and update education about TB, and referral pathways, to primary care colleagues, social workers and voluntary workers who work with homeless people. **D(GPP)**

Cross-referring:
For details of diagnosing active TB, see section 5.2.

13 Preventing infection in specific settings

13.1 Healthcare environments: new employees

13.1.1 Clinical introduction

Studies in the late 1980s suggested that the incidence of TB in healthcare workers, with the general exception of mortuary workers, was no higher than that of the general population.[369] More recently however a study found a twofold increased risk among healthcare workers.[300] Also more recently the NHS has been recruiting staff, particularly nurses, from developing countries with a high incidence of tuberculosis. This is acknowledged as an essential area for improvement in the 2004 Chief Medical Officer's TB Action Plan[2] which gives as a goal: 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.

13.1.2 Methodological introduction

Studies on the prevention of TB transmission in newly employed staff in hospital settings were sought. Only one non-analytic study[370] met the inclusion criteria.

Studies focusing on pre-employment screening measures to prevent and control the transmission of TB in healthcare workers with HIV infection were also targeted. No evidence was found, and hence there are no evidence statements for this area.

13.1.3 Evidence statements

▷ TB prevention and control measures in pre-employment occupational health screening

One retrospective non-analytic study[370] reported on the following interventions for pre-employment occupational health screening in West Midlands NHS hospitals:

- identification of new doctors eligible for TB screening
- identification of new doctors and nurses at risk for active tuberculous disease
- appropriateness of tuberculin skin testing for new employees.

Evidence is summarised in Table 39 overleaf.

13.1.4 From evidence to recommendations

This guideline is not intended to duplicate the guidance which was, at the time of writing, being drafted by the Department of Health ('Health clearance for serious communicable diseases: new health care workers').

The recommendations are also guided by the advice of the Chief Medical Officer to the NHS in England to 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.[2]

There is a possibility that new employees in healthcare environments who have recently entered the UK can miss out on the advanced level of screening given to new entrants. In this regard, the recommendations refer the reader to the section of the guideline for new entrants.

Table 39 Summary of evidence: pre-employment screening

Intervention	Occupational health service pre-employment screening	NICE grade
Doctors eligible for TB screening, N (%)	Identified 7/14 (50) new doctors who developed active TB disease during employment.	3+
Healthcare workers at risk for active TB disease, measured by Heaf test grade	• Did not act on evidence of TB transmission in newly appointed doctors, and found no evidence of TB transmission in newly-appointed nurses. • 3/7 new doctors TST positive (grades 3–4) subsequently diagnosed with active TB via self-referral with symptoms. • Six new nurses TST negative (grades range 0–2) subsequently diagnosed with active TB.	3+
TST, Heaf test	• Inappropriately applied TSTs to 13/26 new employees. • Two without prior BCG vaccination were not tested and developed TB disease. • Nine with prior BCG vaccination were tested. • 1/2 with unknown BCG status was tested.	3+

Limitations in pre-employment screening techniques are reported in the evidence base. Consequently, the GDG agreed that symptoms should be screened first, possibly by questionnaire, as a way to identify any new staff who may have active tuberculosis. Chest X-rays are the first choice of test for those with signs or symptoms.

For the majority of new employees without any signs or symptoms, resources should be used effectively by carrying out an individual risk assessment and choosing screening techniques accordingly. This is familiar current practice for many occupational medicine departments.

The recommendations aim to make sure that new employees are screened before commencing work. It was noted that the NICE guideline cannot dictate screening techniques to non-NHS agencies, and also that such screening may be carried out in other countries with attendant difficulty in receiving documentation. However, the health risks associated with employing an infectious member of staff were deemed to warrant a thorough check before they start work.

The evidence base does not support a significant departure from the details of the recommendations in the BTS code of practice.[6]

Although the evidence is limited to hospitals, the recommendations are applicable to primary as well as secondary care, and to ancillary as well as clinical staff.

RECOMMENDATIONS

R113 Employees new to the NHS who will be working with patients or clinical specimens should not start work until they have completed a TB screen or health check, or documentary evidence is provided of such screening having taken place within the preceding 12 months. **D(GPP)**

R114 Employees new to the NHS who will not have contact with patients or clinical specimens should not start work if they have signs or symptoms of TB. **D(GPP)**

R115 Health checks for employees new to the NHS who will have contact with patients or clinical materials should include: **D(GPP)**

- assessment of personal or family history of TB
- symptom and signs enquiry, possibly by questionnaire
- documentary evidence of TB skin testing (or interferon-gamma testing) and/or BCG scar check by an occupational health professional, not relying on the applicant's personal assessment
- Mantoux result within the last five years, if available.

R116 If an employee new to the NHS has no (or inconclusive) evidence of prior BCG vaccination, a Mantoux or interferon-gamma test (see section 5.1) should be performed. **D(GPP)**

R117 Employees who will be working with patients or clinical specimens and who are Mantoux negative (less than 6 mm) should have an individual risk assessment for HIV infection before BCG vaccination is given. **D(GPP)**

R118 Employees new to the NHS should be offered BCG vaccination, whatever their age, if they will have contact with patients and/or clinical specimens, are Mantoux negative (less than 6 mm) and have not been previously vaccinated. See section 11.5 for more detail. **D(GPP)**

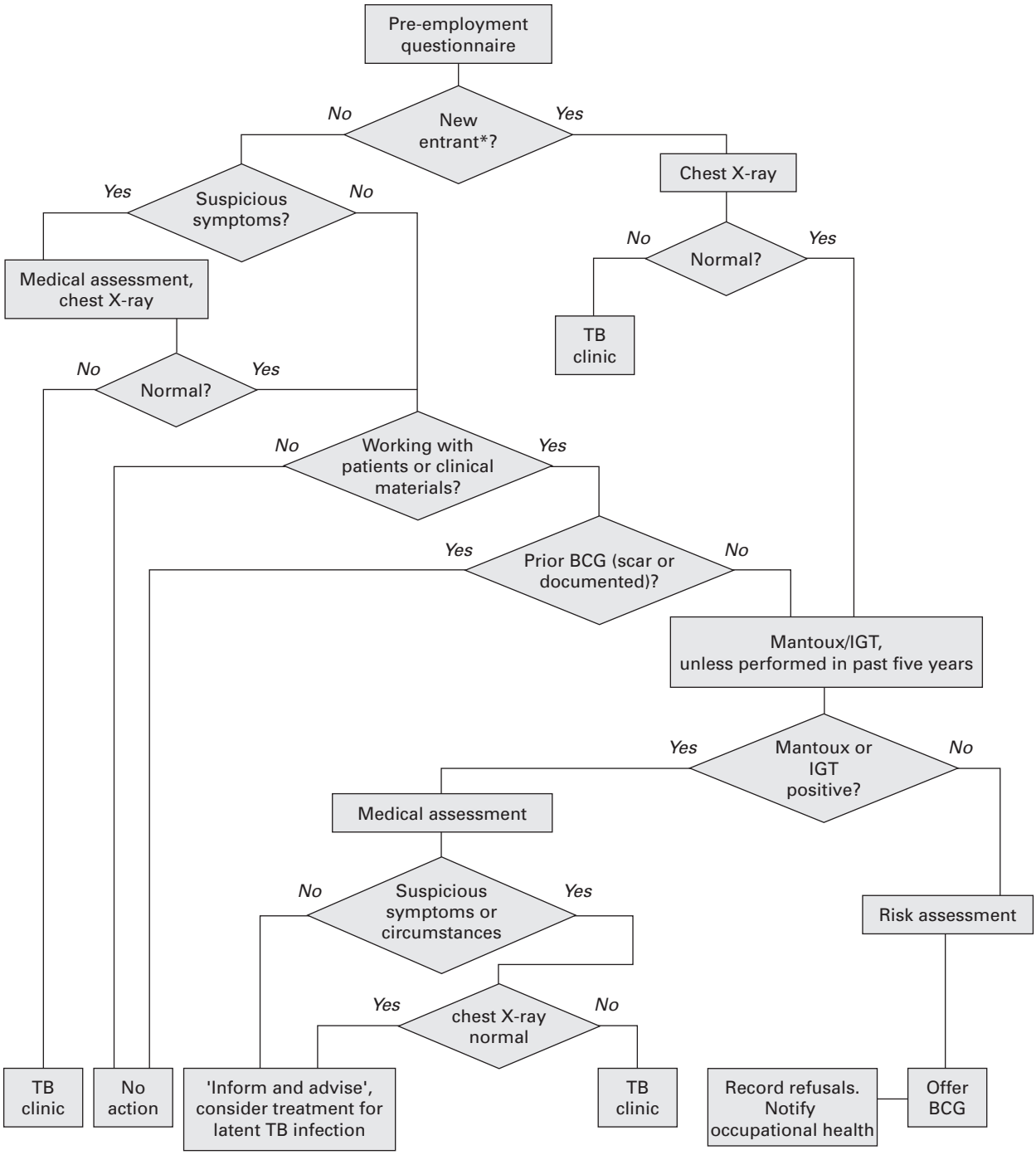
R119 Employees of any age who are new to the NHS and are from countries of high TB incidence, or who have had contact with patients in settings with a high TB prevalence should have a Mantoux test. If negative (less than 6 mm), recommendations R117 and R118 should be followed. If positive (6 mm or greater), the person should be referred for clinical assessment for diagnosis and possible treatment of latent infection or active disease. **D(GPP)**

R120 If a new employee from the UK or other low-incidence setting, without prior BCG vaccination, has a positive Mantoux or interferon-gamma test, they should have a medical assessment and a chest X-ray. They should be referred to a TB clinic for consideration of TB treatment if the chest X-ray is abnormal, or for consideration of treatment of latent TB infection if the chest X-ray is normal. **D(GPP)**

R121 If a prospective or current healthcare worker who is Mantoux negative (less than 6 mm), declines BCG vaccination, the risks should be explained and the oral explanation supplemented by written advice. If the person still declines BCG vaccination, he or she should not work where there is a risk of exposure to TB. The employer will need to consider each case individually, taking account of employment and health and safety obligations. **D(GPP)**

R122 Clinical students, agency and locum staff and contract ancillary workers who have contact with patients or clinical materials should be screened for TB to the same standard as new employees in healthcare environments, according to the recommendations set out above. Documentary evidence of screening to this standard should be sought from locum agencies and contractors who carry out their own screening. **D(GPP)**

R123 NHS trusts arranging care for NHS patients in non-NHS settings should ensure that healthcare workers who have contact with patients or clinical materials in these settings have been screened for TB to the same standard as new employees in healthcare environments (see R113–R122). **D(GPP)**



* New entrants = people arriving in or returning to the UK from a high-incidence country (as defined by HPA website **www.hpa.org.uk**).

Figure 11: Algorithm for new NHS employees

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.5.
For examples of 'inform and advise' information, see Appendix F.

13.2 Healthcare environments: occupational health

13.2.1 Clinical introduction

TB is transmitted through the aerosol route. Hitherto, best practice in hospitals[6] has been that patients with suspected pulmonary tuberculosis are initially admitted to single rooms, vented to the outside, until their sputum status is known and risk assessments for infectiousness and MDR TB are made. The risk assessment should also take into account the immune status of other patients on the ward. These measures should greatly reduce the chance of transmission to staff, but surveys of infection control practice show poor adherence.[371]

Readers should be aware of the Health and Safety Executive guidance in this area, 'Biological agents: managing the risks in laboratories and healthcare premises' (available from **www.hse.gov.uk**).

13.2.2 Methodological introduction

Studies on the prevention of TB transmission in staff currently employed in hospital settings were sought. One cohort study and four non-analytic studies were found.

Five non-analytic studies from the USA[233,372–375] were excluded due to methodological limitations, presented in Appendix G. One non-analytic study from the UK[371] while methodologically sound, was excluded as it addressed the extent to which TB infection control measures recommended by guidelines were applied in practice, but did not seek to evaluate the effectiveness of recommended measures.

One cohort study[376] and four non-analytic studies[235,370,377,378] reported evidence on the following:

- effects of new infection control measures in reducing TB transmission in hospital workers
- the association between ventilation controls and tuberculin skin test conversion in hospital workers
- effectiveness of occupational health screening for identifying cases of active tuberculous disease in hospital workers
- effects of serial tuberculin skin tests in BCG vaccinated hospital workers.

Studies on screening measures to prevent and control the transmission of TB in employed healthcare workers with HIV infection were also targeted. No evidence was found that met the inclusion criteria, and hence there are no evidence statements for this area.

13.2.3 Evidence statements

▷ Effects of new infection control measures in reducing tuberculosis transmission in hospital workers

Evidence statements are presented in Table 40.

Table 40 Summary of evidence: infection control measures

New infection control measures	Population	N (%) decrease in healthcare worker TST conversion rate in response to new measures	Association/ statistical significance	Ref and NICE grade
1) Introduction of new respiratory isolation rooms. 2) Ventilation with at least 25% fresh air in the work area. 3) Laminar airflow from staff to patients. 4) Plastic droplet shields for staff.	Emergency department staff (intervention group) *vs.* other hospital workers not benefiting from interventions	Baseline: 6/50 (12) *vs.* 51/ 2514 (2)	RR 5.9 (95%CI 2.7 to 13.1); absolute difference 10% (95%CI 1% to 19%).	[376] 2+
		Post-intervention: 0/64 *vs.* 36/3000 (1.2)	RR not calculable; absolute difference 1.2% (95%CI 1% to 2%)	[376] 2+
1) Higher diagnostic suspicion for infectious TB. 2) Stricter criteria for discontinuation of patient isolation. 3) Stricter criteria for patient adherence to isolation procedures and use of respiratory protection when outside isolation rooms. 4) Restriction of sputum induction and aerosolised pentamidine treatment to isolation rooms. 5) Expansion of anti-TB therapy to include at least two more drugs. 6) Improvements to negative pressure rooms. 7) Upgraded respiratory protection for employees. 8) Improvement in speed of return for diagnostic tests.	Susceptible healthcare workers on an HIV ward	Initial period 7/25 (28) to early follow-up 3/17 (18) to late follow-up period 0/23	$p<0.01$	[235] 3+

▷ The association between ventilation controls and tuberculin skin test conversion in hospital workers

Evidence statements are presented in Table 41.

Table 41 Summary of evidence: ventilation

Association	TST conversion rates in healthcare workers	Association/ statistical significance	Ref and NICE grade
Ventilation in non-isolation rooms and risk of latent TB infection	Shorter time to conversion significantly associated with being in a non-isolation room with less than two air exchanges *vs.* a room with two plus air exchanges per hour.	Hazard ratio: 3.4 (95%CI 2.1 to 5.8)	[377] 3+
Ventilation in respiratory isolation rooms and risk of latent TB infection	No significant difference in time to conversion for isolation rooms with less than six air exchanges *vs.* those with six plus air exchanges per hour.	Hazard ratio: 1.02 (95%CI 0.8 to 1.3)	[377] 3+
Inadequate ventilation and risk of latent TB infection in nurses and housekeeping staff	Rates significantly associated with inadequately ventilated non-isolation and isolation rooms.	p<0.001	[377] 3+
Inadequate ventilation and risk of latent TB infection in respiratory therapists	Rates significantly associated with inadequate ventilated non-isolation and bronchoscopy rooms.	p<0.001	[377] 3+

▷ Effectiveness of occupational health screening for identifying cases of active tuberculous disease in hospital workers

One study[370] found that occupational health screening in West Midlands NHS hospitals detected fewer cases of active TB in employees than self-referral or contact tracing exercises.

Over a three-year period occupational health surveillance detected one (3.8%) case of active TB *vs.* 23 (88%) TB cases who self-referred with symptoms, and two cases (7.6%) detected via contact tracing exercises. Statistical significance testing was not done. (**3+**)

▷ Effects of serial tuberculin skin tests in BCG vaccinated hospital workers

One prospective study[378] found that an initial TST, followed by a repeat TST administered one week later to BCG vaccinated hospital employees resulted in an increased diameter of induration for the repeat test relative to the first test when read at 48 hours. This was followed by a decreased induration for the repeat test relative to the first at 72 hours.

Mean induration diameter was 7.1 mm for test 1 *vs.* 14.9 mm for repeat test at 48 hours (mean change 7.8 mm; 95%CI 4.2 to 11.4 mm, p<0.001). There was no difference between the tests at 72 hours (mean induration diameter 9.5 mm at test 1 versus 9.7 mm on repeat test, mean change 0.2 mm; 95%CI –4.0 mm to 4.4 mm, p=0.93). (**3+**)

13.2.4 From evidence to recommendations

The evidence base is not easily applicable to a UK NHS setting. Studies to assess the impact of certain isolation and infection control procedures have been performed in North America, using tuberculin skin test conversion (not performed in this context in the UK) as a marker of infection. The population of staff on which these studies are performed is also generally not BCG vaccinated.

There is a duty on staff to report symptoms as part of protecting patients.[62,379]

Annual reminders are appropriate as a regular intervention in selected staff members, and this is best done at the same time as other annual reminders, for example influenza vaccination. In staff in general, it was felt that the recommendations should promote awareness through 'inform and advise' information.

RECOMMENDATIONS

These recommendations set the standard for NHS organisations and therefore should apply in any setting in England and Wales where NHS patients are treated.

R124 Reminders of the symptoms of TB, and the need for prompt reporting of such symptoms, should be included with annual reminders about occupational health for staff who: **D(GPP)**

- are in regular contact with TB patients or clinical materials, *or*
- have worked in a high-risk clinical setting for four weeks or longer.

One-off reminders should be given after a TB incident on a ward.

R125 If no documentary evidence of prior screening is available, staff in contact with patients or clinical material who are transferring jobs within the NHS should be screened as for new employees (see section 13.1). **D(GPP)**

R126 The risk of TB for a new healthcare worker who knows he or she is HIV positive at the time of recruitment should be assessed as part of the occupational health checks. **D(GPP)**

R127 The employer, through the occupational health department, should be aware of the settings with increased risk of exposure to TB, and that these pose increased risks to HIV-positive healthcare workers. **D(GPP)**

R128 Healthcare workers who are found to be HIV positive during employment should have medical and occupational assessments of TB risk, and may need to modify their work to reduce exposure. **D(GPP)**

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.5.
For examples of 'inform and advise' information, see Appendix F.

13.3 Prisons and remand centres

13.3.1 Clinical introduction

In some countries the prison system acts as an amplification system for tuberculosis, with infected inmates causing transmission both within the prison and also in the community after discharge – either while still infectious or without adequate treatment and follow-up arrangements (or both). TB in the prison system of England and Wales was not thought to be a significant problem in the 1980s.[380] Prisoners however are likely to disproportionately include those with social and deprivation risk factors for TB (for example, social exclusion or drug abuse).

More recently, TB in prisons has increased and one community prison in London has been shown to be involved with the transmission of TB in an ongoing isoniazid-resistant TB outbreak.[329]

The 2005 Chief Medical Officer's TB Action Plan[2] sets improvements in prison care as one of the essential activities to be undertaken in improving TB care: 'achieve good coverage of prisons, with arrangements in particular for rapid assessment of suspected cases, supervision of prisoners' TB treatment, and maintenance of uninterrupted care by liaising with the services in their new area of residence prior to their release'. It also calls for strengthened surveillance of TB in prisons.

Throughout this section, the guideline uses the following terminology: in the USA, *jails* mostly house pre-trial detainees or inmates with short-duration sentences, whereas *prisons* house sentenced inmates for longer durations. In the UK, pre-trial detainees are housed in *remand centres* until completion of the trial and sentencing, while sentenced inmates are located in *prisons*. Remand and sentenced prisoners are often mixed within local prisons. In all these circumstances, those detained are referred to as *prisoners*.

13.3.2 Current practice

The review of current services shows that TB service providers either care for prisoners in clinics, or go on prison visits. Prior to the integration of prison medical services into the NHS, prisons would typically have arrangements for secondary care with one local hospital trust. Excluding those that stated that there was no prison or remand centre in their area, about a third cared for prisoners in clinics and a slightly higher proportion undertook prison visits, although some of these were not routine.

13.3.3 Methodological introduction

Studies investigating whether there were effective strategies for the prevention and control of the transmission of TB infection and disease in prisons were targeted. Two randomised controlled trials[206,208] and four non-analytic studies[381–384] were found. However, two of these[383,384] were excluded due to methodological limitations presented in Appendix G. The studies were all conducted in the USA in either prison or jail settings.

13.3.4 Evidence statements

▷ Comparing strategies used in prisons to facilitate completion of prophylaxis in prisoners released back into the community

Two RCTs[206,208] compared :

- one TB education session *vs.* one TB education session plus a financial incentive
- one TB education session *vs.* one TB education session plus a financial incentive *vs.* TB education sessions administered every two weeks for the duration of an inmate's stay.

The evidence is presented in Table 42 overleaf.

