NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1   Guidance title

Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (update)

1.1   Short title

Tuberculosis

2   The remit

The Department of Health has asked NICE: To prepare guidance for the NHS in England and Wales on the clinical management and diagnosis of, and measures to prevent and control tuberculosis (TB). This will replace the current guideline, 'Tuberculosis' (NICE clinical guideline 117).

This is an update of 'Tuberculosis' (NICE clinical guideline 117). See section 5.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

In addition to updating NICE clinical guideline 117, this guidance will aim to incorporate recommendations from 'Tuberculosis - hard-to-reach groups' (NICE public health guidance 37), where possible.

3 Background

Activities related to the diagnosis, management, prevention and control of TB are undertaken in both clinical and public health settings by a range of different practitioners. These different audiences share the same need for evidence-based, cost-effective solutions to the challenges in their day-to-day practice, as well as to inform policies and strategies to improve health.

This guidance will be produced using the Centre for Clinical Practice's standard process, using a single Guidance Development Group with expertise across clinical and public health practice. In addition to the clinical areas identified in the scope, the Centre for Public Health Excellence at NICE will develop a series of public health evidence reviews to inform additional recommendations in relevant areas.

4 Need for the guidance

4.1 Epidemiology

a) Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. TB most commonly affects the lungs (respiratory TB) but can also affect other parts of the body. In the UK in 2011, more than half of reported cases (52%) were respiratory TB.

b) The symptoms of TB are varied and depend on the site of infection, although general symptoms may include fever, loss of appetite, weight loss, night sweats and tiredness. Respiratory TB typically causes a persistent cough that may be accompanied by blood-streaked sputum or, more rarely, expectoration of blood only.

c) Almost all cases of TB in the UK are contracted when a person breathes in infected respiratory droplets from a person with active respiratory TB. The initial infection may:

- be eliminated by the body, or
- remain clinically latent; the person has no symptoms but the TB bacteria remain in the body, or
- progress to active TB over the following weeks or months; in some cases it can take many years for a person to develop active TB.

d)   According to the World Health Organization, people with active TB can infect up to 15 other people through close contact over the course of a year. The risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is. People infected with TB bacteria subsequently have a lifetime risk of progressing to active respiratory TB of about 10%, with the highest risk occurring in the first few years after infection. The risk of progressing to the active disease can be much higher in groups such as children, older people, people who are immunocompromised, and people with chronic poor health. For example, people who are co-infected with HIV and TB that are not treated are 21 to 34 times more likely to develop active TB; this risk is lower in those receiving antiretroviral therapy. Detection of latent TB is therefore important in controlling the incidence of disease.

e)   In England, rates of TB had fallen progressively until the mid-1980s but started to rise again in the early 1990s. In 2011 in the UK, the Health Protection Agency (HPA) reported a total of 8963 cases of TB (an increase of 31% from 2001) at a rate of 14.4 cases per 100,000 (an increase of 26% from 2001). In a 12-month period between 2010 and 2011, 436 people reported to have TB died (5% of the 8171 people for whom outcome data was available).

f)   The majority of TB cases recorded in 2011 were in urban areas, and occurred in young adults, people from countries with a high incidence of TB and people with social risk factors for TB, including

a history of substance misuse, homelessness or a history of imprisonment.

g)   Many cases of TB can be prevented by public health measures and when clinical disease does occur, most people can be cured if treated properly. It is vital that all medication is taken as prescribed. Taking medication in the wrong dose or combination, irregularly or for too short a time can lead to drug resistance. Drug-resistant strains of TB are much harder to treat and significantly increase a person's risk of long-term complications or death.

h)   According to the HPA, strains of TB that are resistant to at least isoniazid and rifampicin, two of the first-line drugs used in the treatment of TB, are known as multidrug-resistant (MDR) TB. MDR-TB that is also resistant to any one of a group of broad-spectrum antibiotics called fluoroquinolones and at least one of three injectable second-line anti-TB drugs (capreomycin, kanamycin or amikacin) is known as extensively drug-resistant TB (XDR-TB).

i)   In 2011, there were increases in the proportion of cases resistant to isoniazid (from 6% in 2010 to 8%), cases resistant to any first-line drug (7% in 2010 to 8%), and cases resistant to multiple drugs (from 1% in 2010 to 2%). In addition, 58% (47/81) of MDR-TB cases were resistant to at least one second-line drug.

j)   Drug-resistant TB is most commonly found in people born outside the UK and in those with social risk factors for TB, including a history of substance misuse, homelessness or a history of imprisonment.