Table 42 Summary of evidence: educational interventions in prisons

Outcomes	One TB education session control	TB education session plus financial incentive	TB education sessions administered every 2 weeks	Association/ statistical significance	Ref and NICE grade
N (%) attendance at follow-up community clinic appointment	7/30 (23.3)	8/31 (25.8)	N/A	NS OR 1.43 (95%CI 0.35 to 3.71, p=0.82)	[206] 1+
	25/104 (24)	42/114 (37)	40/107 (37)	Adjusted OR (pooled results for education and incentive groups): 1.85 (95%CI 1.04 to 3.28, p=0.04)	[208] 1+
N (%) completed prophylaxis	2/31	2/30	N/A	Not reported	[206] 1+
	12/25 (48)	14/42 (33)	24/37 (65)	p=0.02	[208] 1+
			Over twice as likely to complete than control group	Adjusted OR 2.2 (95%CI 1.04 to 4.72, p=0.04)	[208] 1+
		Completion no different from control group		Adjusted OR 1.07 (95%CI 0.47 to 2.4)	[208] 1+

▷ Strategies used to facilitate prevention and control of TB infection and disease within prisons

One non-analytic study[381] investigated the use of screening strategies to detect TB disease in incarcerated inmates.

The evidence is summarised in Table 43.

Table 43 Summary of evidence: detection of active TB in prisons

Population	Prior history/ TB symptom reports	Routine TB screening (TST and chest X-ray)	Cases detected by contact tracing	Statistical significance	NICE grade
N (%) new inmates	13/53 (24)	39/53 (74)	N/A	Not reported	3+
N (%) longer-term inmates (≥ six months)	31/43 (72)	8/43 (19)	4/43 (9)	Not reported	3+

Over the five-year study period, entry screening of 87,518 new prisoners identified 53/55 (96% sensitivity) TB disease cases in this group. (3+)

Another non-analytic study[382] reported on the following screening procedures to detect TB disease in new prisoners:

- routine tuberculin skin tests
- routine chest X-ray tests
- use of isolation for prisoners with suspected TB disease.

The evidence is presented in Table 44.

Table 44 Summary of evidence: process of detecting active TB in prisons

	TST screening period	Chest X-ray screening period	Statistical significance	NICE grade
Detection of cases treated for TB disease, N	8 (denominator not reported)	8/1,830	Not reported	3+
Average time to isolation of suspected TB cases, hours	Exceeded 96 hours	24 hours or less*	Not reported	3+
Prisoners placed in isolation, N (%)	8/72 (11)	64/72 (89%)**	Not reported	3+

** Change in protocol from use of TST to use of chest X-ray screening eliminated the waiting period for reading TST results.*
*** Only 7/16 inmates ultimately met the case definition for active TB disease for both periods.*

13.3.5 From evidence to recommendations

Other than limited data on measures to enhance treatment for latent TB infection in prisoners in the USA, there was little good-quality data in this area. There was a small amount of data to suggest that questionnaires are better than X-rays on initial screening, but that chest X-rays were better for screening symptomatic patients during imprisonment.

It is important to raise awareness of signs and symptoms in prisoners, prison staff and healthcare workers working in prisons and remand centres.

A lack of continuity of care over transfer between prisons and release to the community was seen as a major barrier to treatment completion, and prison medical services should take responsibility for having arrangements in place before either transfer or release.

There is a risk of drug resistance and the possibility of non-adherence, and accordingly DOT is recommended for all prisoners and detainees.

In addition, there is a risk to prison staff, and a level of occupational health equivalent to that of healthcare workers is recommended.

The current practice of taking three sputum samples within 24 hours for microscopy, including a morning sputum sample is supported in the recommendations.

The GDG considered the possibility of screening and BCG vaccination in young offenders' institutions, but agreed that the low number of cases that would be detected could not justify this.

RECOMMENDATIONS

R129 Healthcare workers providing care for prisoners and remand centre detainees should be aware of the signs and symptoms of active TB (see section 5.2). TB services should ensure that awareness of these signs and symptoms is also promoted among prisoners and prison staff. **D(GPP)**

R130 Prisoners should be screened for TB by:

- a health questionnaire on each entry to the prison system, *then* **D(GPP)**
- for those with signs and symptoms of active TB, a chest X-ray, **C** and three sputum samples taken in 24 hours for TB microscopy, including a morning sputum sample (see section 5.2). **D(GPP)**

R131 All prisoners receiving treatment for active or latent TB should receive DOT. **D(GPP)**

R132 Prison medical services should have liaison and handover arrangements to ensure continuity of care before any prisoner on TB treatment is transferred between prisons. **D(GPP)**

R133 If a prisoner is being treated for active or latent TB, the prison medical services should draw up as early as possible a contingency plan for early discharge, which could happen directly from a court appearance. This plan should include firm arrangements for clinical follow-up and treatment monitoring in the intended district of residence, and should take into account that there may not be a fixed residence arranged for the prisoner after release. The prisoner should be given contact details for a named key worker, who will visit and monitor the prisoner after release and liaise between services involved. **D(GPP)**

R134 Prison service staff and others who have regular contact with prisoners (for example, probation officers and education and social workers) should have pre- and on-employment screening at the same level as for healthcare workers with patient contact (see sections 13.1 and 13.2). **D(GPP)**

14 Notification and enhanced surveillance

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

14.1 Tuberculosis surveillance

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

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

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

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

Information for TB case reports is currently mainly based on statutory notifications (NOIDs) implemented in 1913 and Enhanced Tuberculosis Surveillance (ETS) implemented in 1999. Treatment outcome monitoring was implemented as part of ETS in 2002. Information on tuberculosis isolates is based on MycobNet (Mycobacterial Surveillance Network) developed in 1994, which collates information on all isolates of *M. tuberculosis* complex confirmed at reference centres for mycobacteriology, including species and drug susceptibility results. On a yearly basis, data on TB cases reports from ETS are linked at national level with information from MycobNet on initial isolates in order to improve the completeness of laboratory information (including drug susceptibility results) among TB incident cases.

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

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

All new tuberculosis cases (culture-confirmed cases and other than culture confirmed cases) should be reported.

A **culture-confirmed case** is defined as culture confirmed disease due to *M. tuberculosi*s complex (*M. tuberculosis*, *M. bovis* or *M. africanum*).

A **case other than culture confirmed** is defined as a case, that in absence of culture confirmation, meets the following criteria:

a) clinician's judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis,

and

b) clinician's decision to treat the patient with a full course of anti-tuberculosis treatment.

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

14.2 Statutory notifications of infectious diseases

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

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

14.3 Enhanced Tuberculosis Surveillance in England, Wales and Northern Ireland

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

14.4 Treatment outcome monitoring in England, Wales and Northern Ireland

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

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

14.5 MycobNet (UK)

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

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

15 Priorities for future research

Research recommendation 1

A diagnostic and qualitative study, assessing whether interferon-gamma tests are acceptable to patients and more effective than tuberculin skin tests for:

- predicting subsequent development of active TB , *or*
- diagnosing or ruling out current active TB

when undertaking TB screening in:

- new immigrants from high TB prevalence countries
- healthcare workers
- children in high-risk areas who missed neonatal BCG
- contacts of sputum smear-positive TB
- HIV-positive patients.

This study should compare strategies of TST only, TST then IGT if positive, and IGT only.

Population	• New immigrants from high TB prevalence countries. • Healthcare workers. • Children in high-risk areas who missed neonatal BCG. • Contacts of sputum-positive TB. • HIV-positive patients.
Intervention	Interferon-gamma tests.
Comparison	Tuberculin skin tests.
Outcome	Subsequent development of active TB. Qualitative patient acceptability outcome.

Research recommendation 2

A cluster RCT of DOT compared to self-administered treatment for latent and/or active TB should be conducted in a UK population. This should be targeted at homeless people, and those with a history of non-adherence, alcoholism, drug abuse or mental illness.

Population	Homeless people, those with a history of non-adherence, alcoholism, drug abuse, or mental illness.
Intervention	DOT.
Comparison	Self-administered treatment.
Outcome	Treatment completion, cure and relapse rates.

Research recommendation 3

A study is needed of people found by new entrant screening (as set out above in 12.7) to be Mantoux positive and interferon-gamma positive, to establish better estimates of the cost-effectiveness of screening and treatment for latent TB infection in this population. This could identify factors predisposing people to developing active TB so that more effective targeted treatment for latent TB infection programmes can be developed.

Population	New entrants with latent TB infection.
Intervention	Screening and treatment for latent TB infection.
Comparison	Not applicable.
Outcome	Risk factors for the development of active TB and the cost-effectiveness of screening and treatment for latent TB infection (£/QALY).

Research recommendation 4

A case control study, comparing people who developed active or latent TB with those who did not, and comparing the proportion vaccinated and the time since vaccination. The aim will be to derive improved estimates of protective efficacy and duration of protection of the BCG vaccine.

Population	Patients eligible to receive BCG vaccine (this could be neonates, contacts, healthcare workers, new immigrants, schoolchildren).
Intervention	BCG.
Comparison	No BCG.
Outcome	Development of active TB. Possibly the development of latent TB infection as assessed by interferon gamma test (to avoid BCG effects on TST).

Research recommendation 5

A study to ascertain quality of life score estimates from those with TB disease and latent infection including adverse treatment effects, using an appropriate, validated quality of life instrument. This will improve economic decision-making throughout TB.

Population	Those with TB disease or latent infection.
Intervention	Quality of life instrument.
Comparison	None.
Outcome	Quality of life score (single score estimate of health status).

Research recommendation 6

Is contact tracing more effective (in terms of identifying cases of latent infection and active TB disease) among household contacts, than among homeless contacts, of patients with confirmed TB disease?

Population	Adult contacts of index case patients with confirmed: • pulmonary smear-positive TB • pulmonary smear-negative TB • non-pulmonary TB.
Intervention	Contact screening of household contacts.
Comparison	Contact screening of homeless contacts.
Outcome	Case yields for latent TB infection and active TB disease among screened contacts.

Research recommendation 7

Do port of arrival scheme referrals with incentives for attendance of screening identify more cases of latent TB infection and active TB disease in comparison to port of arrival scheme referrals with no incentives for screening attendance in the new immigrant population?

Population	New immigrants from high TB prevalence (40+/100,000) countries.
Intervention	Port of arrival referrals with screening attendance incentives.
Comparison	Port of arrival referrals with no screening attendance incentives.
Outcome	Case yields for TB infection and active TB disease in intervention and comparison groups.

Research recommendation 8

Are incentives for attending chest X-ray screening more effective than no incentives in identifying cases of latent TB infection and active TB disease in the homeless population?

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

Other potential research recommendations

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

- ❑ A multicentre RCT in patients with bacteriologically confirmed tuberculous meningitis, comparing six to 11 months of chemotherapy with 12 months of treatment to ascertain if different treatment duration affects mortality and residual disability.

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

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

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

List of appendices

The appendices to this guideline are available on the RCP website at **www.rcplondon.ac.uk/pubs/books/TB/index.asp**

They are:

A: Clinical questions and search strategies
B: Glossary
C: Unlicensed medicines
D: Scope
E: Summary of healthcare needs analysis
F: Examples of 'inform and advise' information
G: Details of excluded studies
H: Health economic models

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Full version of NICE Guideline No. 33

TUBERCULOSIS: Appendices

National clinical guideline for diagnosis, management, prevention, and control

Developed by
National Collaborating Centre for Chronic Conditions
Royal College of Physicians

Table of Contents

APPENDICES

1 Appendix A: Clinical questions and search strategies

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

Question	Search Filters	Study Type	Database and Year
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 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	Diagnosis		Medline 1966 – 2004 Embase 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

Question	Search Filters	Study Type	Database and Year
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 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) 136 abstracts reviewed

Question	Search Filters	Study Type	Database and Year
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

Question	Search Filters	Study Type	Database and Year
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

Question	Search Filters	Study Type	Database and Year
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

Question	Search Filters	Study Type	Database and Year
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 morbidity?	None	All study designs	Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 108 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			

Question	Search Filters	Study Type	Database and Year
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 disease in comparison with other prophylactic drug treatment regimens?	Systematic reviews and RCTs		Medline 1966 – 2004 Embase 1980 – 2004 Cochrane (all years) Cinahl 1982 – 2004 237 abstracts reviewed

Question	Search Filters	Study Type	Database and Year
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			

Question	Search Filters	Study Type	Database and Year
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

Question	Search Filters	Study Type	Database and Year
BCG4: In health care workers, 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 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

Question	Search Filters	Study Type	Database and Year
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

Question	Search Filters	Study Type	Database and Year
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?			

Question	Search Filters	Study Type	Database and Year
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 years) Health PROMIS (All years) 464 abstracts reviewed
NHS2: What measures are effective in staff in employment in NHS hospitals in terms of the prevention and control of TB?			
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?			

Question	Search Filters	Study Type	Database and Year
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 Appendix B: Glossary and Abbreviations

Abbreviations:

AFB	Acid Fast Bacilli
BAL	Bronchoalveolar Lavage
BCG	Bacille Calmette-Guerin
BTS	British Thoracic Society
CCDC	Consultant in Communicable Disease Control
CFP-10	Culture Filtrate Protein 10
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
DOR	Diagnostic Odds Ratio
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy Short Course
DS	Diagnostic Study
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immunospot
ESAT-6	Early Secretion Antigen Target 6
FM	Fluorescence Microscopy staining
GDG	Guideline Development Group
GPP	Good Practice Point
HCW	Health Care Workers
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
HPU	Health Protection Unit
HTA	Health Technology Assessment
IFN Gamma	Interferon Gamma
JCVI	Joint Committee on Vaccination and Immunisation
LJ Slope	Lowenstein-Jensen Slope solid-media
LTBI	Latent Tuberculous Infection
MDR-TB	Multi-Drug Resistant Tuberculosis
MR	Magnetic Resonance
NAAT	Nucleic Acid Amplification Technologies
NCC-CC	National Collaborating Centre for Chronic Conditions
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNT	Number Needed to Treat

OR	Odds Ratio
PA	Posterior-Anterior (chest X-ray)
PCR	Polymerase Chain Reaction
PHLS	Public Health Laboratory Service
PPD	Purified Protein Derivative
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Relative Risk
TB	Tuberculosis
TST	Tuberculin Skin Test
WHO	World Health Organization
ZN	Ziehl-Neelsen microscopy staining

System for Drug Regimen Abbreviations:

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

H = isoniazid
R = rifampicin
Z = pyrazinamide
E = ethambutol

Examples:

2HRZE/4HR is the standard "six month, four drug regimen": 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin.
2HRE/7HR is 2 months of isoniazid, rifampicin and ethambutol followed by 7 months of isoniazid and rifampicin
2HRZ/7HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 7 months of isoniazid and rifampicin
2HRZ/4HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 4 months of isoniazid and rifampicin

Glossary:

Acid fast bacilli (AFB)	Bacteria which, having been stained with a dye, retain their colour in acid alcohol. Used as a technique for microscopic detection of mycobacteria.
Action Plan	See "TB action plan"
Active tuberculosis	Infection with mycobacteria of the *M. tuberculosis* complex, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent TB, where mycobacteria are present, and may be dormant, but are not causing disease. The symptoms of disease include weakness, weight loss, fever, no appetite, chills and sweating at night. Other symptoms of TB disease depend on where in the body the bacteria are growing. If TB is in the lungs (pulmonary TB), the symptoms may include a cough, pain in the chest, and coughing up blood. (Source: www.hpa.org.uk)

Adherence	The term adherence refers to the patient's ability or choice to adhere to a treatment regimen. Also see "Concordance")
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked by arrows.
Atypical mycobacteria	Mycobacteria other than those of the *M. tuberculosis* complex
Audit	See "Clinical audit"
Automated liquid culture system	Automated systems allow continuous monitoring of cultures grown using a liquid medium (see "Liquid culture"). Time to detection is more rapid than traditional methods.
Bacille Calmette-Guerin vaccine (BCG)	A vaccine for TB named after the French scientists Calmette and Guerin. (Source: www.hpa.org.uk)
Bacteriological conversion rate	The proportion of people tested for latent TB infection who convert from a negative to a positive test.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chemoprophylaxis	Treatment for latent TB infection. The administration of anti-tuberculosis drug(s) to prevent the acquisition or progression of tuberculosis infection. The former may be referred to as *primary chemoprophylaxis* or *preventive therapy*, the latter as *secondary chemoprophylaxis*. (Source: www.hpa.org.uk)
Class of recommendation	See "Grade of recommendation".
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinician	In this guideline, the term clinician means any health care professional.
Chemotherapy	The multi-drug antibiotic treatment regimens used to treat active TB.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or

	intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Compliance	The extent to which a patient complies with a recommended treatment regimen. In recent years use of the term compliance has been discouraged due to its connotations of patient subservience. (See "Concordance" and "Adherence").
Concordance	Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.
Confidence interval (CI)	A range of values which contains the true value for the population with a stated "confidence" (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.
Contact (domestic, close, casual, workplace)	A person who has spent time with a person with infectious TB. (Source: www.hpa.org.uk)
Contact tracing	The identification of contacts (See "Contact") to find associated cases, to detect people with latent TB infection and to identify those not infected but for whom BCG vaccination might be appropriate.
Conversion rate	See "Bacteriological conversion rate".
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYS).
Culture	The process of growing TB bacteria from sputum or other samples for identification and diagnosis.
Cure and completion rate	The proportion of people receiving treatment for active TB who either have negative culture results during the continuation phase of treatment, or who complete treatment without documented culture status.
Decision analytic model/ techniques	A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities and

	then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.
Descriptive study	Observational studies or surveys designed to quantify current service provision or clinical conditions. Such studies are not designed to test hypotheses about the data.
Diagnostic odds ratio (DOR)	This is a single summary of diagnostic performance (it describes the ratio of the odds of a positive test result in a patient with disease compared to a patient without disease). The DOR can be calculated from sensitivity and specificity data and where a test provides no diagnostic evidence the DOR is 1.
Directly observed therapy (DOT)	A way of helping patients take their medicine for TB. A person receiving DOT, will meet with a health care worker every day or several times a week. They will meet at an agreed place. This can be the TB clinic, the patient's home or work, or any other convenient location. They will take their medicine at this place. Sometimes someone in their family or a close friend will be able to help in a similar way to the health care worker. (Source: www.hpa.org.uk)
Directly observed therapy short-course (DOTS)	The World Health Organization has developed a control strategy known as Directly Observed Therapy, Short-course, which requires microscopy based diagnosis, standardised treatment under direct supervision, a secure supply of quality drugs and equipment, careful monitoring and supervision, and political commitment to support these activities. (Source: www.hpa.org.uk)
Disseminated (including miliary) tuberculosis	Blood borne spread of TB which may or may not be accompanied by chest X-ray or high resolution CT changes.
Environmental mycobacteria	Mycobacteria other than those of the *M. tuberculosis* complex.
Gamma-interferon test (correctly, Interferon-gamma)	A blood test used to diagnose latent TB (which may be used as an alternative, or an addition, to tuberculin skin tests) based on detecting the response of white blood cells to TB antigens.
Gastric washings (Gastric lavage)	Some patients (particularly children) with suspected TB are unable to cough up any sputum. As an alternative, in a gastric lavage, saline solution is introduced into the stomach through a tube, the contents are pumped out and are examined for *M. tuberculosis* complex bacteria.
Gold standard	See "Reference standard"
Good practice point (GPP)	Recommended good practice based on the clinical experience of the guideline development group (GDG) in the absence of robust, published clinical evidence.
Grade (Class)of	All recommendations are assigned a grade (A,B,C,D or D(GPP)) according to the level of evidence the

recommendation	recommendation is based on (See "Level of evidence").
Guideline development group (GDG)	The guideline development group (GDG) agrees the clinical questions for the guideline, considers the evidence and develops the recommendations. The GDG membership is multidisciplinary comprising clinicians, patients and/or carers and technical experts.
Heaf test	A type of tuberculin skin test in which tuberculin is injected intradermally with a multiple puncture apparatus. The injection site is examined for signs of an immune response within 7 days. (Also see "Tuberculin skin test" and "Mantoux test").
Health Technology Assessment (HTA)	These consider the effectiveness, appropriateness and cost of technologies and are funded by the NHS Research and Development Division.
High-incidence country	Following the widely used threshold, any country with an incidence equal to or greater than 40 cases per 100,000 population per year. A similar definition can be made for parts of the UK, for instance for neonatal BCG vaccination. This guideline categorises, in Table 27, Section 10.2, the countries which are the most common origins of people successfully applying for residence in the UK according to this threshold. Up-to-date and comprehensive information is held by the Health Protection Agency and is available online.
Histology	Microscopic examination of cells and clinical samples.
Incremental cost-effectiveness ratio	A measure of the additional cost of a health care activity per unit of benefit (usually a QALY, see below).
Index case	The initial person found to have TB, whose contacts are screened. Consequently, the source of their infection may be found, but the initial presenting patient is regarded as the index case.
Infectious TB	Active sputum smear-positive pulmonary tuberculosis, i.e. with acid fast bacilli visible on microscopy . Active TB affecting other parts of the respiratory tract or oral cavity, though rare, is also considered infectious.
Inform & Advise information	Information provided to patients so that they are able to recognise the symptoms of TB and be aware of the action they should take should these symptoms arise. Examples are given in Appendix F.
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Interferon-gamma test	A blood test used to diagnose latent TB (which may be used as an alternative, or an addition, to tuberculin skin tests) based on detecting the response of white blood cells to TB

	antigens.
Latent tuberculosis	Infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. Also known as latent TB infection, or LTBI.
Level of evidence	A code (e.g. 1++, 1+,2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.
Liquid culture	Culture grown using a liquid medium where mycobacteria grow faster (compared to solid media). (Also see "Automated liquid culture systems").
Mantoux test	A type of tuberculin skin test in which tuberculin is injected intracutaneously. The injection site is examined for signs of an immune response after 2-3 days. (Also see "Tuberculin skin test" and "Heaf test").
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Methodological limitations	Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
Molecular probe	A process used to detect the presence of a particular genetic sequence in the cells of interest, using suitably labelled complementary sequences. In the case of TB, particular genetic sequences can confirm the mycobacterial species or the presence of certain drug resistance mutations.
Multi-drug resistant tuberculosis (MDR-TB)	Tuberculosis resistant to isoniazid and rifampicin, with or without any other resistance.
Mycobacterium tuberculosis complex (M. TB Complex)	The related mycobacterial species *M. tuberculosis*, *M. bovis* and *M. africanum* which can cause tuberculosis in humans.
Non-respiratory TB	Active TB affecting any part of the body other than the lungs, bronchi, pleura or thoracic lymph nodes (for example, the meninges or cervical lymph nodes).
Nucleic Acid Amplification Test (NAAT)	A test to detect fragments of nucleic acid, allowing rapid and specific diagnosis of *M. tuberculosis* directly from a range of clinical samples.
National Health Service (NHS)	This guideline is written for the NHS in England and Wales.
National Collaborating Centre	A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the Patient

for Chronic Conditions (NCC-CC)	Involvement Unit at NICE, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient and Carers Liaison Committee, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2000 to undertake commissions from NICE to develop clinical guidelines for the NHS.
National Institute for Health and Clinical Excellence (NICE)	NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
Needs assessment	An assessment of the potential benefit from health care activities at a population-wide level. A needs assessment takes into account epidemiology, current service provision, and evidence of clinical effectiveness and cost-effectiveness.
Negative predictive value	The proportion of individuals with a negative test result who do not have the disease.
Negative pressure room	Used for the isolation of certain patients known or suspected to have infectious TB. A negative pressure room is one where the air from the room is sucked out into dedicated ducting through a filter and into the outside air, at a distance from all other air intakes. The level of pressure should be 10 Pascals below the ambient pressure.
New entrant	Anyone coming to work or settle in the UK. This will include immigrants, refugees, asylum seekers, students and people on work permits. This group is intended to include UK-born people, or UK citizens, re-entering the country after a prolonged stay in a high-incidence country.
Non-analytic study	Any study with a level of evidence grading of 3 in the NICE levels of evidence hierarchy.
Number needed to treat (NNT)	The number of patients who must be treated to prevent a single occurrence of the outcome of interest, based on an average calculated from the available data.
Non-respiratory TB	See "Extra pulmonary TB"
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The "odds" is the ratio of non-events to events.
Outbreak	There is no robust, widely accepted threshold for an outbreak of a disease, but in practical terms, an outbreak is the occurrence of an unusually high number of cases in associated individuals, in a small geographical area, and/or in a relatively short period of time.
Positive predictive value	The proportion of individuals with a positive test result who actually have the disease.
Post-primary tuberculosis	The stage following primary tuberculosis, when infection with the bacteria has advanced to disease, possibly

	symptomatic, with bacterial growth demonstrable by culture.
Primary tuberculosis	The initial stage of infection with TB bacteria, which is often asymptomatic, but can be detected by tuberculin conversion or interferon-gamma testing.
Quality-adjusted life-year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Reactivation	The advancement of old latent TB (whether previously detected or not) into active TB
Reference standard	An agreed standard, for example for a test or treatment, against which other interventions can be compared.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A, divided by the risk of the event in group B).
Schools vaccination programme	BCG vaccination programme performed in schools in children aged 10-14 years.
Sensitivity (of a test)	The proportion of individuals classified as positive by the gold or reference standard, who are correctly identified by the study test.
Short-course treatment	Modern 6 month treatment regimens for active TB (previously treatment had been for at least 12 months).
Six month, four drug regimen	These guidelines recommend a drug treatment regimen using four different drugs over a duration of 6 months. This is not applicable in all cases.
Skin test	See "Tuberculin skin test"
Smear-positive	See "Sputum smear-positive"
Specificity (of a test)	The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.
Sputum	Mucus expelled from the bronchi and lungs by coughing (or retrieved from gastric washings, see above) Sputum is examined for TB bacteria by microscopic examination of a stained smear; part of the sputum can also be used for culture.
Sputum smear-positive ("Smear positive")	Respiratory tuberculosis in which mycobacteria ('acid-fast bacilli', AFB) have been seen in a stained smear of sputum examined under a microscope. Confirmation of the diagnosis requires culture to differentiate the organisms from atypical mycobacteria (those which are not in the *M. Tuberculosis* complex). (Source: www.hpa.org.uk)

Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
TB action plan	"Stopping Tuberculosis in England: An Action Plan from the Chief Medical Officer" (October 2004) is a Department of Health publication which sets out actions regarded as essential to keep TB under control.
Treatment failure	Failure of the prescribed drug regimen to eliminate the TB bacteria from the body. Demonstrated by a lack of clinical improvement, or by positive culture after the end of the fourth month of treatment.
Tuberculin conversion	A change from a negative to a positive test for latent TB. Tuberculin conversion is defined as the second of two tuberculin skin tests increasing by 2 Heaf grades, or >10mm Mantoux, over the first test. This does not apply if vaccination takes place in the meantime.
Tuberculin skin test (TST)	Any one of a range of simple tests which inject tuberculin (purified protein derivative, PPD) into the skin. Immune reaction can be assessed after a few days according to the size of induration at the site of injection. They can demonstrate acquired immunity to TB, lack of immunity, or possible current infection (a strong response), but are confounded by immuno-compromise, serial TST, and prior exposure to atypical mycobacteria. The results are generally referred to as "positive" or "negative". (Also see "Heaf test" and "Mantoux test" (Source: www.hpa.org.uk)
Tuberculosis (TB)	Active TB; disease due to infection with *M. tuberculosis* complex.

3 Appendix C: Unlicensed medicines

This guideline does not contain any recommendations for medicines outside their licensed indications. Tuberculin purified protein derivative for Mantoux testing has no marketing authorisation in the United Kingdom at the time of writing but is administered on a named patient directive.

4 Appendix D: Scope

All NICE guidelines are developed in accordance with a scope document that defines what the guideline will and will not cover. The scope of this guideline was established, after a period of consultation, at the start of the guideline development process; it is set out below in full.

This guideline sets out best practice guidance for the diagnosis, treatment, prevention and control of TB in the NHS in England and Wales. It covers latent TB infection and active TB of the following sites:

- respiratory (lung, bronchus, pleura, thoracic lymph nodes)
- meningeal
- pericardial
- bone and joint
- peripheral lymph nodes
- genitourinary
- disseminated (including miliary)

The guideline does not extend to co-morbidities such as HIV, drug dependencies, diabetes, hepatic disease, renal disease, or mental illness, nor does it give guidance on highly specialised and individualised activities such as treatment of multi-drug resistant (MDR) TB. It does not include special guidance for patients who are pregnant, planning pregnancy, unconscious, or for older people in long-term care. It considers only the *M. TB* complex of bacteria, and therefore does not provide guidance on other mycobacterial infections. In particular, *M. Bovis* is considered only in terms of infection in humans.

National Institute for Clinical Excellence

Scope

Guideline title

Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control.

4.1 Short title

Tuberculosis

4.2 Background

a) The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on tuberculosis (TB) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see Appendix). The guideline will provide

recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

4.3 Clinical need for the guideline

a) Most cases of TB are potentially preventable by comprehensive application of public health measures and when clinical disease does occur, almost all cases can be cured if treated properly.

However, tuberculosis continues to increase in England and Wales at an annual rate of approximately 5%, increasing from a low of approximately 5000 cases in 1987 to nearly 7000 in 2002.

b) The previous evidence-based guidelines on chemotherapy and management (1998) and control and prevention of tuberculosis (2000) (see References) from the Joint Tuberculosis Committee of the British Thoracic Society, will be respectively 7 and 5 years old in 2005, and need revision in light of advances in diagnosis and management, and newer data. This will however be a single guideline document.

4.4 The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information'). The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope

is based on the referral from the Department of Health and Welsh Assembly Government (see Appendix).

The areas that will be addressed by the guideline are described in the following sections.

4.5 Population

4.5.1 Groups that will be covered

a) People with clinical disease caused by *Mycobacterium tuberculosis* complex (*Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis)*, including people with HIV.

b) People with latent infection with Mycobacterium tuberculosis complex but not clinical disease, including people with HIV.

c) People at increased risk of infection by Mycobacterium tuberculosis complex (e.g. recent arrivals and returns, household contacts of respiratory TB, street homeless, HIV infected persons).

d) Adults and children. Single combined searches will be performed, except for specific evidence for children in the areas of chemoprophylaxis regimen and chemotherapy for respiratory and meningeal TB.

e) TB in specific settings: prisons, schools, schoolteachers and others working with children

f) M Bovis will be considered only insofar as it relates directly to humans.

4.5.2 Groups that will not be covered

a) People with other mycobacterial infections (Leprosy, M. avium complex and other opportunist mycobacteria)

b) Treatment of TB in sites other than pulmonary, meningeal, peripheral lymph nodes, spine, pericardial, disseminated including miliary, and genitourinary.

c) Intravenous drug users, pregnant women or those planning pregnancy, people with diabetes, liver disease, renal disease, mental illness or cognitive losses, people who are unconscious, and older people in long-term care. Renal insufficiency will be considered in terms of treatment and chemoprophylaxis.

d) Social determinants of risk (the responsibility of non-NHS agencies)

e) Service models will be excluded from this guideline, except for areas in the public health topics where the GDG agree that the needs assessment indicates a priority for guidance to inform effective practice.

4.6 Healthcare setting

a) Primary and secondary care NHS settings

b) Occupational health within the NHS: infection control, staff protection

c) Public Health (including the Health Protection Agency)

4.7 Areas to be covered

Clinical management: Diagnosis and management of TB disease

a) diagnosis of clinical disease (respiratory and non-respiratory sites) including:
   - people with HIV
   - clinical suspicion of disease
   - radiological patterns (respiratory TB only)
   - microbiological confirmation, excluding liquid culture
   - molecular testing will not be included in this clinical section.

b) management of clinical TB disease: pulmonary, menigeal, peripheral lymph nodes, bone and joints, pericarditis, disseminated tuberculosis and other sites (including genitourinary).

c) diagnosis and management of latent infection without disease, including people with HIV, and prophylaxis for adults and children

d) diagnosis and referral of multiple drug resistance and isolated and combined resistances, but excluding treatment.

e) Tests and follow-up after treatment completion

f) The role of Directly Observed Therapy (DOT).

g) Approaches to promote concordance.

Public health measures: Prevention and control of TB

h) BCG vaccination of uninfected, at-risk groups, including neonates.

i) Contact tracing services in preventing spread of infection (including *M Bovis* in human contacts of cattle with tuberculosis).

j) Finding active cases from groups at increased risk of infection

k) Investigating outbreaks

l) Prevention and control of TB in specific settings (i.e. prisons, schools, schoolteachers and others working with children).

m) Measures to ensure that those with clinical disease (other than Multi-drug resistant TB) do not infect other patients or NHS staff are included.

n) Rapid diagnostic techniques: liquid culture and molecular testing.

o) Notification and enhanced surveillance, including legal obligations and outcome monitoring.

4.8 Audit support within guideline

a) The guideline will include Level 1 clinical audit criteria.

4.9 Status

4.9.1 Scope

This is the final draft of the Scope.

4.9.2 Guideline

The development of the guideline recommendations will begin in the first quarter of 2004.

4.10 Further information

Information on the guideline development process is provided in:
The Guideline Development Process – Information for the Public and the NHS

The Guideline Development Process – Information for Stakeholders

The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health and Welsh Assembly Government

The Department of Health and the Welsh Assembly Government asked the National Institute for Clinical Excellence:

> "To prepare clinical guidelines for the NHS in England and Wales on the clinical management and diagnosis of, and measures to prevent and control, tuberculosis to replace the current guidance from the British Thoracic Society."

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5 Appendix E: Summary of Healthcare Needs Analysis

The epidemiology of tuberculosis in England and Wales (2004)

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The following people have contributed to this epidemiology review by providing raw data, references to relevant research, or comments on earlier drafts.

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%), South-East 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 15-24, TB cases per 100 000	Males aged 25-34, TB cases per 100 000	Females aged 15-24, TB cases per 100 000	Females aged 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	0-14yrs	15-24yrs	25-34yrs	35-44yrs	45-64yrs	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 socio-economic 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 10^{th} 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 was18%.
- 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.

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6 Appendix F: Examples of Inform & Advise information

These are typically provided as standard letters to individual patients, but can take other form such as leaflets. Readers should be aware of the guideline recommendations about translation and non-verbal communication.

Example letter for a contact of a person with sputum smear-positive TB, with negative TST / interferon-gamma test

Dear...

You have been screened as a close contact of someone who has tuberculosis (TB).

Not all forms of TB are infectious. The test you had shows no evidence of TB infection.

It is very unlikely that you will have any problem from TB in the future and no further check-ups are needed.

However, if in the future you develop weight loss, cough up blood, have a persistent cough or fever or swollen glands in the neck, which lasts for over four weeks, you should contact your family doctor.

Yours etc.

Example letter for a new entrant to the UK with positive TST / interferon-gamma test, but negative chest X-ray

Dear...

You have been screened for tuberculosis (TB) as you recently arrived in the United Kingdom from abroad.

The test you had was stronger than we would normally expect, but the X-ray you had was clear, so no follow-up arrangements are needed.

However, if in the future you develop weight loss, cough up blood, have a persistent cough or fever or swollen glands in the neck, which lasts for over four weeks, you should contact your family doctor.

Yours etc.

7 Appendix G: Papers excluded due to methodological limitations

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 characteristics 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 of latent TB	[214]	No details of randomization 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 of close versus casual contacts	[313]; [314]; [315]; [316]; [317]; [312]	• Missing values for tuberculin 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], [272]	• 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	[292] [353]	• The service models compared used different screening procedures and resulted in

immigrants	[392]	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	[356]	• Baseline characteristics apart from age were not

different TB screening methods for new immigrants		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 prison settings	394 379 380	• It was not reported how many of the inmates who received the 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.

8 Appendix H: Health Economic Models

Economic analysis of diagnostic tests for latent infection

INTRODUCTION

This analysis addresses the question of whether the newer interferon gamma tests (IGT) based on ESAT-6 and CFP 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 PPD. We do 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 commercial immunological tests, which use a combination of ESAT-6 and CFP-10 antigens.

A decision model is used to compare the expected costs (£) and health effects (QALYs) of four strategies of testing in the context of a contact tracing programme 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 (inform and advise only). It is assumed that treatment follows current policy: with appropriate therapy for people diagnosed with active TB, treatment for latent TB infection for those testing positive for latent infection, and BCG when appropriate for others.

Various assumptions are made about the epidemiology and likely concordance with testing and treatment programmes. However, these factors will vary with the context of contact tracing. There is also considerable uncertainty over the relative accuracy of the TST and IGT tests, as well as over some of the other model parameters. Sensitivity analysis is 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. However, ***estimates of the relative cost-effectiveness of contact tracing per se are less robust and should be treated with caution.***

METHODS

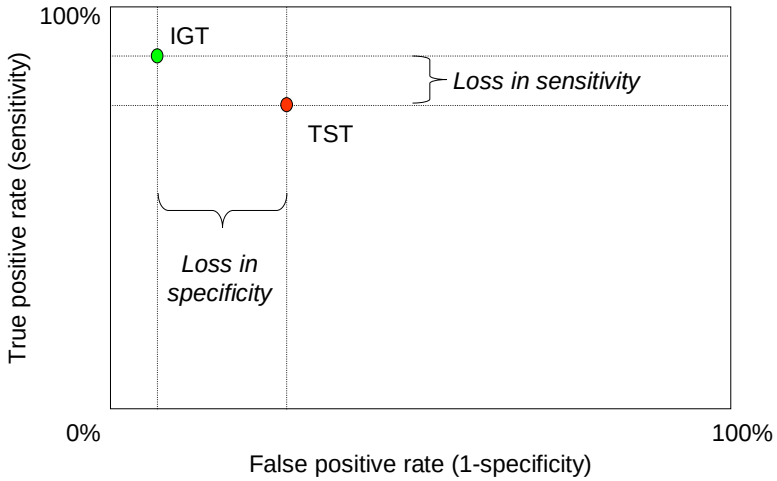
Estimation of test accuracy

The effectiveness of the tests largely depends on their accuracy (sensitivity and specificity). Direct comparisons of IGT with TST suggest that the ESAT-6/CFP immunological tests are likely to be more specific than the PPD skin tests due to the confounding of the latter with prior BCG status. The greater correlation of the IGT with exposure also suggests that they are likely to be more specific (and possibly also more sensitive?), than TST. However, as discussed in the clinical review, the absolute sensitivity and specificity of the tests is difficult to assess in the absence of a 'gold standard' test for latent infection.

One possible approach would be to treat IGT as the new gold standard. However, unless it really does have 100% sensitivity and specificity, this would artificially inflate its cost-effectiveness. Another possibility would be to use estimates of sensitivity and specificity from studies in selected populations (active disease and very low-risk respectively)[20], but it not clear that these results translate to the population with suspected infection in the context of contact tracing.

The approach that we take here is a 'what if' analysis, in which we assume values of sensitivity and specificity for IGT (*Se* and *Sp*) and then comparative losses of sensitivity and specificity for TST (*LossSe* and *LossSp*). The baseline values of *Se*, *Sp*, *LossSe* and *LossSp* are then varied and the impact on costs and effects is estimated.

Figure 1. Relative accuracy of TST and IGT



Testing Strategies

The decision tree is shown in Appendix 1. We start with a cohort of people suspected of having latent TB infection, as identified from a contact tracing programme. The prevalence of latent infection in this cohort (*prev*) depends on their characteristics (age, prior BCG, …) and the circumstances within which they have been identified (degree of exposure to an infectious case, time since exposure, …).

Four possible testing strategies are compared:

a) TST

We assume that a TST is administered to the whole cohort, but that only some patients (*pRead*) return to have the result read. This parameter is intended to reflect the final proportion with a TST result, including those who have to have a repeat skin test administered because, for whatever reason, the result of their first test is not read within the necessary time. To estimate the average cost of administering skin tests we assume that some proportion (*pRepeat*) require a second test. Patients who do not end up with a TST result are assumed to have the same prevalence of latent infection and of active disease as those who do.

Patients with a TST result have a probability p1 of a positive finding, where p1 is a function of the prevalence of active or latent infection in the cohort being tested (*prev*), and the sensitivity and specificity of TST:

p1 = ((prev*(Se-LossSe))+((1-prev)*(1-(Sp-LossSp))))

The proportion of those who test positive who really have a TB infection is called the 'Positive Predictive Value', *p2*:

p2 = (prev*(Se-LossSe))/((prev*(Se-LossSe))+((1-prev)*(1-(Sp-LossSp))))

Similarly, the proportion of those who test negative who do not have a TB infection is the 'Negative Predictive Value', *p3*:

p3 = ((1-prev)*(Sp-LossSp))/((prev*(1-(Se-LossSe)))+((1-prev)*(Sp-LossSp)))

There are five possible outcomes from this strategy: 1) true positive; 2) false positive; 3) false negative; 4) true negative and 5) no test. The costs and consequences of these outcomes are described below.

b) IGT

With IGT the sequence of possible events and outcomes is similar to scenario a, except that it is assumed that fewer patients will be lost to follow-up, since there is no need for them to return to have the result of the test read. The sensitivity and specificity of IGT are also assumed to be higher than those of TST. The formulae for the probability of a positive test (*p4*), the Positive Predictive Value (*p5*) and the Negative Predictive Value (*p6*) of IGT are:

p4 = ((prev*Se)+((1-prev)*(1-Sp)))

p5 = (prev*Se)/((prev*Se)+((1-prev)*(1-Sp)))

p6 = ((1-prev)*Sp)/((prev*(1-Se))+((1-prev)*Sp))

c) IGT for TST positive patients

Here we assume that all patients are given a TST, followed by an IGT only for those who are TST positive. The proportion of positive results and the Negative Predictive Value for the skin test are *p1* and *p3*, defined as above. The prevalence of infection in the subgroup of patients with a positive TST result is *p2*, the positive predictive value of TST. We assume that within this group the sensitivity and specificity of IGT is the same as in the wider population with suspected infection (*Se* and *Sp*). The chance of a positive result and the positive and negative predictive values of IGT are thus:

p7 = ((p2*Se)+((1-p2)*(1-Sp)))

p8 = (p2*Se)/((p2*Se)+((1-p2)*(1-Sp)))

p9 = ((1-p2)*Sp)/((p2*(1-Se))+((1-p2)*Sp))

d) No test (inform and advise only)

Finally, for comparison, we include the possibility of no testing.

Treatment outcomes

There are five possible outcomes from the above strategies: 1) true positive; 2) false positive; 3) false negative; 4) true negative and 5) no test.

Those patients who test positive, including both true and false positives, are assessed for active TB. We assume that this incurs a cost of one visit to a respiratory medicine clinic, and that this is 100% accurate at detecting active disease, which occurs in a proportion (*pTB*) of infected patients. Patients diagnosed with active TB are treated according to the guideline recommendations, using the same resource use and cost assumptions as in the schools BCG model. Early diagnosis of active disease is assumed to reduce the QALY loss for the individual and also the number of secondary cases.