4.2   Current practice

a)   NICE clinical guideline 117 ('Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control') and NICE public health guidance 37 ('Identifying and managing tuberculosis among hard-to-reach groups'), represent the current standards for TB diagnosis, management and prevention in England and Wales.

b)   Clinical suspicion of TB may arise 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.

c)   When a person presents with a suspected case of active respiratory TB, a chest X-ray is taken. If the X-ray is suggestive of TB, multiple sputum samples will be sent for TB microscopy and culture. Treatment of active respiratory TB is with a combination of antibiotics; the 'standard recommended regimen' consists of:

- isoniazid and rifampicin: every day for 6 months
- two additional antibiotics, pyrazinamide and ethambutol: every day for the first 2 months.

d)   When a person presents with suspected active TB outside the lungs, several tests can be used to confirm a diagnosis. These include a variety of radiological and laboratory tests, the combination of which will depend on the suspected site of the infection. Treatment of non-respiratory TB generally uses the same regimen of antibiotics as for respiratory TB. However, in people with suspected involvement of the nervous system, a 12-month rather than a 6-month course is used. Additionally, a 2–3-week

course of corticosteroids may also be prescribed for people with suspected heart or nervous system involvement.

e) All people diagnosed with active TB undergo a risk assessment for drug resistance, and those at increased risk are closely monitored for their response to treatment. If the risk is regarded as significant, rapid diagnostic tests for drug resistance may be used to confirm the presence of drug-resistant TB. Drug-resistant TB is treated with various combinations of antibiotics, depending on the type of resistance present.

f) Mantoux tests and/or interferon-gamma testing are used to diagnose latent TB. These tests are performed as part of contact-tracing initiatives following the diagnosis of a case of active TB or as part of case-finding programmes among high-risk groups. Treatment for latent TB is usually recommended for:

- people who are 35 years or younger
- people with HIV, regardless of their age
- healthcare workers, regardless of their age
- people with evidence of scarring caused by TB, as shown on a chest X-ray, but who were not adequately treated.

Different regimens of antibiotics are prescribed to treat latent TB depending on the age of the person, their HIV status and whether or not they are a contact of someone with drug-resistant TB.

g) Directly observed therapy (DOT) is widely used to promote adherence to treatment regimens. It is standard care for people who request it, or for those who:

- represent a particular risk for non-adherence to treatment or
- are unable to administer the treatment themselves or
- are currently (or have previously been) in prison or

- have MDR-TB.

h)   With the increases in drug resistance observed in the UK over the last few years, and the treatment difficulties and risks to both patients and the wider population that this entails, there is a need to ensure that people with TB are identified, and their disease is managed, in a timely and effective manner.

5   The guidance

The guidance development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guidance will (and will not) examine, and what the guidance developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guidance are described in the following sections.

5.1   Population

5.1.1   Groups that will be covered

a)   Adults, young people and children who have, or who are suspected to have, active TB caused by *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. africanum, M. bovis*).

b)   Adults, young people and children who have latent infection with *Mycobacterium tuberculosis* complex, but not active disease.

c)   Adults, young people and children at increased risk of infection with *Mycobacterium tuberculosis* complex and/or at increased risk of progressing to the active disease.

d)   Consideration will also be given to specific subgroups for whom the diagnosis and management of TB may vary. These may include, but are not limited to:

- neonates, children and young people
- adults older than 35 years
- people with HIV and other comorbidities or conditions that impact on the diagnosis and management of TB.

e)   Both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis* complex will be considered.

5.1.2   Groups that will not be covered

a)   People with other mycobacterial infections, for example *M. leprae, M. avium* complex and other opportunist mycobacteria.

b)   People at risk of contracting *Mycobacterium bovis* from animals, including cattle.