Patients with a positive test result but no active disease are offered treatment for latent TB infection, although only some of them (*pPro*) actually commence treatment. Without prophylaxis, patients with a latent infection have a greater chance of later contracting active disease, compared with non-infected members of the cohort (relative risk *rrLatent*). With prophylaxis, this chance is reduced (relative risk *rrPro*). We assume that patients without current latent infection have a baseline risk *r15* of contracting TB over the fifteen year time horizon of the model, and that they derive no benefit from prophylaxis.

We assume that patients with a negative test result have no further assessment, but are offered BCG vaccination if appropriate (ie if they are aged 35 or younger and there is no evidence of prior vaccination). The proportion of TST- patients given BCG is *pBCG*. BCG vaccination is assumed to reduce the risk of later TB disease for uninfected individuals (relative risk *rrBCG*), but offers no protection for those who are already infected.

Economic analysis

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 (where appropriate) using an annual rate of 3.5%. We assume an average time delay of *lagLatent* years before people with latent infection who go on to develop active disease do so. Similarly, where TB occurs in later life for people without current latent infection or active disease, 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. Sensitivity analysis is used to investigate variation between contact tracing programmes and uncertainty over modelling parameters. In the base case analysis, the best point estimate for each parameter was used. Each parameter was then varied between a lower and upper limit, chosen to reflect the extent of uncertainty or possible variation.

Input parameters
The parameters required to evaluate the model were estimated from various sources. Where possible, parameter values are based on best available evidence from the literature. However, figures were not available for all the necessary parameters. In these cases subjective judgements were made by the guideline economist (and checked by the GDG). The base case, range for sensitivity analysis, and source for each input parameter are listed in Annex 2 below.

RESULTS

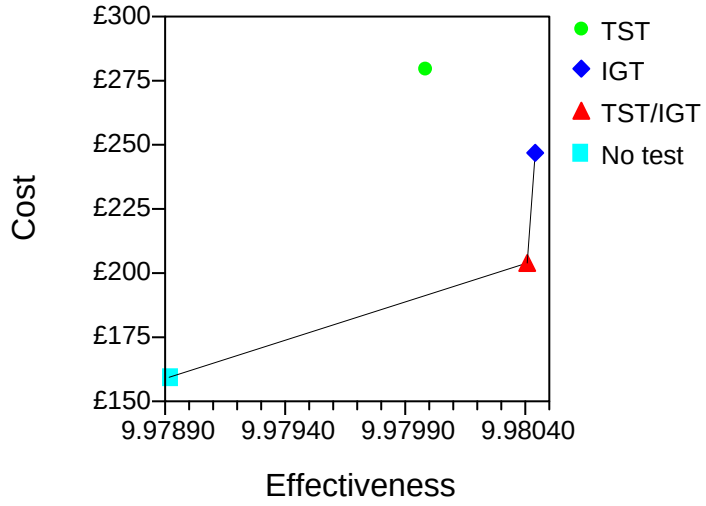
Basecase results

The basecase analysis is shown in Table 1. This shows that the two-stage strategy (TST/IGT) is within the range usually considered 'cost-effective', since the Incremental Cost-Effectiveness Ratio (ICER) is around £20-30,000 per QALY. Compared with this, IGT is not cost-effective (over £1m per QALY gained). TST is both less effective and more expensive than all of the other options (it is 'dominated'). This basecase analysis is illustrated in Figure 2.

Table 1. Base case results

Strategy	Cost (£)	Effect (QALYs lost)	ICER (£ per QALY gained)
No test	£159	0.02108	
TST/IGT	£204	0.01959	£29,955
IGT	£246	0.01956	£1,351,382
TST	£279	0.02002	(Dominated)

Figure 2. Cost-effectiveness graph (basecase analysis)



Variation in results with prevalence of infection

These results are highly dependent on the context of the contact tracing scheme – with a higher-risk cohort of contacts, the expected benefits of early diagnosis of active cases, prophylactic treatment of latent infection, and vaccination will be greater. This is illustrated in Table 2, which shows the estimated costs and effects of the four strategies as we vary the prevalence of infection within the cohort (holding all other parameters constant at their basecase level). If we assume a cost-effectiveness threshold of £30,000 per QALY (at the upper limit of what is considered appropriate for the NHS), then none of the testing strategies is cost-effective below a prevalence of TB infection of about 8%. At intermediate levels of prevalence (between about 8% and 40%), the two-stage TST/IGT strategy is cost-effective. Above 40% IGT on its own is the most cost-effective option.

Table 2. Results by prevalence of infection (active and latent) in the cohort

Prevalence of infection	Strategy	Cost (£)	Effect (QALYs lost)	ICER (£ per QALY gained)
0	No test	£31	0.00409	
	TST/IGT	£58	0.00402	£396,905
	IGT	£102	0.00425	(Dominated)
	TST	£139	0.00465	(Dominated)
10%	No test	£191	0.02533	
	TST/IGT	£240	0.02348	£26,583
	IGT	£282	0.02339	£429,873
	TST	£314	0.02386	(Dominated)
20%	No test	£351	0.04658	
	TST/IGT	£423	0.04295	£19,652
	IGT	£463	0.04252	£93,463
	TST	£489	0.04306	(Dominated)
30%	No test	£512	0.06782	
	TST/IGT	£605	0.06242	£17,283
	IGT	£643	0.06165	£50,283
	TST	£664	0.06226	(Dominated)
40%	No test	£672	0.08907	
	TST/IGT	£788	0.08188	£16,087
	IGT	£824	0.08079	£33,316
	TST	£838	0.08147	(Dominated)
50%	No test	£832	0.11031	
	TST/IGT	£970	0.10135	£15,367
	IGT	£1,005	0.09992	£24,251
	TST	£1,013	0.10067	(Dominated)

Variation in results with relative specificity of tests

The results also depend on the assumptions that are made about the relative accuracy of the two types of test. Table 3 shows how the results vary with the difference in specificity between the IGT and TST (from no difference to a difference of 40 percentage points) and with the prevalence of infection in the cohort. All of the other input parameters are held at their basecase levels for this analysis, including the assumed sensitivities of the two tests (90% for TST and IGT). The shaded cells show the most cost-effective options, using a threshold of £20-30K:

- It can be seen that at 4% prevalence none of the testing options is cost-effective.
- At 10% prevalence, TST/IGT falls below the upper £30K limit, provided that the specificity of TST is no more than about 10 percentage points lower than the specificity of IGT.
- At 20% prevalence, TST/IGT falls below the £30K limit at all levels of specificity tested.
- At 40% prevalence, IGT falls under the £30K threshold if the specificity of TST is 20 percentage points or more less than that for IGT.
- And at 60% prevalence, IGT falls under the £30K threshold at all levels of specificity tested.

Table 3. ICER by prevalence of infection and relative specificity of tests

		Prevalence of infection in cohort				
Specificity	***Strategy***	4%	10%	20%	40%	60%
TST 90%	No test					
IGT 90%	TST/IGT	£35,935	£22,853	£18,000	£15,470	£14,610
	IGT	(Dominated)	£727,910	£113,606	£37,793	£23,793
	TST	(Dominated)	(Dominated)	(Ext Dom)	(Ext Dom)	£18,120
TST 80%	No test					
IGT 90%	TST/IGT	£45,930	£26,583	£19,652	£16,087	£14,884
	IGT	(Dominated)	£429,873	£93,463	£33,316	£18,610
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TST 70%	No test					
IGT 90%	TST/IGT	£56,830	£30,444	£21,329	£16,709	£15,159
	IGT	(Dominated)	£277,371	£75,791	£29,009	£16,920
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TST 60%	No test					
IGT 90%	TST/IGT	£68,765	£34,441	£23,032	£17,334	(Ext Dom)
	IGT	(Dominated)	£184,724	£60,161	£24,861	£15,409
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TST 50%	No test					
IGT 90%	TST/IGT	£81,888	£38,583	£24,763	£17,962	(Ext Dom)
	IGT	(Dominated)	£122,475	£46,238	£20,865	£15,409
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)

Variation in results with relative sensitivity of tests

Similarly, we show how the cost-effectiveness results change with the assumptions about the relative sensitivity of the TST and IGT (Table 4). Again, we hold all other parameters fixed at their base case levels (including 90% and 80% specificity for IGT and TST respectively).

- At 4% prevalence, no testing is cost-effective.
- At 10% prevalence, TST/IGT falls under the £30K threshold if the sensitivity of TST is no more than 20 percentage points different than that of IGT.
- At 20% prevalence, TST/IGT falls below £30K at all levels of sensitivity tested.
- At 40% prevalence, TST/IGT is the optimal strategy, unless the sensitivity of TST is 20 percentage points or more worse than that of IGT, in which case IGT falls under the £30K threshold.
- And at 60% prevalence, TST/IGT is the optimal strategy if the sensitivity of TST is 10 percentage points better than that of IGT. Otherwise, IGT is the optimal strategy.

Table 4. ICER by prevalence of infection and relative sensitivity of tests

		Prevalence of infection in cohort				
Sensitivity	***Strategy***	4%	10%	20%	40%	60%
	No test					
TST 100%	TST/IGT	£42,882	£25,266	£18,998	£15,784	£14,701
IGT 90%	IGT	(Dominated)	(Dominated)	£1,073,454	£87,091	£30,315
	TST	(Dominated)	(Dominated)	(Dominated)	£122,255	£37,101
	No test					
TST 90%	TST/IGT	£45,930	£26,583	£19,652	£16,087	£14,884
IGT 90%	IGT	(Dominated)	£429,873	£93,463	£33,316	£18,610
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
	No test					
TST 80%	TST/IGT	£49,672	£28,219	£20,466	£16,466	£15,114
IGT 90%	IGT	(Dominated)	£150,567	£54,840	£24,789	£16,363
	TST	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Ext Dom)
	No test					
TST 70%	TST/IGT	£54,374	£30,303	£21,510	£16,953	(Ext Dom)
IGT 90%	IGT	£787,132	£95,391	£41,280	£21,312	£15,409
	TST	(Dominated)	(Dominated)	(Dominated)	(Ext Dom)	(Ext Dom)
	No test					
TST 60%	TST/IGT	£60,462	£33,053	£22,896	£17,602	(Ext Dom)
IGT 90%	IGT	£337,936	£71,813	£34,364	£19,424	£15,409
	TST	(Dominated)	(Dominated)	(Dominated)	(Ext Dom)	(Ext Dom)

Uncertainty over other parameters

As might be expected, given how close the basecase model is to the borderline of cost-effectiveness, the results are also sensitive to most of the other input parameters. The sensitivity of the results is illustrated in Table 5. This shows the absolute difference in the expected net benefit of the optimal strategy (calculated using a cost-effectiveness threshold of £30,000) as each parameter is varied from its lower to its upper limit.

It can be seen that the model is particularly sensitive to some other parameters that define the current and future risk of TB within the cohort (the risk of TB in the general population and relative risk of TB in currently uninfected contacts, and the proportion of currently infected patients with active disease) and also to the rate of transmission (mean number of secondary cases per primary case). The results also change greatly with the expected QALY loss and cost of treating each case of active TB.

Table 5. One-way sensitivity analysis

Parameter	Low Input	High Input	Range of net benefit (£30K cost-effectiveness threshold)
Relative risk of later TB in contacts (not due to current infection)	1	50	£2,747
QALY loss due to one case of active disease	0.139	1.557	£1,269
Prevalence of active TB in infected patients	0.1	0.5	£899
Incidence of TB in population (15 year)	0.001	0.008	£595
Mean number of secondary cases per primary case	0.1	0.75	£309
Cost of treating one active case of TB (£ per patient)	1900	12000	£300
Relative risk of TB with latent infection	2	8	£54
Proportion of secondary cases prevented by early detection of index case through contact tracing	0	0.8	£38
Mean delay in development of active disease without current latent infection (years)	3	8	£23
Specificity of IGT	0.5	1	£15
QALY gain due to early diagnosis of active disease	0	0.05	£14
Cost of treatment for latent TB infection (£ per patient)	250	850	£8
Proportion of those offered prophylaxis who start treatment	0.2	0.8	£8
QALY loss during prophylaxis for latent infection	0	0.01	£7
Proportion of those who test negative who are eligible for BCG and accept	0.01	0.2	£6
Sensitivity of IGT	0.5	1	£6
Cost of administering TST (£ per patient)	3	15	£4
Cost of assessment for active disease (£ per patient)	200	300	£4
Cost of visit to have TST result read (£ per patient)	3	29	£4
Mean delay for transmission from primary to secondary cases (years)	0	1	£4
Relative risk of TB with BCG (for currently non-infected person)	0.34	0.7	£2
Cost of interferon gamma test (£ per patient)	14	33	£2
QALY loss from adverse effects of TST	0	0.00046	£2
Relative risk of TB for patients treated with treatment for latent TB infection	0.31	0.52	£2
Mean delay in development of active disease with latent infection (years)	0	1	£1
Proportion of repeat TST required	0	0.2	£1
Proportion of those given TST who return to have it read	0.8	1	£1
Cost of BCG vaccination (£ per patient)	1	11	£0

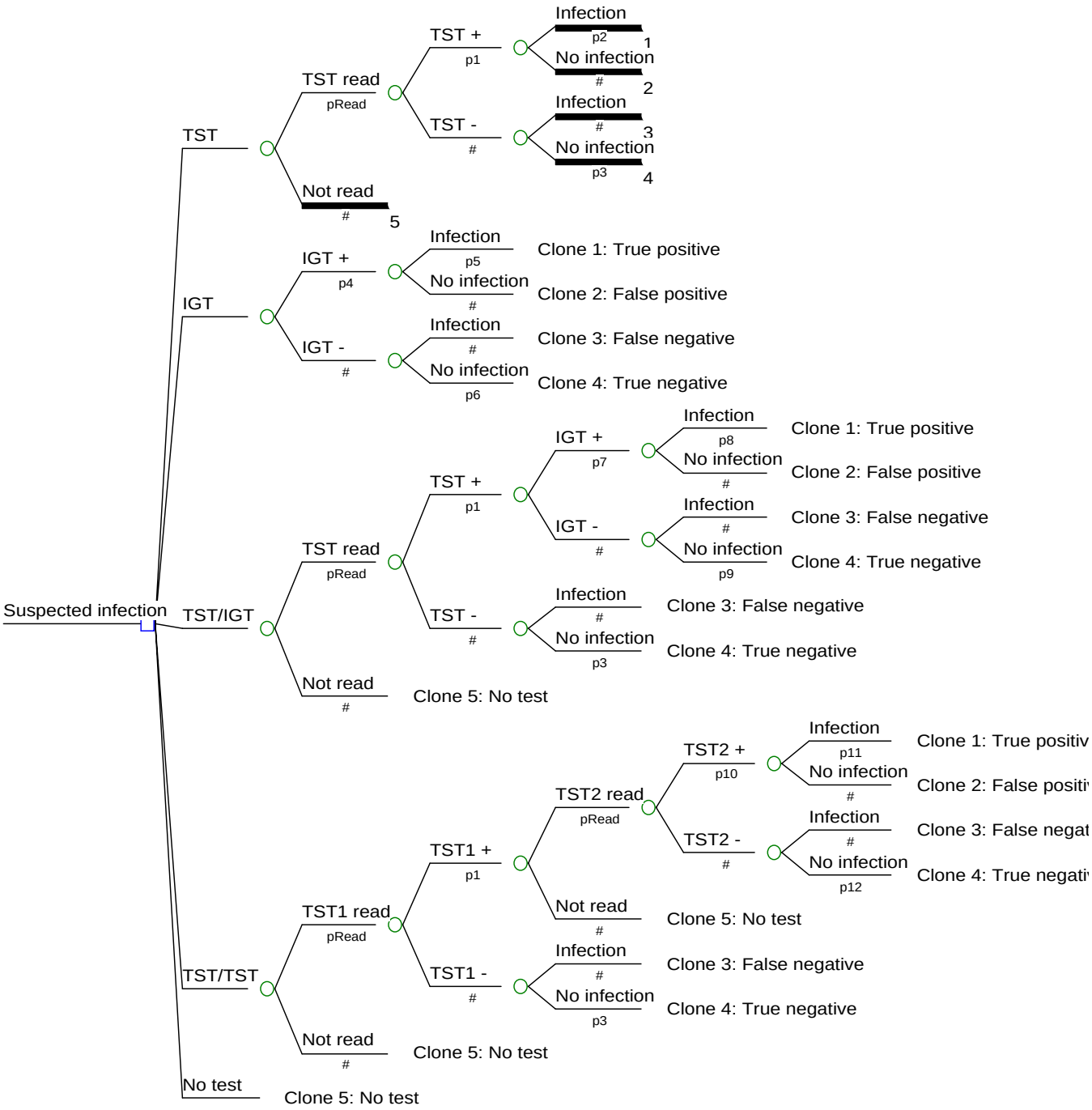
QALY loss from adverse reactions to BCG	0	0.00046	£0

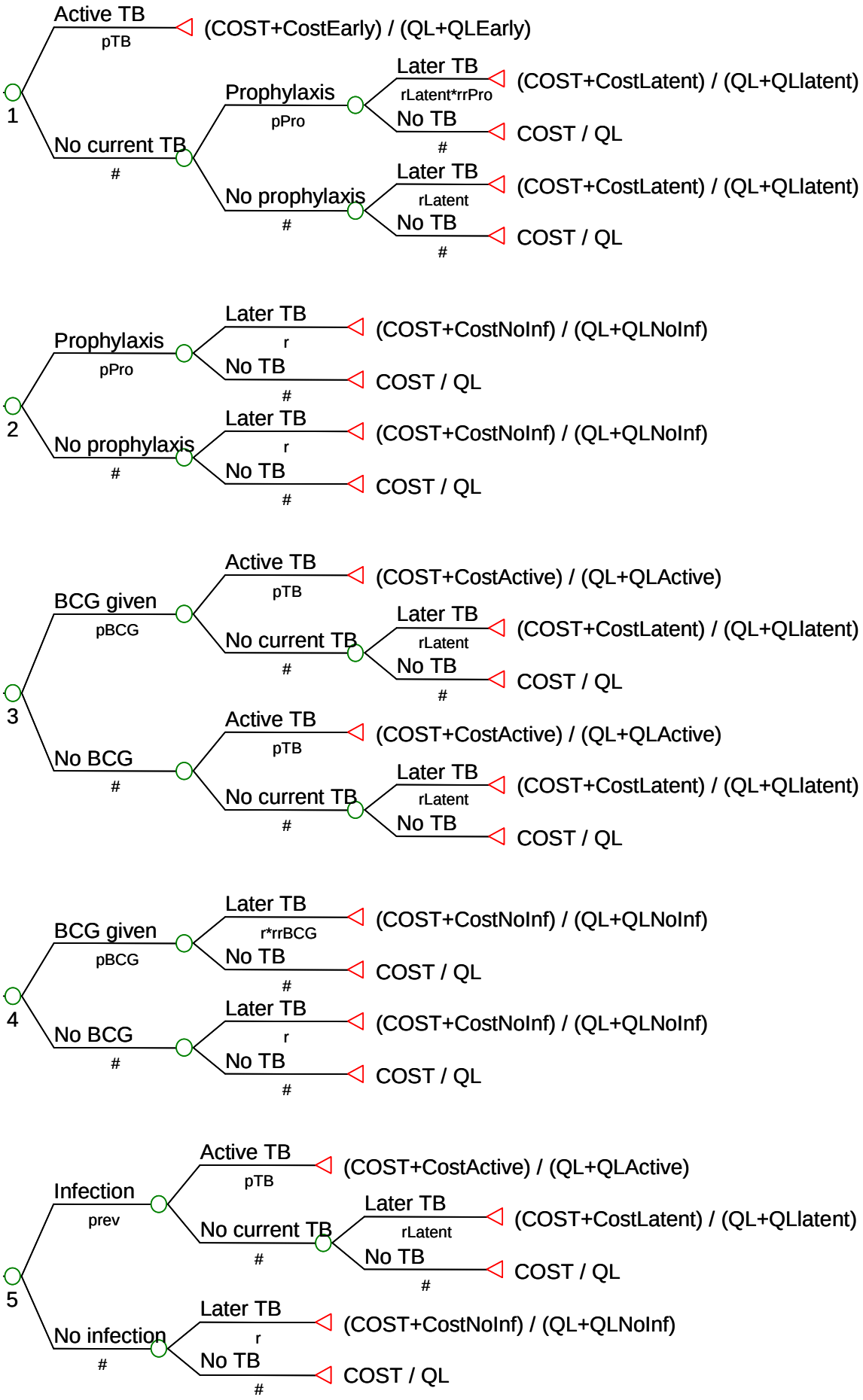
CONCLUSIONS

This analysis has demonstrated the very great degree of uncertainty over the cost-effectiveness of contact tracing strategies. The results were highly sensitive to assumptions about the relative accuracy of the two types of test, the risk of current and future TB in the cohort, the level of transmission to the wider population, and also to the expected net benefit of avoiding each active case of TB.

Under the basecase assumptions, the two-stage TST/IGT strategy appears to be cost-effective. This result depends greatly on the circumstances of the contact tracing exercise. Where the target group is at relatively low risk, it is possible that none of the strategies tested is cost-effective. Alternatively, for a high-risk cohort, one step IGT testing may be the most cost-effective strategy, particularly if the sensitivity and/or specificity of TST is a lot worse than that of IGT.

ANNEX 1 - Decision tree




Active TB
pTB
(COST+CostEarly) / (QL+QLEarly)
1
Prophylaxis
pPro
Later TB
rLatent*rrPro
(COST+CostLatent) / (QL+QLlatent)
No TB
#
COST / QL
No current TB
#
No prophylaxis
#
Later TB
rLatent
(COST+CostLatent) / (QL+QLlatent)
No TB
#
COST / QL
2
Prophylaxis
pPro
Later TB
r
(COST+CostNoInf) / (QL+QLNoInf)
No TB
#
COST / QL
No prophylaxis
#
Later TB
r
(COST+CostNoInf) / (QL+QLNoInf)
No TB
#
COST / QL
3
BCG given
pBCG
Active TB
pTB
(COST+CostActive) / (QL+QLActive)
No current TB
#
Later TB
rLatent
(COST+CostLatent) / (QL+QLlatent)
No TB
#
COST / QL
No BCG
#
Active TB
pTB
(COST+CostActive) / (QL+QLActive)
No current TB
#
Later TB
rLatent
(COST+CostLatent) / (QL+QLlatent)
No TB
#
COST / QL
4
BCG given
pBCG
Later TB
r*rrBCG
(COST+CostNoInf) / (QL+QLNoInf)
No TB
#
COST / QL
No BCG
#
Later TB
r
(COST+CostNoInf) / (QL+QLNoInf)
No TB
#
COST / QL
5
Infection
prev
Active TB
pTB
(COST+CostActive) / (QL+QLActive)
No current TB
#
Later TB
rLatent
(COST+CostLatent) / (QL+QLlatent)
No TB
#
COST / QL
No infection
#
Later TB
r
(COST+CostNoInf) / (QL+QLNoInf)
No TB
#
COST / QL

ANNEX 2. Input parameters

		Base case	Lower limit	Upper limit	Source	Comments
Population and baseline risks						
Prevalence of infection in cohort	*prev*	8%	0%	50%	Estimate from Birmingham data	From 17,730 contacts tested, 333 found with active disease and 504 given prophylaxis. Assuming 50% of those offered prophylaxis start treatment, 333+2*504 contacts infected. Wide range to illustrate different contexts.
Proportion of infected patients with active disease	*pTB*	25%	10%	50%	"	333/(333+2*504)
Incidence of TB (15 year)	*risk*	0.2%	0.1%	0.8%	HPA 2003	Estimated from general population incidence (12.9 per 100,000 pa). Although SE is low (0.0002%) a wider range is shown to illustrate geographical variation (approx 4x in London).
Relative risk of later TB in contacts (not due to current infection)	*rrContact*	3	1	50	Assumption	Basecase figure reflects assumed incidence of 40/100,000 compared with 12.9/100,000 in the general population. Range to represent variation in different contexts.
Relative risk of TB with latent infection	*rrLatent*	4	2	8	Sutherland 1968 and Hart and Sutherland 1977	Over 15 years follow-up of school BCG, 121 out of 2550 (4.7%) unvaccinated participants with TST conversion developed TB. This compares with an estimated rate of 1.2% in the remaining, unvaccinated cohort (32,274). Although SE is low (0.004), a wider range is used to represent uncertainty over applicability to this context.
Mean number of secondary cases per primary case	*nSec*	0.20	0.10	0.75	Estimate from Birmingham data	333 secondary cases detected from 2866 index cases (11.6%). Assuming 50% transmission rate. Upper limit from Saeed et al 2004 estimates, as in schools BCG model.
Mean delay in transmission from primary to secondary (years)	*lagSec*	0.5	0	1	Assumption	6 months
Mean delay in incidence with latent infection (years)	*lagLatent*	0.5	0	1	Assumption	6 months
Mean delay in incidence without current latent infection (years)	*lagNoInf*	5	3	8	Assumption	Over 15 year time horizon

		Base case	Lower limit	Upper limit	Source	Comments
Effectiveness of preventive interventions						
Relative risk of TB with chemoprophylaxis	*rrPro*	0.40	0.31	0.52	Smieja et al 2004	Relative risk with isoniazid treatment of 6 months or more (95% CI).
Relative risk of TB with BCG	*rrBCG*	0.49	0.34	0.70	Colditz et al 1994	Meta-analysis of 6 CCTs and 7 RCTs (relatively more conservative than results from just RCTs).
Proportion of TST results read (at first or second attempt)	*pRead*	95%	80%	100%	Assumption	
Proportion of repeat TSTs required	*pRepeat*	10%	0%	20%	Assumption	
Proportion of those offered prophylaxis who start treatment	*pPro*	50%	20%	80%	Assumption	
Proportion of those who test negative who have BCG	*pBCG*	10%	1%	20%	Assumption	Only those with no prior BCG and under 35 should be offered BCG, and not all of these will accept.
Proportion of secondary cases prevented by early detection	*pEarly*	50%	0%	80%	Assumption	
Accuracy of tests						
Sensitivity of Interferon Gamma tests	*Se*	0.9	0.5	1	Assumption	
Specificity of Interferon Gamma tests	*Sp*	0.9	0.5	1	Assumption	
Loss of sensitivity for TST compared with interferon gamma	*LossSe*	0	-0.1	0.4	Assumption	Baseline assumption that TST and interferon gamma have similar sensitivity.
Loss of specificity for TST compared with interferon gamma	*LossSp*	0.1	0.0	0.4	Assumption	Baseline assumption based on results of Ewer study (largest UK study). Range reflects results of other UK studies.
QALY loss						
QALY loss from adverse effects of TST	*qTST*	0.00005	0	0.00046	Various	Estimates of mean QALY loss (weighted by age of incidence). See school's BCG model for methods of calculation.
QALY loss from adverse effects of BCG	*qBCG*	0.00005	0	0.00046		
QALY loss during prophylaxis for latent infection	*qPro*	0.007	0	0.01		
QALY loss due to active TB	*qTB*	0.676	0.139	1.557		
Gain in QALYs due to early diagnosis of active disease	*qGainEarly*	0.020	0.000	0.050		

		Base case	Lower limit	Upper limit	Source	Comments
Costs						
Cost for tuberculin and disposables		£1.22	£1.00	£1.50	BNF 48, 2004	0.1mL Tuberculin + £1 for disposables
Time to administer TST - nurse (hours)		0.17	0.08	0.25	Assumption	10 minutes (5-15)
Time to read and report TST result - doctor (hours)		0.17	0.08	0.25	Assumption	10 minutes (5-15)
Cost for nurse (£ per hour)		£34	£21	£53	PSSRU 2004	Staff nurse (healthcare assistant- ward manager)
Cost for doctor (£ per hour)		£42	£37	£114	PSSRU 2004	Registrar (SHO-consultant): per hour worked (including qualifications)
Cost for TST administration (£ per patient)	*cTST*	£7	£3	£15		
Cost for TST reading (£ per patient)	*cRead*	£7	£3	£29		
Cost of interferon gamma test (labour and disposables)		£16	£12	£20	Estimate from HPA Newcastle	Includes QuantiFERON-TB Gold kit, 1.3 mins of lab staff time per test and sundries.
Time to collect blood sample for IGT - nurse (hours)		0.17	0.08	0.25	Assumption	10 minutes (5-15)
Cost for interferon gamma test (£ per patient)	*cIGT*	£22	£14	£33		
Cost for assessment after positive test (£ per patient)	*cAssess*	£250	£200	£300	DH Tariff 2005/6	First visit, respiratory medicine.
Cost of BCG (£ per patient)	*cBCG*	£4	£1	£11		
Cost of chemoprophylaxis (£ per patient)	*cPro*	£500	£250	£850	Various	Assumptions as in school model
Cost of treating an active case of TB (£ per patient)	*cTB*	£5,100	£1,900	£12,000	Various	Assumptions as in school model (estimated cost per active case, weighted by age of incidence)
Economic variables						
Discount rate for health outcomes	*drH*	0.035				
Discount rate for costs	*drM*	0.035				

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

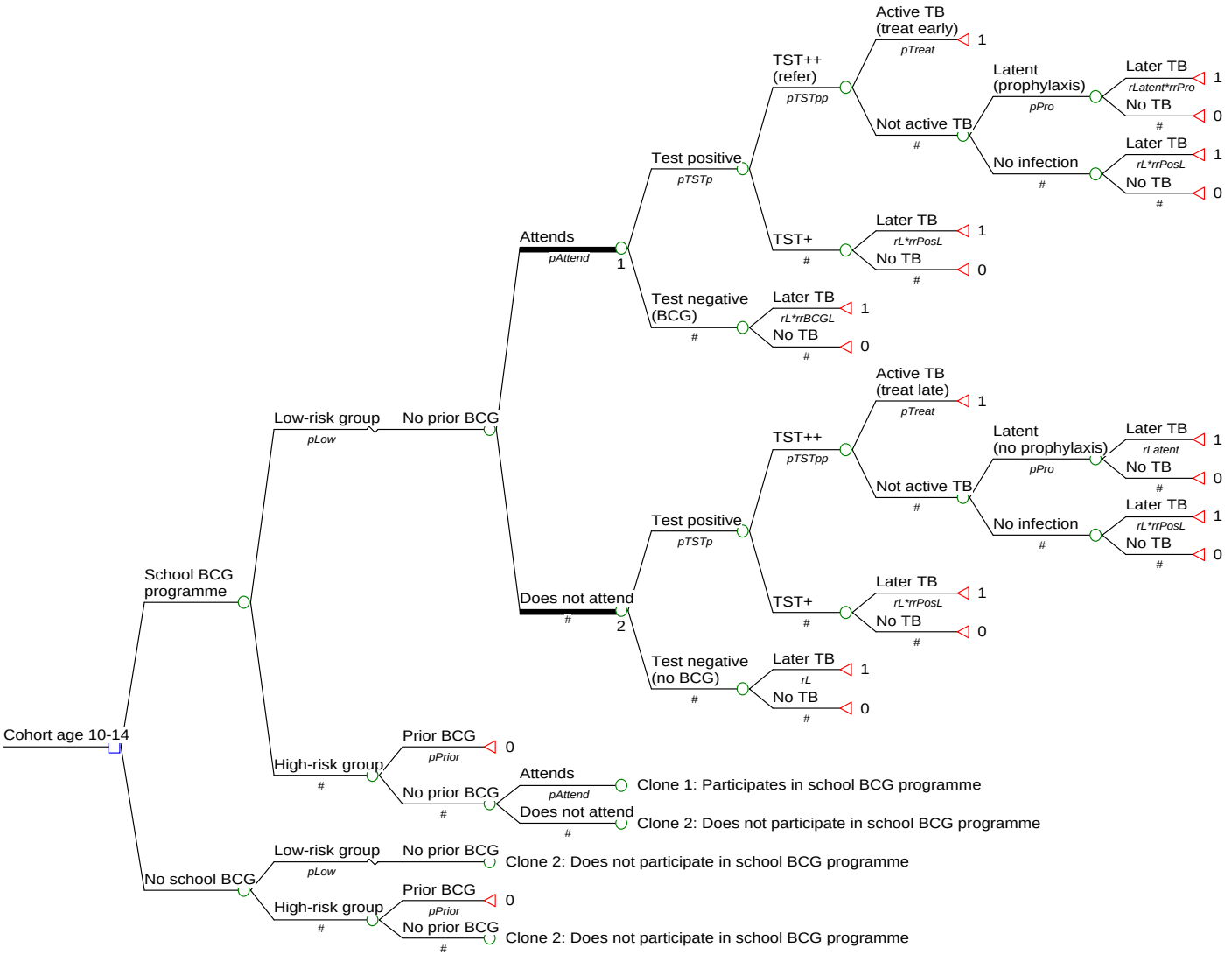


Table 6. Programme effectiveness and epidemiology parameters used in the model

Parameter	Name	Base case	Range for simple sensitivity analysis		Distribution for probabilistic sensitivity analysis			
							Parameters	
			Lower	Upper	Distribution	SE	P1	P2
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	*pTSTpp*	*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			
							Parameters	
			Lower	Upper	Distribution	SE	P1	P2
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			
							Parameters	
			Lower	Upper	Distribution	SE	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)	*cSec10*	*£4,107*	*£1,535*	*£9,237*	gamma	*2617.48*	6,443	1.569
Cost per secondary case (index age 15-29)	*cSec15*	*£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)	*cPro10*	*£398*	*£202*	*£690*	gamma	*149.34*	1,059	2.664
Cost per treated latent case (index age 15-29)	*cPro15*	*£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)

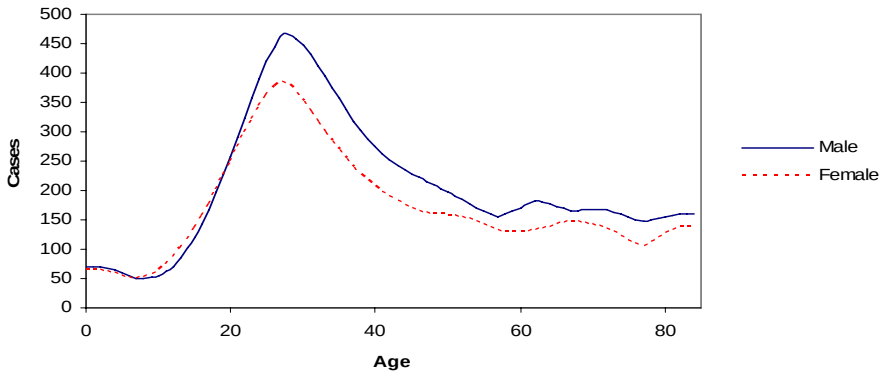


Figure 5 – Estimated case fatality rate by age
(HPA data, mean TB deaths and cases 1999-2003, curve fitted by cubic interpolation)

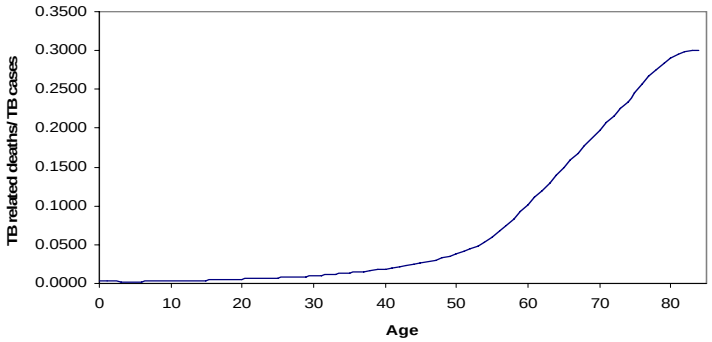
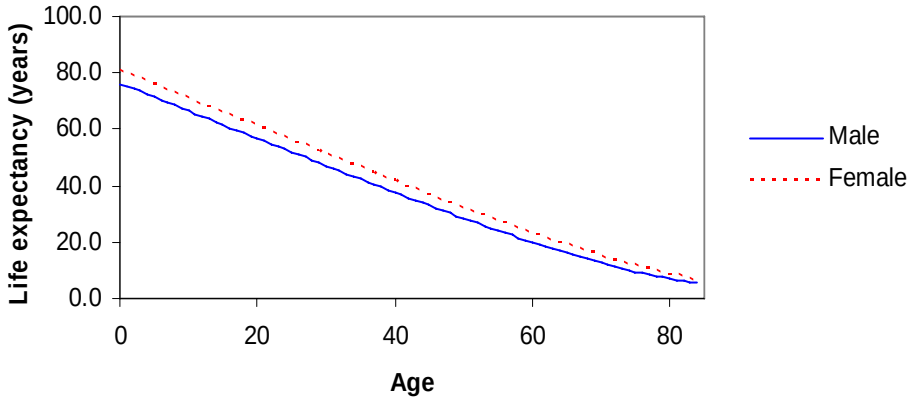


Figure 6 – Life expectancy by age (GAD life tables, based on 2000-2 data)



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)

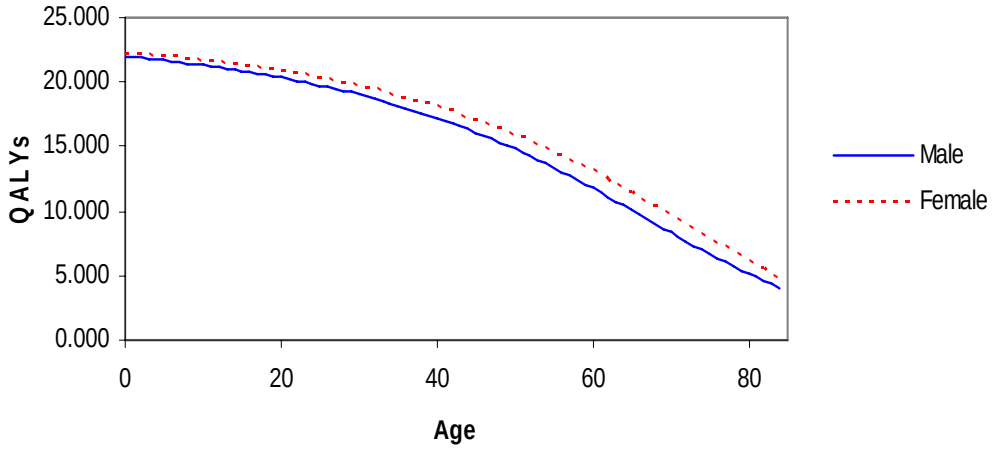


Figure 8 – Estimated QALY loss due to mortality per case (discounted to age of death)

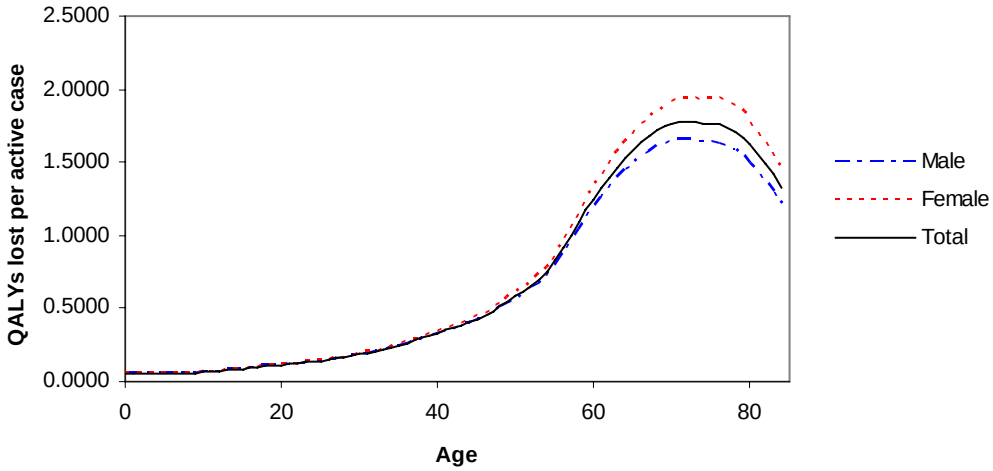
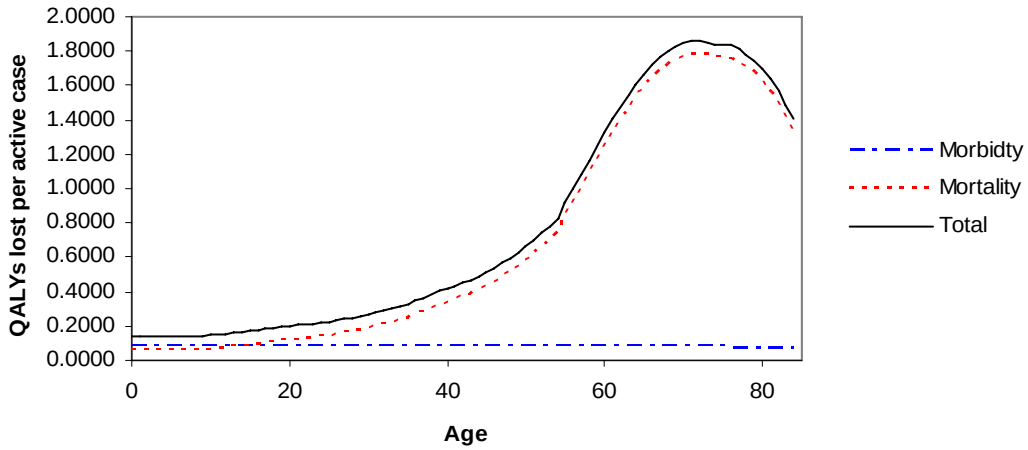


Figure 9 – Estimated QALY loss for morbidity and mortality per case (discounted to age of incidence)



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

	10 year protection			15 year protection		
'High-risk' as % of cohort	*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

	10 year protection			15 year protection		
Risk of TB over period of protection	*Additional cost (£K)*	*QALYs gained*	*ICER (£/QALY)*	*Additional cost (£K)*	*QALYs gained*	*ICER (£/QALY)*