5.2   Setting

a)   Any setting in which NHS or public health services for TB are received, provided or commissioned in the public, private and voluntary sectors.

5.3   Topics of interest

5.3.1   Key issues that will be covered

Areas from the original guidelines ('Tuberculosis' [NICE clinical guideline 117]) that will be updated by an evidence review

Areas to be developed by the Centre for Clinical Practice

a)   Diagnosis of active respiratory and non-respiratory TB, including:

- clinical suspicion of disease
- radiological patterns

- microscopy and culture techniques
- biopsy
- interferon-gamma release assays
- rapid diagnostics, including molecular assays.

b)   Treatment of active TB. Specific consideration will be given to when treatment should deviate from the 'standard recommended regimen', taking into account factors such as the site and severity of the disease, and individual patient characteristics including age and the presence of comorbidities such as HIV, renal or liver disease and drug dependency. Alterations to the standard recommended regimen might include:

- dose frequency
- duration of treatment
- the use of adjunctive treatments, including corticosteroids and surgery.

c)   Identification of multiple drug resistance and isolated and combined resistances, including:

- risk factors
- microbiological drug susceptibility testing
- rapid diagnostics.

d)   Treatment of drug-resistant TB (excluding MDR- or XDR-TB).

e)   General principles for the management of drug resistance.

f)   Response to treatment interruptions.

g)   Infection control measures to ensure that people with infectious, active TB (including drug-resistant TB) do not infect others.

h) Diagnosis of latent TB infection using Mantoux testing and interferon-gamma release assays in:

- children
- people who are immunocompromised, such as people with HIV or renal disease, or at known risk of immunosuppression, such as people about to start immunosuppressive regimens
- new entrants from high incidence countries, in the context of opportunistic case-finding rather than proactive screening programmes.

i) Treatment of latent TB infection. Including:

- isoniazid
- rifampicin.

j) Note that for pharmacological interventions recommendations will normally fall within licensed indications; exceptionally and only where clearly supported by evidence, use outside of a licensed indication may be recommended. The guidance will assume that prescribers will use the Summary of Product Characteristics to inform their decisions for individual patients.

Areas to be developed by the Centre for Public Health Excellence

k) Encouraging uptake of BCG vaccination among people at increased risk of developing active or latent TB.

l) Promoting the uptake of, and improving adherence to, treatment for people with active and latent TB.

Areas not in the original guideline that will be included in the update by the Centre for Public Health Excellence

m)   Provision of education, information and support for people with TB, their families and carers, and healthcare workers across the care pathway (from diagnosis to follow-up after completion of treatment).

Areas not in the original guideline that will be included in the update using the Centre for Clinical Practice's interim methods for developing service delivery guidance

This question will be addressed by the Centre for Public Health Excellence using the Centre for Clinical Practice's interim methods for developing service delivery guidance. A subgroup of the Guideline Development Group, plus additional experts, will be used for this question.

n)   Organisation and management of clinical and public health TB services.

5.3.2   Issues that will not be covered

Areas from the original guideline that will not be updated by an evidence review (recommendations from CG117 will appear in the final guidance)

a)   Diagnosis of active respiratory TB, in terms of:

- the symptoms suggestive of a diagnosis of respiratory TB
- the number of sputum samples required for an accurate diagnosis
- approaches to collecting sputum samples in adults unable to expectorate spontaneously.

b)   Treatment of active TB, in terms of:

- the combination of anti-TB drugs used for people both with and without HIV co-infection, except where related to drug interactions

- the frequency of dosing in adults both with and without HIV co-infection

- the use of combination formulations, where available, for any drug-susceptible or drug-resistant disease.

c) Monitoring of patients after treatment completion.

d) Diagnosis of latent infection for groups other than those listed in 5.3.1h.

e) Occupational health measures to prevent the transmission of TB in the workplace.

f) Effectiveness of BCG vaccination.

Areas not covered by the original guidelines or the update

g) Interventions to address the social determinants of risk, except where they relate directly to the diagnosis, management, prevention or control of TB.

Areas covered by the original guidelines that will not be included in the update

h) New entrant screening programmes.