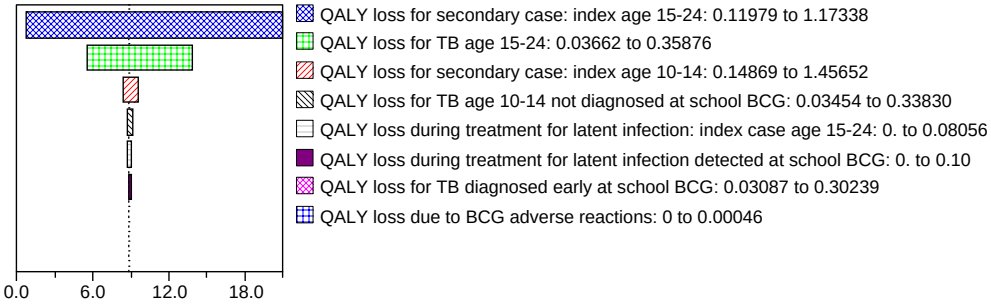
0.03%	£651	5	£123,600	-	-	-
0.04%	£617	8	£78,700	-	-	-
0.05%	£584	10	£56,000	£588	10	£56,200
0.06%	£551	13	£42,400	£555	13	£42,600
0.07%	£518	16	£33,200	£523	16	£33,500
0.08%	£485	18	£26,700	£491	18	£26,900
0.09%	£452	21	£21,800	£458	21	£22,000
0.10%	£419	23	£18,000	£426	23	£18,200

One-way Simple Sensitivity Analysis

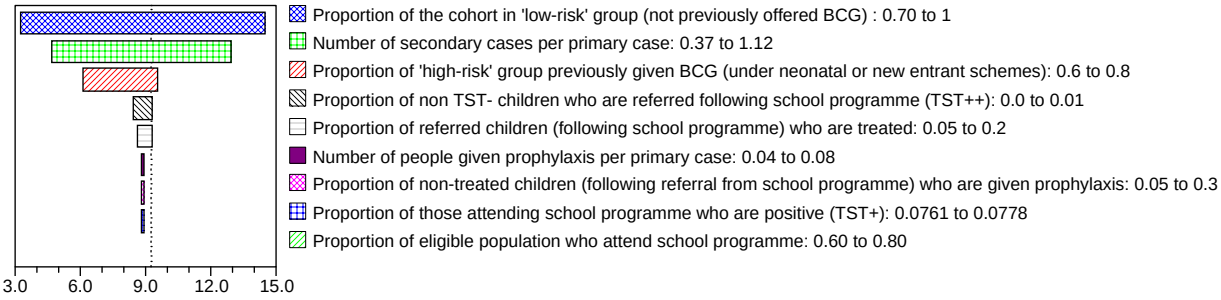
The results of the one-way sensitivity analysis are shown in the 'tornado diagrams' in Figures 10 and 11. These indicate that the cost-effectiveness of the schools' programme is most sensitive to:

- 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)



Net Monetary Benefit (wtp=30000)



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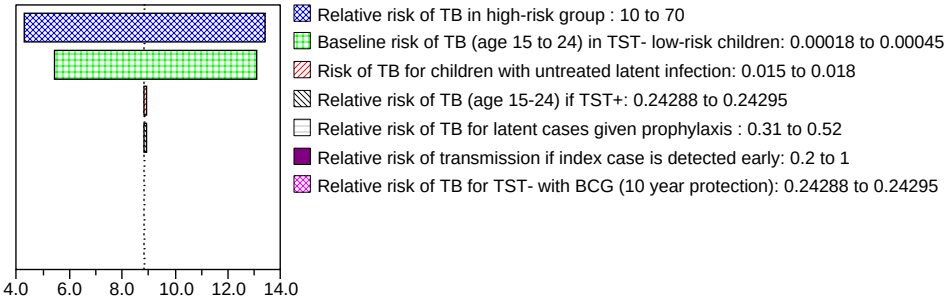

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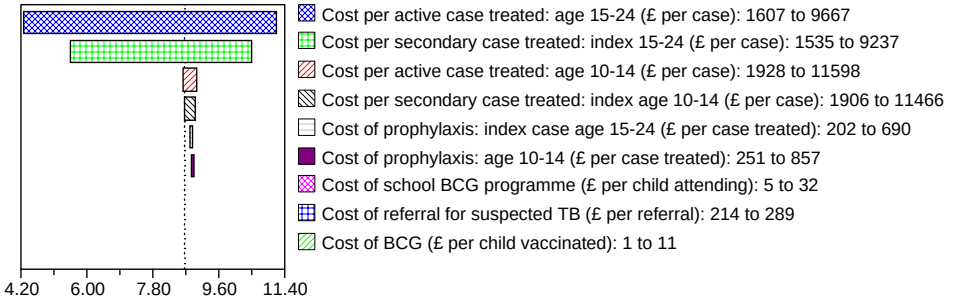
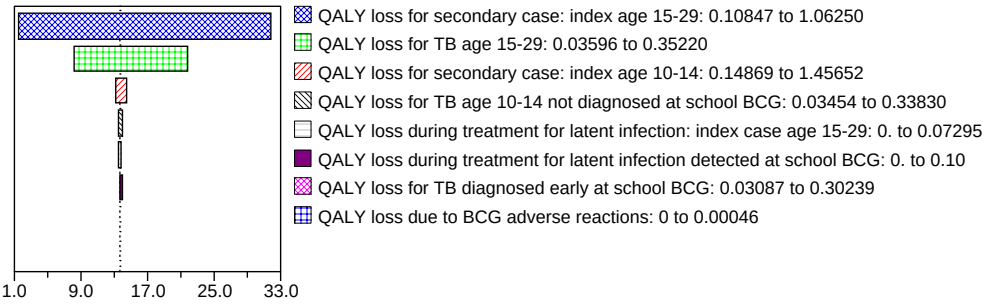
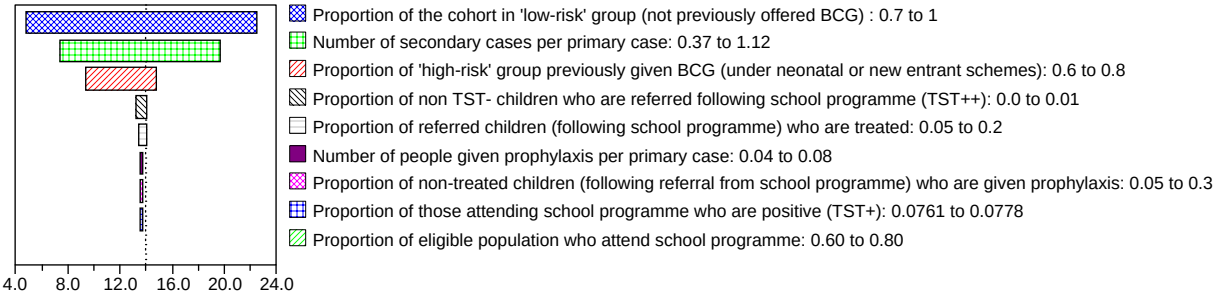


Net Monetary Benefit (wtp=30000)

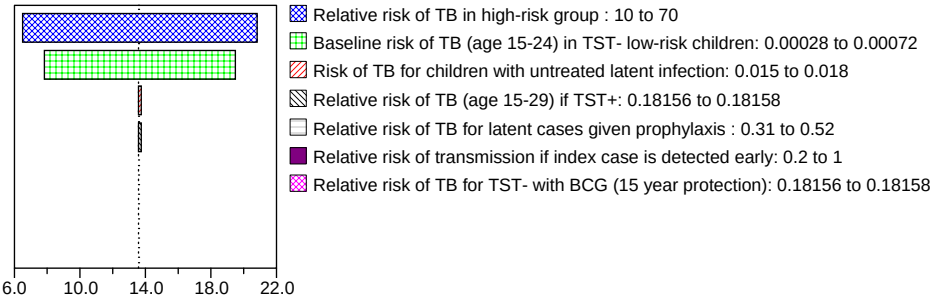
Figure 11 – Tornado diagrams (15 year protection)



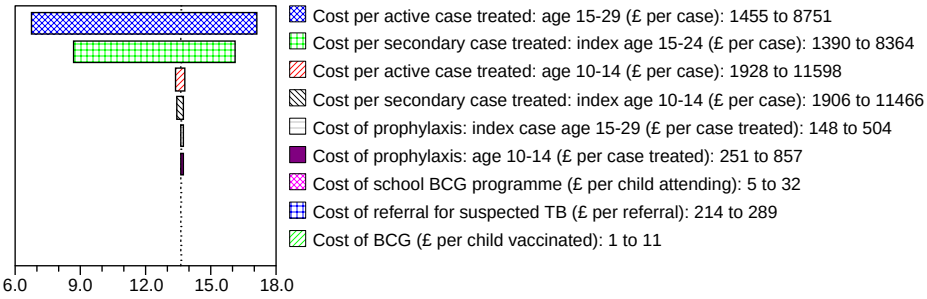
Net Monetary Benefit (wtp=30000)



Net Monetary Benefit (wtp=30000)



Net Monetary Benefit (wtp=30000)

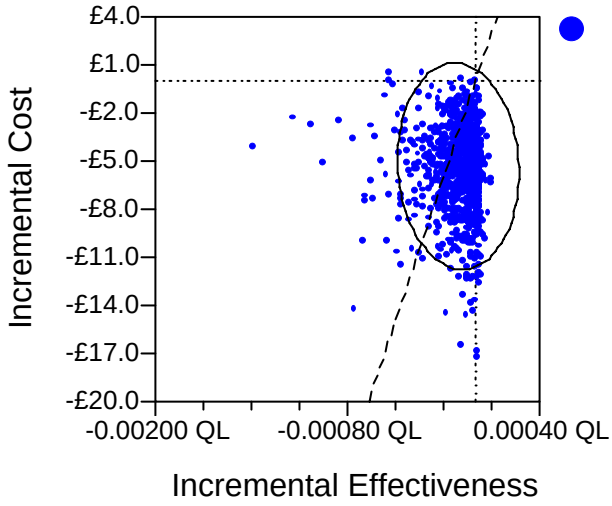


Net Monetary Benefit (wtp=30000)

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)

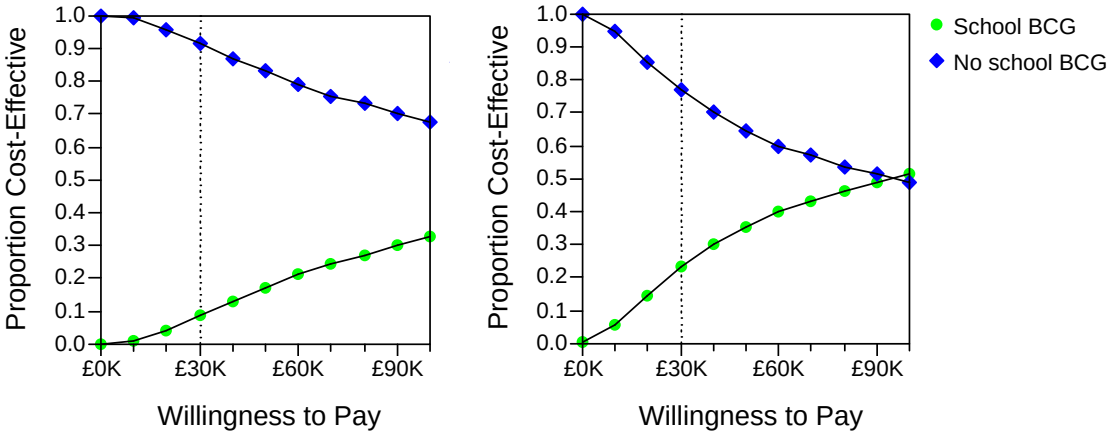


This uncertainty is further illustrated by the cost-effectiveness acceptability curves (CEACs) shown below. With no high-risk children in the cohort, there is a high estimated probability that withdrawing the schools programme would be cost-effective: 90% assuming 10 year BCG protection, and 80% with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

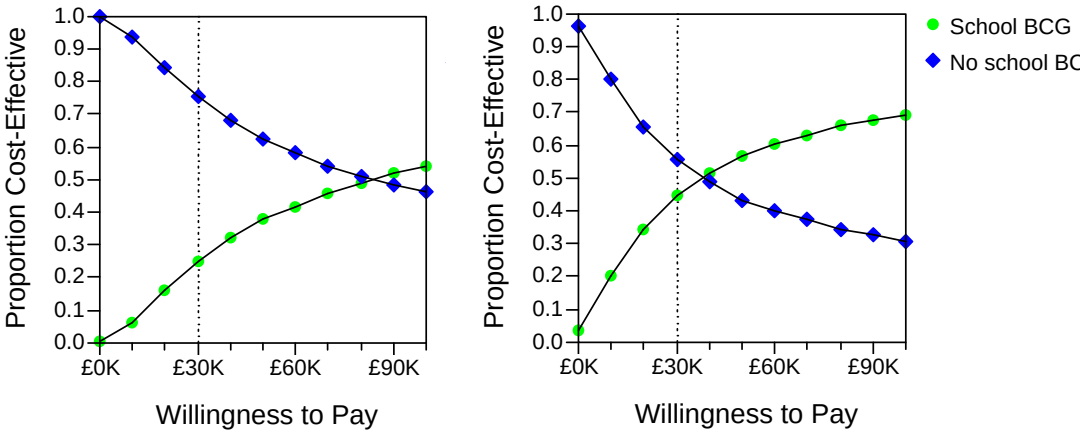
However, with 10% high-risk children, the estimated probability that withdrawing the school programme would be cost-effective is lower: approximately 60% with 10 year protection, and only 40% with 15 year protection (Figure 13).

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



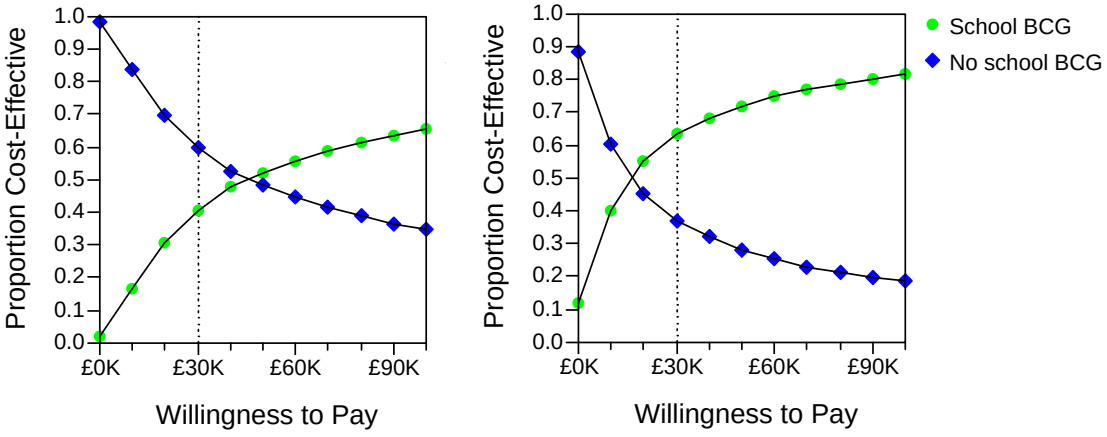
10 year BCG protection *15 year BCG protection*

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*

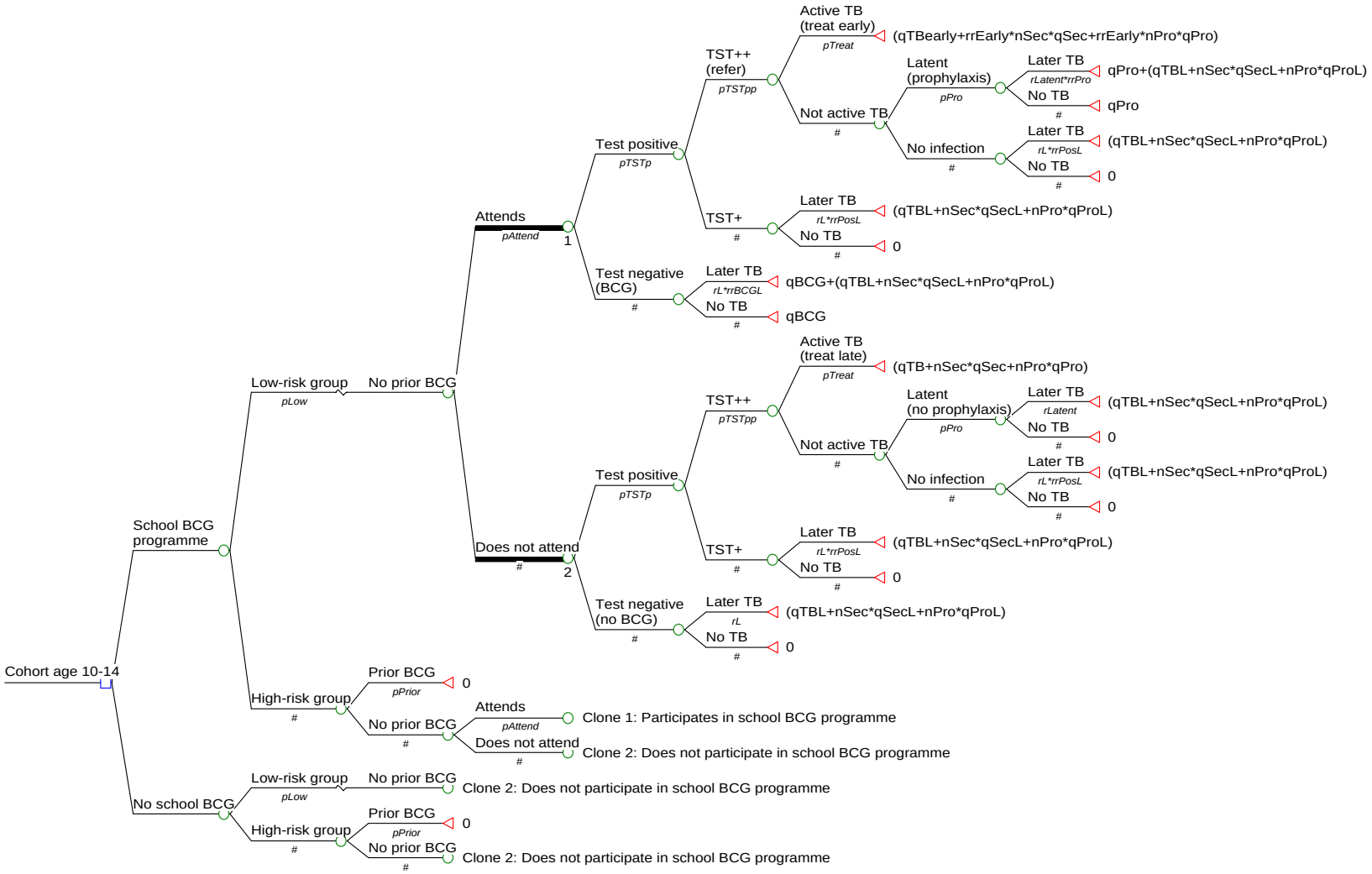
CONCLUSIONS

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.

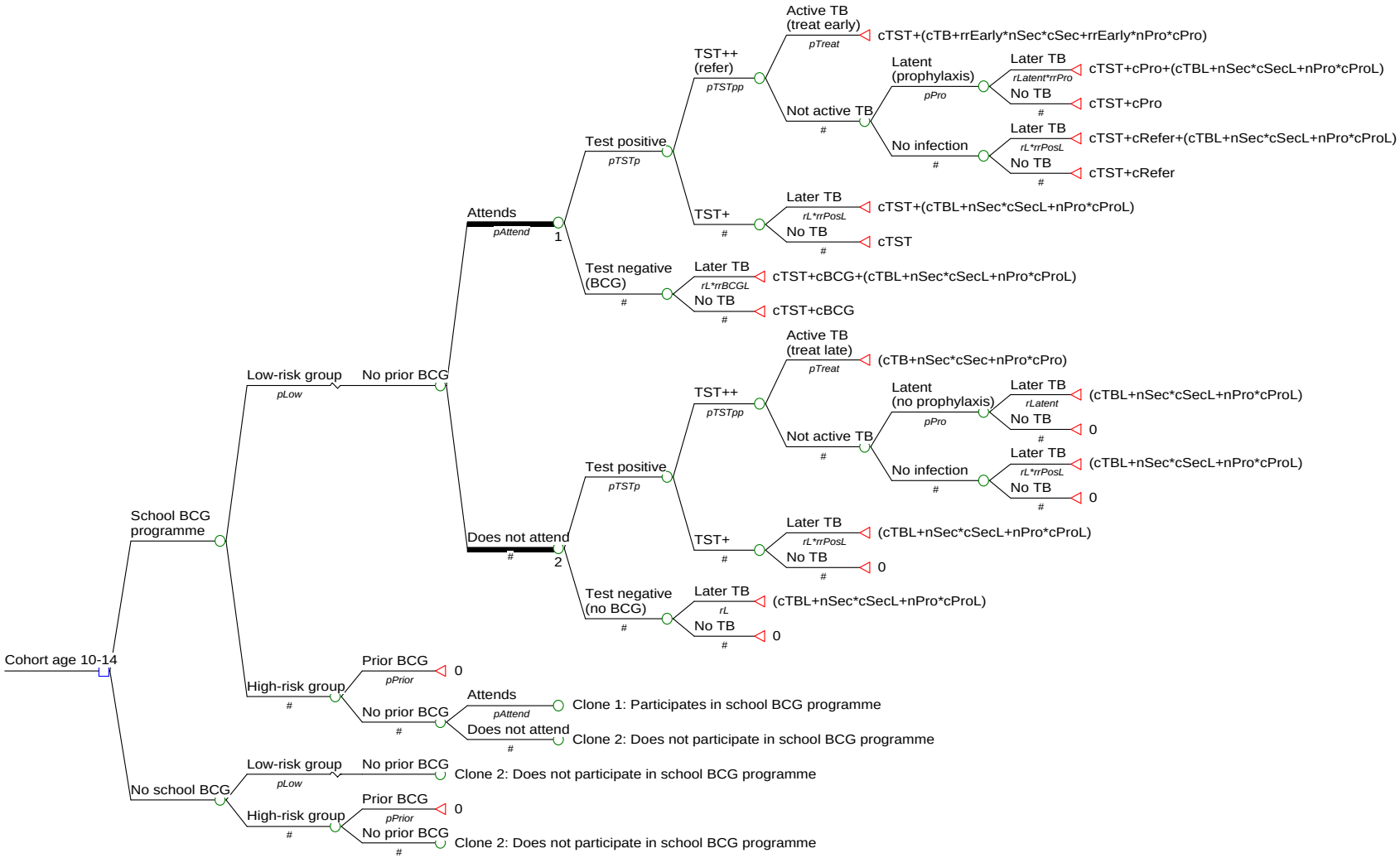
This analysis has only considered the costs and consequences of the schools programme. It is therefore unclear whether even in high-incidence areas, the resources used for the schools programme could be better directed towards improving the uptake of neonatal or new entrant schemes, or by introducing 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 in3197 - 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 (age 15-29) if TST+	*rrPos15*	0.18157	0.18156	0.18158	Assumption	Assumed same as for 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	

		Base case	Lower limit	Upper limit	Source	Comments
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*	0.00005	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 (per case)	*Qhome*	0.03	0.00	0.08	QoLhome*delay	
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

		Base case	Lower limit	Upper limit	Source	Comments
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	*QLlive*	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)	*qTBearly*	0.1403	0.0309	0.3024	Q-Qearly	
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 per child)	*qNrs2*	0.03			"	1 nurse for 3 hours per school.
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*qDr	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+(qOPAR-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	

		Base case	Lower limit	Upper limit	Source	Comments
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*ucEth)	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	

		Base case	Lower limit	Upper limit	Source	Comments
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 case)	*cTest*	£61	£18	£140	IGtest*ucIGtest+Ctest*ucCtest+Xray*ucXray	
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.

		Base case	Lower limit	Upper limit	Source	Comments
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 case treated)	*cdrugsP*	£74	£37	£111	(IsoP*ucIso+RifP*ucRif+PyrP*ucPyr+EthP*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+(OPP-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 case treated	*IGtestP*	1	0	1	GDG 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

		Base case	Lower limit	Upper limit	Source	Comments
Cost of tests (£ per latent case treated)	*ctestsP*	£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	

Economic analysis of new entrant screening

INTRODUCTION

The UK has had a policy of screening entrants from high-risk countries for several years now through the 'Port of Arrival' scheme (Hogan et al 2005). New arrivals from high-incidence countries (40/100,000 or over) who are intending to stay for six months or more are identified by immigration staff and referred for initial clinical and radiographic assessment at port health control units. Local consultants in communicable disease are then notified of the results for people moving into their area and are expected to organise appropriate follow-up. In practice, follow-up is patchy, with variations in the level and type of services provided. In addition to the Port of Arrival scheme, the Home Office has more recently introduced a TB screening system for asylum seekers at fast-track induction centres. However, it is not clear whether any of these new entrant screening policies or practices represent a cost-effective use of NHS resources, since they have not been subject to formal economic evaluation.

A review of economic literature yielded only one UK-based economic evaluation of new entrant screening [351]. Bothamley and colleagues appraised three screening schemes in East London: assessment at a hospital clinic for new entrants notified from the Port of Arrival scheme; screening at general practice registration; and screening of homeless people. Their results suggested that hospital-based screening of people referred from the Port of Arrival scheme appears to be cost-saving compared with no screening: the estimated cost for screening 199 people was £22,600, resulting in an estimated 9.5 cases prevented and a saving of £25,600 in potential treatment costs. However, these figures do not appear to include the costs of identification, initial assessment and notification at the port. It is also not clear how robust they are to various assumptions used to estimate the costs and savings, nor how transferable the findings are to other areas of the country with different screening systems.

There is a limited economic literature on the cost-effectiveness of TB new entrant screening overseas. For example, Dasgupta *et al* (2000) evaluated the cost-effectiveness of two TB screening programmes of foreign born populations and screening of resident close contacts in Montreal in 1996/7. Their results indicated that active contact tracing is cost saving, but that the costs of X-ray screening of new entrants and post-arrival surveillance are relatively high (estimated at $39,400 and $65,100 per case detected respectively). Another Canadian study (Schwartzman and Menzies 2000) used a modelling approach to estimate the cost-effectiveness of radiography and tuberculin skin testing for screening of immigrants. The authors concluded that neither method is cost-effective for low-risk groups, but that X-ray screening at or before entry may be cost-effective for high-risk groups. However, the applicability of this Canadian evidence to the UK is questionable because of obvious differences in the organisation of screening programmes and the general health care context.

Given the importance of new entrant screening in policy terms, and the lack of strong evidence on its cost-effectiveness, the GDG prioritised this as an area for economic analysis. The aims, methods and results of this analysis are presented in this Appendix.

AIMS

The cost-effectiveness of new entrant screening depends on the design and implementation of the screening programme and the context in which it is applied. It was not possible to investigate every

possible permutation of the screening system within this analysis. Instead we chose to focus on four key questions:

1. At what level of prevalence of active disease or latent infection does screening become cost-effective?
2. What screening test is most efficient for detecting active disease in this population: a symptom checklist alone or chest X-ray combined with assessment of symptoms?
3. What test is most efficient for identifying people with latent infection: tuberculin skin tests (TST) or interferon gamma tests (IGT)?
4. What preventive treatments are cost-effective for this group: treatment for latent TB infection, vaccination, both or neither?

We started by building a decision tree representing an initial screening algorithm, designed as an interpretation of current screening policy. We then estimated the cost-effectiveness of some variations around this algorithm to address the above questions. Firstly, we changed the prevalence of active disease and latent infection in the population and observed the impact on the cost-effectiveness of the screening algorithm. Secondly, we investigated how the cost-effectiveness would be likely to change with different screening tests for active disease. Thus we estimated the impact of substituting X-ray screening for a simple symptom checklist for the initial identification of people with active disease at the port of arrival. Thirdly, we estimated what would happen if interferon gamma tests were to be used instead of skin tests for detection of those at risk from latent infection. In this analysis we did not include a two-stage testing strategy (TST followed by IGT) because of the greater risk of loss to follow-up in this population. Finally, we estimated how cost-effectiveness might change if we were to drop the use of prophylaxis for people with suspected latent infection and/or vaccination for young unvaccinated and uninfected individuals.

In order to estimate the cost of the screening algorithm it was necessary to make some assumptions about the organisation of services. However, we did not systematically investigate different service models. For example, we did not consider the relative costs and effects of local follow-up through hospital clinics or primary care. National and local bodies responsible for screening and follow-up services will need to consider the most efficient way to organise and deliver these services. The model also excludes other possible benefits from screening – for example, community based services could help to introduce new entrants to local health services and improve detection of other health problems. These ‘externalities’ may be an important consideration for the design of local services.

METHODS

General approach to modelling

The modelling approach taken was similar to that used for evaluation of school BCG and tests for latent infection. We used a simple decision tree to estimate the expected costs and health effects of some variations to an initial screening algorithm. The model is illustrated in Figure 1 and described in detail below. Note that, for simplicity, the dynamics of transmission within the population was not modelled. Instead, the results depend on an assumed fixed number of secondary cases per primary case. Dynamic population modelling would be expected to yield more accurate results, particularly in the longer term.

The data and assumptions used to estimate the input parameters of the model are all listed in Table 1. Parameter estimates were based on published evidence where possible. If no appropriate evidence was available, estimates were made by the guideline economist and checked by the GDG. There is a high level of uncertainty about the values for some of the model parameters. The robustness of the model results to input data and assumptions is explored in a sensitivity analysis.

The analysis is conducted according to the general principles of the NICE reference case. This includes the use of an NHS perspective, discounting of costs and effects at a rate of 3.5% per annum, incremental analysis, and sensitivity analysis. The time horizon for the model is 15 years, as this is the maximum expected period for benefit of BCG vaccination.

Population characteristics

The model estimates the costs and effects of a screening programme for a hypothetical cohort of new entrants. The cohort is characterised by an initial prevalence of active disease (*pTB*) and TB infection (*pInfect*) at entry. Those members of the cohort without active disease or latent infection have a risk of TB incidence over the model time horizon of 15 years of *rNI*. The risk of incident disease over this time period in those with latent infection at entry is rather higher (*rLI*). The proportion of the cohort unvaccinated at entry is *pPrior*. We also assume an age cut-off of 35 for vaccination and for treatment for latent TB infection, based on consensus view of the GDG. The proportion of the cohort aged under this cut-off is *pYoung*.

Screening algorithm

The initial algorithm for new entrant screening is shown as a decision tree (Figure 1). This assumes that individuals from the cohort are first invited to complete a brief questionnaire; either at the port of arrival or later at a general practice or hospital clinic. Some proportion of the total cohort (*pScreen*) completes the questionnaire, which has sensitivity and specificity for detecting active cases of *seSQ* and *spSQ* respectively. In addition, people aged 35 or younger are offered a tuberculin skin test (TST), which is assumed to have sensitivity and specificity for detecting TB infection of *SeTST* and *SpTST* respectively. A proportion of skin tests (*pTST2*) have to be repeated because they cannot be read at the appropriate time. The resulting proportion of TST results that are available, after a second attempt if necessary, is *pRead*.

Figure 1. Decision tree representing baseline algorithm for new entrant screening

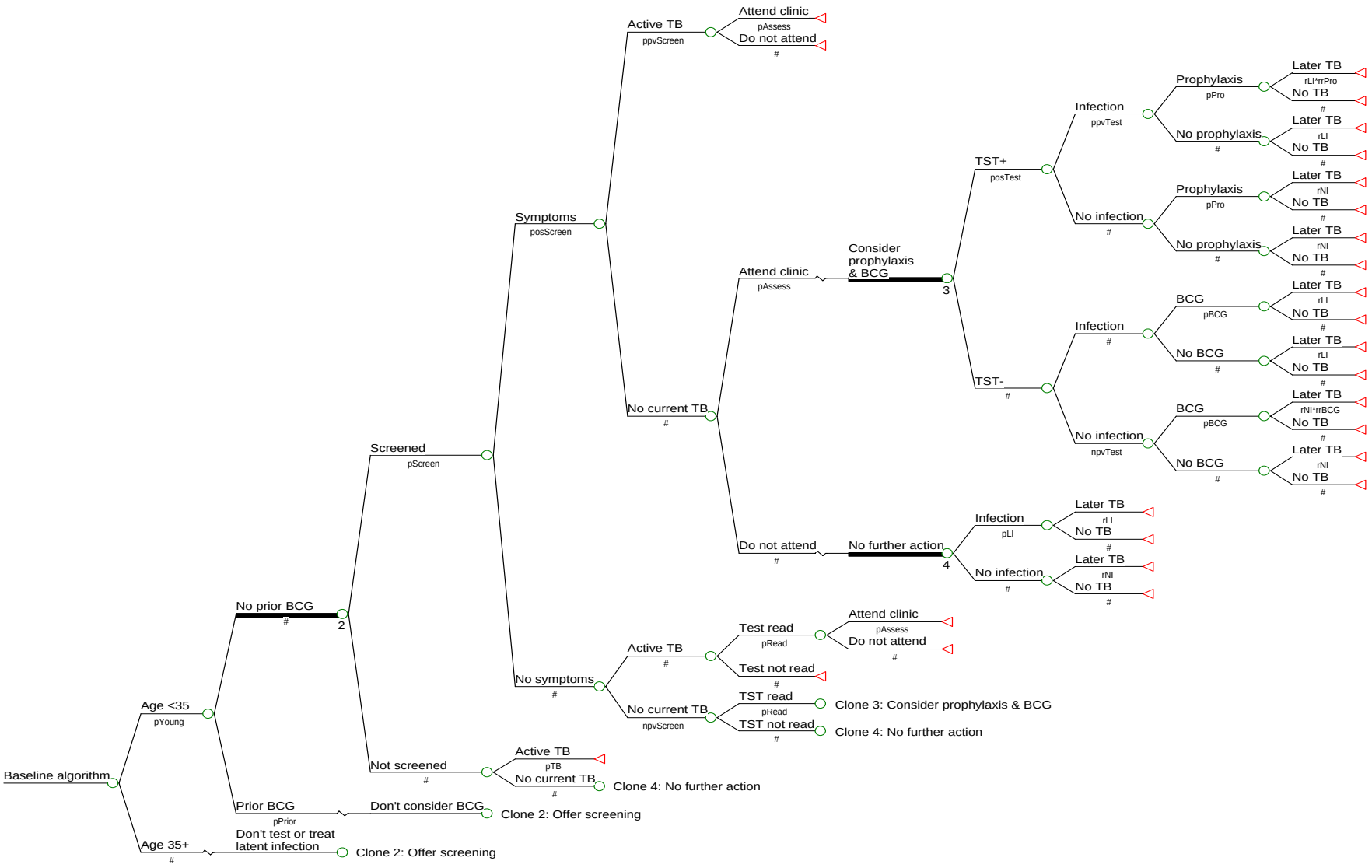

Baseline algorithm
Age <35
pYoung
Age 35+
#
No prior BCG
#
2
Prior BCG
pPrior
Don't consider BCG
Clone 2: Offer screening
Don't test or treat latent infection
Clone 2: Offer screening
Screened
pScreen
Not screened
#
Active TB
pTB
No current TB
#
Clone 4: No further action
Symptoms
posScreen
Active TB
ppvScreen
Attend clinic
pAssess
Do not attend
#
No current TB
#
Attend clinic
pAssess
Consider prophylaxis & BCG
3
TST+
posTest
Infection
ppvTest
Prophylaxis
pPro
Later TB
rLI*rrPro
No TB
#
No prophylaxis
#
Later TB
rLI
No TB
#
No infection
#
Prophylaxis
pPro
Later TB
rNI
No TB
#
No prophylaxis
#
Later TB
rNI
No TB
#
TST-
#
Infection
#
BCG
pBCG
Later TB
rLI
No TB
#
No BCG
#
Later TB
rLI
No TB
#
No infection
npvTest
BCG
pBCG
Later TB
rNI*rrBCG
No TB
#
No BCG
#
Later TB
rNI
No TB
#
Do not attend
#
No further action
4
Infection
pLI
Later TB
rLI
No TB
#
No infection
#
Later TB
rNI
No TB
#
No symptoms
#
Active TB
#
Test read
pRead
Attend clinic
pAssess
Do not attend
#
Test not read
#
No current TB
npvScreen
TST read
pRead
Clone 3: Consider prophylaxis & BCG
TST not read
#
Clone 4: No further action

Table 1. Model parameters

EPIDEMIOLOGY		Base case	Lower limit	Upper limit	Source	Comments
Prevalence of active TB in cohort (at time of screening)	*pTB*	0.5%	0.1%	5%	Bell et al (in preparation)	Systematic review of new entrant screening programmes found reported rates of active disease from 0.24-4.5 % (17 studies, n=343,519), with most under 1% (13/17 studies). For comparison, Newham service identified 8 cases from 1223 screened (0.6%) in 2003. The Dover Induction Centre (AH) and Heathrow Port of Entry (Hardie and Wilson1993, Callister et al 2002) schemes, found a lower rate of active TB (0.13% and 0.1%-0.2% respectively), hence the lower limit for sensitivity analysis.
Prevalence of TB infection in cohort (at time of screening)	*pInfect*	20%	5%	55%	Ormerod 1990 and Bell et al (in preparation)	Systematic review found four studies reporting TST+ results: 38%-55%. However, some of these will be due to prior BCG or environmental mycobacteria. Ormerod 1990 found Heaf grade 2-4 in BCG unvaccinated new entrants aged under 30: 20-25% from Pakistan, 35% from India.
Incidence of TB (15 year) in currently uninfected people	*rNI*	0.4%	0.2%	0.6%	Challenor and Ormerod 2002, and Colditz et al 1994	Challenor and Ormerod found a rate of 14.5/100,000 in a cohort of TST- new entrants given BCG. If we assume a relative risk of 0.5 (0.3-0.7) for BCG (Colditz 1994), then this gives an estimated rate of TB for unprotected TST- new entrants of 30 (21-43) per 100,000, or 0.4% (0.3%-0.6%) for 15 year risk. As a more conservative lower limit, the general population incidence of 13/100,000 is used (this comprises 4/100,000 for UK born and 90/100,000 for foreign born).
Incidence of TB (15 year) in infected people (without active TB)	*rLI*	2%	1%	5%	Marks et al 2000, Sutherland 1968 and Hart and Sutherland 1977	Over 15 years follow-up of school BCG, 121 out of 2550 (4.7%) unvaccinated participants with TST conversion developed TB. Incidence is expected to be lower in new entrants, as they are less likely to have been recently infected. Marks et al estimated the risk of TB for a new entrant with TST reaction over 15mm and normal CXR of 0.9% over 5 years, and 6.7% for life (for 35 year old new entrant).
Proportion of new entrants aged under 35	*pYoung*	65%	50%	88%	ONS 2002 (Population Trends, table 7.1)	Estimated proportion of new entrants aged under 35 from migration data for England and Wales. Upper limit from Bothamley et al study, in which only 28 out of 235 new entrants screened were aged over 35.
Proportion of new entrants previously vaccinated	*pPrior*	70%	60%	80%	Dover audit, Ormerod 1990, Ormerod 1998	Prevalence of prior BCG in audit at Dover Induction Centre was 80%. However, two studies (Ormerod 1990, and Ormerod 1998) reported giving BCG to 24% and 31% of cohorts, which must imply a maximum of 69-76% with prior BCG, though some of this group will have been TST+ without prior BCG.
Mean number of secondary cases per primary case	*nSec*	0.2	0.1	0.75	Estimate from Birmingham data	333 secondary cases detected from 2866 index cases (11.6%). Assuming 50% transmission rate. Upper limit from Saeed et al 2004 estimates, as in schools BCG model.
Proportion of secondary cases prevented by early detection	*pEarly*	50%	0%	80%	Assumption	
Mean delay in incidence with latent infection (years)	*lagLI*	3	1	5	Assumption	
Mean delay in incidence without current latent infection (years)	*lagNI*	5	3	8	Assumption	
Mean delay in transmission from primary to secondary (years)	*lagSec*	3	1	5	Assumption	

Table 1 continued

EFFECTIVENESS		Base case	Lower limit	Upper limit	Source	Comments
Relative risk of TB with chemoprophylaxis (in patients with latent infection)	*rrPro*	0.40	0.31	0.52	Smieja et al 2004	Relative risk with isoniazid treatment of 6 months or more (95% CI).
Relative risk of TB with BCG (in patients without latent infection)	*rrBCG*	0.49	0.34	0.70	Colditz et al 1994	Meta-analysis of 6 CCTs and 7 RCTs (relatively more conservative than results from just RCTs).
CONCORDANCE						
Proportion of new entrants attending for symptom screen	*pScreen*	30%	20%	80%	Newham 2003, Bell et al 2005, Hogan et al 2005	Basecase taken from Newham PCT New Entrant Service (1223 out of 4123 seen). Very wide range of uptakes in published studies (Bell et al 2005): 16-98% in 17 new entrant screening programmes. UK studies (Bothamley 2002, Grenville-Mathers 1979, Ormerod 1990 and Callister 2002) reported uptake rates of: 16%, 36%, 83%, 75%. Survey by Hogan et al also showed wide variation in follow-up of cases notified by Heathrow Port of Entry scheme.
Proportion of referred patients attending hospital clinic	*pAssess*	80%	50%	90%	Levesque 2004	Proportion attending clinic for investigation following suspicious X-ray or symptom screen. This is assumed higher than the proportion attending screening in the first place. In a Canadian new entrant screening programme (Levesque et al 2004) 39/49 patients with a positive skin test attended for clinic assessment.
Proportion of TST results available (at first or second attempt)	*pTST*	95%	70%	100%	Newham 2003	Readings available for 1118 out of 1173 heaf tests performed (95%). Lower limit from Bothamley study: 54/181 TST (30%) not read.
Proportion of repeat TSTs required	*pTST2*	10%	0%	20%	Assumption	
Proportion of those offered prophylaxis who start treatment	*pPro*	94%	50%	100%	Levesque 2004	In a Canadian study, of 35 offered prophylaxis, 33/35 commenced treatment, 24 of whom completed the full 6 months therapy.
Proportion of previously unvaccinated TST- given BCG	*pBCG*	98%	50%	100%	Assumption	18 out of 18 Heaf grade 0 or 1 with no BCG scar in Bothamley study.
TEST ACCURACY						
Sensitivity of screening questionnaire for detecting TB	*seXR*	95%	50%	100%	Schwartzman & Menzies 2000, Kelly et al 2002	Kelly et al 2002 report 96% of those diagnosed with TB had abnormal chest X-ray. Similar rates from other studies reported in Schwartzman & Menzies.
Specificity of screening questionnaire for detecting TB	*spXR*	98%	50%	100%	Assumption	
Sensitivity of screening questionnaire for detecting TB	*seSQ*	80%	50%	100%	Assumption	Kelly et al 2002 report low sensitivity and specificity for a symptom questionnaire compared with chest Xray (no numerical data given).
Specificity of screening questionnaire for detecting TB	*spSQ*	70%	50%	100%	Assumption	
Sensitivity of TST for latent TB	*seTST*	90%	50%	100%	Assumption	As in tests for latent infection model. Given these assumptions of prevalence, sensitivity and specificity, about 27% will be TST+, 33% of whom actually have latent infection
Specificity of TST for latent TB	*spTST*	80%	50%	100%	Assumption	
Sensitivity of IGT for latent TB	*seIGT*	90%	50%	100%	Assumption	As in tests for latent infection model. Given these assumptions of prevalence, sensitivity and specificity, about 18% will test positive, 50% of whom actually have latent infection
Specificity of IGT for latent TB	*spIGT*	90%	50%	100%	Assumption	