5.4   Main outcomes

Main outcomes to be considered include:

a) Diagnosis:

- diagnostic utility and accuracy
- time to diagnosis or treatment initiation
- prognostic value of tests
- acceptability of approach
- adverse events
- health-related quality of life

- resource use and cost.

b)   Treatment:

- mortality
- adverse events
- adherence and treatment completion
- treatment success and rate of recovery, or treatment failure, relapse and emergence of drug resistance
- health-related quality of life
- resource use and cost.

c)   Infection control:

- TB transmission rate
- acceptability of approach
- health-related quality of life
- resource use and cost.

d)   Promoting the uptake of, and improving adherence to, treatment, including:

- uptake and completion of treatment
- acceptability of approach
- direct and indirect measures of adherence (for example, direct observation of people taking their medication and self-reported medication taking)
- barriers to uptake and adherence to treatment.

e)   BCG vaccination uptake in at-risk groups:

- uptake of BCG vaccination
- barriers to uptake.

f)   Information, education and support:

- knowledge and awareness of TB among people who have, or who are at high-risk from TB and relevant staff, including how to recognise symptoms, the need for rapid diagnosis, referral and access to specialist TB services, and the need for prompt, complete treatment
- health, social and economic outcomes for people affected by TB.

5.5 Draft review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

5.5.1   Areas to be developed by the Centre for Clinical Practice

Diagnosis of active TB

Respiratory TB

a)   What are the most effective methods for (i) sputum smear microscopy and (ii) sputum culture in establishing an accurate diagnosis of active respiratory TB?

b)   What is the most effective method of collecting sputum samples from children unable to expectorate spontaneously?

c)   While awaiting culture results in adults with suspected respiratory TB, what other tests are effective in establishing an accurate diagnosis of active respiratory TB?

d)   While awaiting culture results in children and young people with suspected respiratory TB, what other tests are effective in establishing an accurate diagnosis of active respiratory TB?

e) In the presence of a negative culture, what other tests may support an accurate, positive diagnosis in people with suspected respiratory TB?

Non-respiratory TB

f) What clinical signs, symptoms or risk factors are suggestive of a diagnosis of active non-respiratory TB? (note: analysis will be conducted by site of disease)

g) While awaiting culture results in people with suspected non-respiratory TB, what other tests are effective in establishing an accurate diagnosis of active non-respiratory TB? (note: analysis will be conducted by site of disease)

h) In the presence of a negative culture, what other tests may support an accurate, positive diagnosis in people with suspected non-respiratory TB? (note: analysis will be conducted by site of disease)

Treatment of active TB

i) In children with active TB receiving drug treatment, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

j) In people co-infected with TB and HIV receiving drug treatment for both infections, what are the key pharmacological considerations that should be taken into account when selecting a treatment regimen for eradicating TB infection?

k) What comorbidities or conditions affect the choice of regimen for the treatment of TB? How should the standard recommended regimen be adapted to accommodate these comorbidities or conditions?

Respiratory TB

l)   In adults with active respiratory TB receiving drug treatment, are there particular circumstances in which a treatment period longer than 6 months would provide an additional benefit in terms of reducing mortality and morbidity? What duration of treatment is appropriate in these patients?

m)   In children with active respiratory TB receiving drug treatment, is the standard recommended regimen of 6 months effective in reducing mortality and morbidity? Are there circumstances in which a longer treatment period is indicated?

n)   In people with active respiratory TB receiving drug treatment, do corticosteroids (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone?

o)   In people with active respiratory TB receiving drug treatment, does surgery (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone?

Non-respiratory TB

p)   In people with active non-respiratory TB receiving drug treatment, is the standard recommended regimen of 6 months effective in reducing mortality and morbidity? Are there circumstances in which a longer treatment period is indicated? (note: analysis will be conducted by site of disease)

q)   In people with active non-respiratory TB, do corticosteroids (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone? (note: analysis will be conducted by site of disease)

r)　　　　In people with active non-respiratory TB, does surgery (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone? (note: analysis will be conducted by site of disease)

Identification of drug-resistant TB

s)　　　　In people with suspected or confirmed active TB, which relative risk factors are associated with a higher level of: i) multidrug resistance, or ii) any drug resistance?

t)　　　　Other than review of a patient's risk factors for drug resistance, what diagnostic methods should be used for the identification of drug resistance?