Table 1 continued

COSTS		Base case	Lower limit	Upper limit	Source	Comments
Cost of administering questionnaire (£ per patient)	*cSQ*	£1	£0.5	£2	PSSRU 2004	Assumes 2 (1-4) min consult with primary care nurse (£27 per hour in clinic). Time to administer questionnaire in general practice reported as 45 seconds (Bothamley 2005)
Cost of Chest X-ray (£ per patient)	*cXR*	£17	£11	£18	DH tariff 2004/5	Range: interquartile range from 2003 reference costs
Cost for TST administration (£ per patient)	*cTST*	£7	£3	£15	Various	Assumptions as in latent infection model
Cost for TST reading (£ per patient)	*cTSTread*	£7	£3	£29	Various	Assumptions as in latent infection model
Cost for interferon gamma test (£ per patient)	*cIGT*	£22	£14	£33	Various	Assumptions as in latent infection model
Cost for assessment after positive test (£ per patient)	*cAssess*	£250	£200	£300	Various	Assumptions as in latent infection model
Cost of BCG (£ per patient)	*cBCG*	£4	£1	£11	Various	Assumptions as in school model
Cost of chemoprophylaxis (£ per patient)	*cPro*	£500	£250	£850	Various	Assumptions as in school model
Cost of treating an active case of TB (£ per patient)	*cTB*	£5,100	£1,900	£12,000	Various	Assumptions as in school model (estimated cost per active case all ages, weighted by age of incidence)
Discount rate for costs	*drM*	0.035				
HEALTH OUTCOMES						
QALY loss from reactions to TST	*qTST*	0.00003	0.00000	0.0005	Assumption	Assumes mean quality of life loss of 0.1 for 9 weeks for 0.3% of people tested.
QALY loss from reactions to BCG	*qBCG*	0.00003	0.00000	0.0005	Assumption	Assumed similar to TST.
Incidence of isoniazid-induced hepatitis	*pHep*	0.26%	0.1%	0.5%	IUAT trial, Thompson 1982	Increased rate of hepatitis with isoniazid (vs placebo) from IUAT trial was 0.26% for six months treatment (0.52% for one year).
Mortality rate for hepatitis	*mHep*	1%	0.5%	3%	IUAT Thompson 1982, Shelley et al 1997	Hepatitis fatality rate of 3.1% in the IUAT trial (3/95), but this sample included older patients and the trial did not include active monitoring of hepatitis, hence we might expect a lower mortality rate in our cohort. Shelley et al estimate incidence of fatal hepatitis at about 0.001% for people aged 35 based on a review of trials with hepatitis monitoring.
Incidence of other non-fatal adverse reactions to prophylaxis	*pAR*	2%			Snider et al 1986	Snider et al report incidence of GI and other side effects from two previous studies (Thompson 1982 and Kopanoff et al 1978).
Mean QALY loss for non-fatal hepatitis	*qHep*	0.025			Assumption	Assumes mean quality of life loss of 0.1 for 3 months per case.
Mean QALY loss for other adverse reactions	*qAR*	0.008			Assumption	Assumes mean quality of life loss of 0.1 for 1 month per case.
QALY loss due to prophylaxis	*qPro*	0.0008	0.0003	0.0033	Calculated from above assumptions	Estimated QALY loss due to side effects of prophylaxis (fatal and non-fatal hepatitis and other side effects), discounted to current age, for
QALY loss due to active TB, under 35	*qTByoung*	0.221	0.110	0.441	Various	Same assumptions as in other models. Estimated QALY loss due to TB morbidity and mortality for under 35s, discounted and weighted by
QALY loss due to active TB, over 35	*qTBold*	0.581	0.291	1.162	Various	As above, but estimated for over 35 year olds weighted by age distribution of UK migrants over 35
QALY loss due to active TB, any age	*qTBsec*	0.676	0.338	1.352	Various	As above, but estimated for all ages weighted by UK incidence of TB.
Gain in QALYs due to early diagnosis of active disease	*qEarly*	0.02	0.00	0.05	Assumption	Same assumptions as in other models.
Discount rate for health outcomes	*drH*	0.035				

Accuracy of screening and tests for latent infection

The proportion of people screening positive for symptoms is estimated as:

posScreen = (pTB*seSQ)+((1-pTB)*(1-spSQ))

The proportion of people with symptoms who actually have active TB (the 'Positive Predictive Value' of the symptom checklist) is:

ppvScreen = (pTB*seSQ)/(posScreen)

The proportion of people without symptoms who do not have active TB (the 'Negative Predictive Value') is:

npvScreen = ((1-pTB)*spSQ)/(1-posScreen)

The proportion of individuals without active TB who have a positive skin test is:

posTest = (pLI*seTST)+((1-pLI)*(1-spTST))

where

pLI = (pInfect-pTB)/(1-pTB)

The estimated positive and negative predictive values of the TST are:

ppvTest = (pLI*seTST)/(posTest)

npvTest = ((1-pLI)*spTST)/(1-posTest)

Treatment algorithm

People who screen positive for TB symptoms are invited for clinic assessment, although only some proportion of them attends (*pAssess)*. We assume that all people with active disease who attend the clinic are accurately diagnosed (and that no people without active disease are falsely diagnosed). However, some active cases will be missed by the screening questionnaire (false negatives). These people may still be identified earlier than in the absence of screening due to a strongly positive test for TB infection. If they do not attend to have their skin test result read, or if they miss the clinic appointment, then diagnosis is delayed until clinical presentation. People without active TB are considered for preventive treatment. The algorithm assumes that prophylaxis will be offered to individuals aged 35 or younger with a positive test for latent infection. The proportion of those offered prophylaxis who start treatment is *pPro*. For those with latent infection, prophylaxis reduces the risk of future TB (relative risk *rrPro*). It is assumed that prophylaxis offers no benefits for people without current latent infection. The baseline algorithm also includes an offer of vaccination for those aged 35 or younger with a negative skin test and no evidence of prior BCG. It is assumed that a proportion *pBCG* of those offered vaccination accept. For uninfected individuals, vaccination reduces the risk of future disease (relative risk *rrBCG*). We assume that there is no benefit from vaccination of infected individuals. People with a negative diagnosis following clinic assessment for active disease are considered for treatment for latent infection or vaccination in the same way as if they had not presented with symptoms.

Health outcomes

The morbidity and mortality impact of each case of TB is estimated in terms of Quality Adjusted Life Years (QALYs). The methods used to estimate the mean QALY loss per case (*qTB*) are explained in the school vaccination model. For the new entrant model we used an estimate based on the expected QALY loss due to TB-related mortality and morbidity for all ages, weighted by age of TB incidence.

For each case of active TB we also assume that there are *nSec* secondary cases, which occur after an average delay of *lagSec* years. In addition to prevalent cases, the model includes QALY losses due to future incidence over the 15-year time horizon. For members of the cohort without current infection at the time of screening, we assume an average delay of *lagN*I years for any incident cases. For people with latent infection at the time of screening, the average time to occurrence of any incident cases is assumed to be rather lower, *lagLI* years. All estimated health gains are discounted to the time of screening using an annual discount rate of 3.5%, as recommended the NICE 'reference case' for economic evaluations.

There are three mechanisms by which the screening algorithm can improve outcomes: earlier diagnosis of active disease; prevention of future disease due to prophylactic treatment of people with latent infection; and prevention of future disease by vaccination of currently uninfected people. Early diagnosis is assumed to reduce the quality of life and mortality impact of TB for the index case by *qEarly* QALYs. Early diagnosis is also assumed to reduce the number of secondary cases by a proportion *pEarly*. Cases prevented by vaccination or prophylaxis yield a QALY gain for the index case, and also for expected secondary cases.

These QALY gains due to early diagnosis and prevention will be partially offset by QALY losses due to side effects of tests or treatment. We assume fixed QALY losses for each skin test and vaccination performed (*qTest* and *qBCG*). In addition we estimate the QALY loss due to adverse reactions to prophylaxis as *qPro*. This figure includes an estimate of mortality due to isoniazid-related hepatitis as well as the quality of life impact of non-fatal hepatitis and other side effects. The QALY loss during treatment of active disease is already included in the *qTB* figure.

Costs

The model includes estimates of the cost of screening (*cScreen*), testing for latent infection (*cTest*) and reading test results (*cRead*), clinic assessment for suspected cases (*cAssess*), vaccination (*cBCG*), prophylaxis (*cPro*) and management of active disease (*cTB*). These cost estimates are the same as in the other two economic models. Note that for people with active disease, the model does not include an additional cost for clinic attendance, since the cost cTB already includes initial costs of assessment. Where appropriate, costs are discounted using an annual rate of 3.5%.

RESULTS

Cost-effectiveness of baseline algorithm

Under baseline assumptions the screening algorithm does not appear to be cost-effective (see Table 2). With 0.5% active and 20% latent TB in the cohort at the time of screening, the algorithm is estimated to cost over £250,000 per QALY gained, which far exceeds the usual NICE threshold of £20-30,000. This result was robust to changes in the input parameters. Each parameter was varied, one at a time, from the lower to the upper limit shown in Table 1 (a simple 'one-way' sensitivity analysis). For all except three parameters (*pTB*, *nSec* and *rLI*) the estimated cost per QALY of the baseline algorithm remained above £200,000, and in no case did it fall below £30,000 per QALY.

Table 2. Cost-effectiveness of baseline algorithm

	Per 1,000 people offered screening			
	Cost (£)	*Effect (QALYs lost)*	*Incremental cost (£)*	*Incremental effect (QALYs gained)*
No screening	£67,500	5.26	-	-
Baseline algorithm	£113,330	5.09	£45,830	0.17
		Incremental cost-effectiveness ratio (ICER)		**£276,084**

The cost per QALY fell to about £39,000 when the prevalence of active TB in the cohort at the time of screening (*pTB*) was increased to our upper limit of 5%. For the algorithm to meet a £30,000 cost-effectiveness threshold, the prevalence of active TB in the cohort would have to be greater than 6% (see Table 3). To meet a more stringent cost-effectiveness threshold of £20,000 per QALY, the prevalence would have to be over 8%.

Table 3. Sensitivity of algorithm cost-effectiveness to TB prevalence

	Per 1,000 people offered screening		
TB prevalence in cohort	*Incremental cost (£)*	*Incremental effect (QALYs gained)*	*ICER (£ per QALY gained)*
0%	£46,760	0.078	£596,455
1%	£44,900	0.254	£177,122
2%	£43,050	0.429	£100,429
3%	£41,190	0.604	£68,226
4%	£39,340	0.779	£50,504
5%	£37,480	0.954	£39,289
6%	£35,630	1.129	£31,552
7%	£33,770	1.304	£25,893
8%	£31,910	1.479	£21,573
9%	£30,060	1.654	£18,169
10%	£28,200	1.83	£15,415

The next most sensitive input parameter was the number of secondary cases per primary case (*nSec*). At our upper limit of 0.75 the estimated cost per QALY for the baseline algorithm was about £91,000. There would have to be over 2 secondary cases per primary case to reach a cost-effectiveness threshold of £30,000 per QALY. The 15-year incidence of TB in people

with latent infection at the time of screening (*rLI*) would have to rise from a baseline estimate of 2% to about 18% to meet a cost-effectiveness threshold of £30,000 per QALY.

Cost-effectiveness of radiographic screening for active disease

In the baseline model the symptom checklist used to identify people with suspected TB for further investigation is assumed to have a sensitivity of 80% and specificity of 70%. Given the expected prevalence of 0.5%, this means that only about 1% of people with symptoms would actually have the disease, and that over 99% of those without symptoms would not have the disease. Radiographic screening is more expensive than symptom screening alone (about £16 more per person), but if is also expected to be more accurate. In our baseline model we assumed that chest X-rays would have a sensitivity of 95% and specificity of 98% in this population. If true, this would improve the targeting of further investigation: about 20% of those with a suspicious X-ray would have TB and over 99% with a clear X-ray would not have TB. This would reduce the overall cost of the screening programme by about £10 per patient and give a slight improvement in health outcomes.

The superiority of radiographic screening is robust to changes in its sensitivity. Even if the sensitivity of chest X-ray for active TB were only 50% it would remain highly cost-effective (the symptom checklist would cost over £1m for each additional QALY gained). This is not surprising given the low baseline estimate of prevalence in this population, and hence the limited scope for gain by reducing false negatives. The results depend more on the avoidance of false positive results, and hence on the relative specificities of the screening methods. Provided that the specificity of X-ray screening is no lower than 78.5% it remains more cost-effective than purely symptomatic screening. The result is also quite robust to changes in the relative cost of radiographic and symptomatic screening: as long as the additional cost of the chest x-ray is no more than £50 greater then it remains cheaper overall in the base case.

Cost-effectiveness of Interferon Gamma test for latent infection

The baseline results reported above depend on an assumed sensitivity of 90% and specificity of 80% for the skin test. With 20% prevalence of infection this implies that only 53% of those with a positive skin test will be infected and that 97% of those with a negative skin test are not infected. Although it costs an estimated £15 more per person, the interferon gamma test may still be more cost-effective than skin testing in this context if it offers a sufficient improvement in specificity and hence better targeting of preventive treatment. In our baseline model, where we assume that the interferon gamma test has a sensitivity of 90% and specificity of 80% (10% lower than the skin test), it appears to be cost-saving: saving about £4 per person and slightly improving expected health outcomes. In fact, the interferon gamma test appeared to be cost-effective provided that its specificity was no less than 4% better than the skin test. At 90% specificity, the interferon gamma test is cost-effective provided that it costs no more than about £45. At 85% specificity a cost of only £27 could be justified.

Cost-effectiveness of vaccination

The model predicts that vaccination is a cost-effective component of a new entrant screening programme. Removing vaccination from the baseline algorithm led to a small increase in overall NHS costs and a small reduction in health gains: an extra cost of about £200 and loss of about 0.02 of a QALY per 1,000 offered screening. The result was robust under one-way sensitivity analysis. The cost of the BCG would have to be over £27 per patient before vaccination drops below the cost-effectiveness threshold of £30,000 per QALY. Vaccination remained cost-saving in all other scenarios tested.

Cost-effectiveness of prophylaxis

The use of prophylaxis for people with suspected latent TB infection was not supported by this model. Under the baseline analysis it was estimated to cost an extra £400,000 per QALY gained. It remained highly cost ineffective under sensitivity analysis. The parameter with the biggest impact of the cost-effectiveness of prophylaxis was the future risk of TB in people with latent infection at screening (*rLI*). This had to rise to over 12% over the fifteen year time horizon of the model before prophylaxis appeared to be cost-effective.

Comparison of screening strategies

Finally, we compared the cost-effectiveness of eleven possible strategies, based on permutations of:

i) The method for screening for active disease - none, symptoms (SQ), or x-ray (XR);
ii) The method of screening for latent infection - none, TST or IGT;
iii) The preventive interventions offered - none, BCG and/or prophylaxis.

The results of this analysis under the baseline parameter values are shown in Table 4. Applying a standard £20-30,000 cost-effectiveness threshold, this suggests that the optimum strategy is 'no screening'.

Table 4. Baseline comparison of 11 screening strategies

	Per 1,000 people offered screening		*ICER **
	Cost (£)	*Effect (QALYs lost)*	*£ per QALY gained*
No screening	£67,500	5.258	-
XR only	£73,260	5.165	ED
XR, TST and BCG	£73,870	5.147	£57,542
XR, IGT and BCG	£74,290	5.142	£77,749
SQ only	£85,260	5.18	SD
SQ, TST and BCG	£85,760	5.16	SD
SQ, IGT and BCG	£86,290	5.155	SD
XR, IGT, BCG and prophylaxis	£98,520	5.058	£289,018
XR, TST, BCG and prophylaxis	£102,930	5.082	SD
SQ, IGT, BCG and prophylaxis	£109,280	5.069	SD
SQ, TST, BCG and prophylaxis	£113,330	5.092	SD

* The incremental cost per QALYs are calculated with respect to the previous non-dominated option.
SD – 'simple dominance' (options is more expensive and less effective than another option).
ED – 'extended dominance' (option is more expensive and less effective than a combination of two options).

This result is robust to changes in all parameters except two (*nSec* and *pTB*). Firstly, if transmission of TB is higher than expected (greater than about 0.4 secondary cases per primary case) then X-ray screening and skin testing followed by BCG if appropriate becomes cost-effective. At even higher levels of transmission (above about 1.2 secondary cases per primary case) substitution of interferon gamma testing for skin testing appears cost-effective.

Secondly, the optimum strategy is sensitive to the baseline prevalence of TB in the cohort at the time of screening. This is illustrated in Table 5. Strategies that are subject to either simple or extended dominance have been removed from this table. It can be seen that at low levels of prevalence none of the screening strategies is cost-effective. For populations with a

high prevalence of active TB (above about 100 in 10,000) radiographic screening, and possibly skin testing followed by vaccination if appropriate, starts to become cost-effective.

Table 5. Cost effectiveness of non-dominated strategies by prevalence

Prevalence of TB	*Strategy*	*Per 1,000 people offered screening*		*ICER*
		Cost (£)	*Effect (QALYs lost)*	*£ per QALY gained*
0%	No screening	£37,940	2.96	
	XR, IGT, BCG and prophylaxis	£69,860	2.85	£298,511
1%	No screening	£97,050	7.56	
	XR only	£102,290	7.38	£28,379
	XR, TST and BCG	£102,890	7.36	£30,952
	XR, IGT and BCG	£103,310	7.35	£77,351
	XR, IGT, BCG and prophylaxis	£127,170	7.27	£285,224
2%	No screening	£156,170	12.17	
	XR only	£160,340	11.80	£11,317
	XR, TST and BCG	£160,930	11.78	£27,665
	XR, IGT and BCG	£161,350	11.77	£76,576
	XR, IGT, BCG and prophylaxis	£184,470	11.69	£277,587
3%	No screening	£215,280	16.77	
	XR only	£218,400	16.22	£5,629
	XR, TST and BCG	£218,970	16.19	£24,892
	XR, IGT and BCG	£219,400	16.19	£75,827
	XR, IGT, BCG and prophylaxis	£241,770	16.10	£269,883
4%	No screening	£274,390	21.38	
	XR only	£276,450	20.64	£2,785
	XR, TST and BCG	£277,010	20.61	£22,521
	XR, IGT and BCG	£277,440	20.61	£75,103
	XR, IGT, BCG and prophylaxis	£299,070	20.52	£262,111
5%	No screening	£333,510	25.98	
	XR only	£334,500	25.06	£1,079
	XR, TST and BCG	£335,050	25.03	£20,470
	XR, IGT and BCG	£335,480	25.02	£74,402
	XR, IGT, BCG and prophylaxis	£356,380	24.94	£254,271

* Incremental cost per QALY calculated with respect to previous non-dominated option

CONCLUSIONS

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

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

It is important to recognise that the model does not take account of other potential benefits of screening – for example, community based screening may act to introduce new entrants to local health services, and as a screen for other possible health problems. The model also does not take account of other ways in which screening and treatments could be better targeted. For example, the decision to offer prophylaxis could be informed by the individuals' likely exposure to TB, their social environment, and/or indicators of latent infection from Xray. The economic model suggests that prophylaxis is not cost-effective in the context of new entrant screening. Using the basecase assumptions, the estimated incremental cost per quality adjusted life year gained for including prophylaxis in the new entrant screening algorithm was nearly £400,000. This result was robust to variation in the model parameters.

The model predicts that BCG vaccination is cost-saving for the NHS in the context of new entrant screening. Removing vaccination for TST negative new entrants from the new entrant screening algorithm led to a cost saving of £20,000 and a QALY gain of 1.8 per 100,000 screened, under the basecase assumptions.

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

The model suggests that, despite its higher initial cost, interferon gamma testing might be a cost-effective alternative to skin testing if it is demonstrated to give a lower number of false positive results. Under the basecase assumptions, the model predicted that interferon-gamma tests would be cost-saving in comparison with skin tests.
At low levels of prevalent TB in the cohort tested, none of the screening algorithms was cost-effective. The algorithm without prophylaxis achieves an incremental cost-effectiveness ratio (ICER) of £30,000 per QALY at a TB prevalence of about 3%, and an ICER of £20,000 per QALY at about 4% prevalence. This is relatively high compared with rates of disease found in many new entrant screening programmes.
If a more accurate method of screening for active disease (such as chest X-ray) is substituted for simple symptomatic screening, screening becomes cost-effective at lower levels of prevalence (at about 1% or higher).