Treatment of drug-resistant TB

u)　　　　In people with drug-resistant TB (excluding MDR- and XDR-TB), i) what is the most effective combination of anti-TB drugs for reducing mortality and morbidity? ii) What is the most effective duration of treatment? (note: analysis will be conducted by type of resistance)

v)　　　　In people with drug-resistant TB, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

w)　　　　In people with drug-resistant TB, do corticosteroids (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone?

x)　　　　In people with drug-resistant TB, does surgery (as an adjunct to an anti-TB drug treatment regimen) decrease morbidity and mortality compared with an anti-TB drug regimen alone?

General principles for the management of drug resistance

y)   What general principles should apply to the management of all cases of drug-resistant TB?

Response to treatment interruptions

z)   For people receiving drug treatment for active TB who experience treatment interruptions, what approach to re-establishing appropriate treatment is the most effective in reducing mortality and morbidity?

Infection control

aa)   For people in hospital who have active TB, what infection control measures are the most effective in preventing transmission of TB infection to others?

bb)   For people who have active TB who are not in hospital but who are in congregate settings (for example residential homes or homeless shelters), what infection control measures are the most effective in preventing transmission of TB infection to others?

cc)   For people who have active TB that is not suspected to be MDR-TB, and for whom isolation is indicated, what factors should determine the duration of isolation necessary to minimise the risk of infection to others? What is the optimum duration?

dd)   For people who have active TB that is suspected to be MDR-TB, and for whom isolation is indicated, what factors should determine the duration of isolation necessary to minimise the risk of infection to others? What is the optimum duration?

Diagnosis of latent TB

ee)   Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in children?

ff)　　　Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in people who are immunocompromised or at risk from immunosuppression?

gg)　　　Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in people who are recent arrivals from countries with a high incidence of TB?

Treatment of latent TB

hh)　　　According to their risk factors, which people with either latent TB infection or in close contact with people who have active TB should receive drug treatment to prevent the development of active TB?

ii)　　　For people with latent TB infection, is a drug treatment regimen effective in preventing the development of active TB in comparison with placebo? If so, which regimen is the most effective in preventing the development of active TB?

5.5.2　　Areas to be developed by the Centre for Public Health Excellence

BCG vaccination uptake

jj)　　　Which strategies and interventions are effective and cost effective in increasing the uptake of BCG vaccination among people at increased risk of developing active or latent TB?

kk)　　　What are the barriers to uptake of BCG vaccination among people at increased risk of developing active or latent TB?

Promoting the uptake of, and improving adherence to, treatment for people with active and latent TB

ll)　　　Which strategies and interventions are effective and cost effective in promoting the uptake of, and improving adherence to, treatment for people with active and latent TB?

mm) What are the barriers to uptake and adherence to treatment for people with active and latent TB?

Information, education and support

nn) What information, education or other support-based interventions are currently used in practice to support the diagnosis, treatment and management of TB?

oo) How effective and cost effective are strategies and interventions aimed at providing and delivering information and education about the symptoms and risk of TB, clinical management of the illness and broader social support to people affected by TB?

Service delivery and configuration

pp) What are the optimal service models for configuring and delivering TB services – in terms of intermediate ('process') and final service outcomes, clinical outcomes, and costs – taking into account the differing requirements posed by:

- differences in incidence across areas and regions
- active and latent TB
- drug-resistant TB.

5.6 Economic aspects

Developers will take into account clinical and public health effectiveness and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate.

The preferred unit of effectiveness is the quality-adjusted life year (QALY). The costs considered in a clinical cost-effectiveness review will usually only be from an NHS and personal social services (PSS) perspective. The costs considered in a public health cost-effectiveness review will usually only be

from a public sector perspective, as well as the perspective of the department that administers the interventions.

Further detail on the methods can be found in 'The guidelines manual' and 'Methods for development of NICE public health guidance (third edition, 2012)' (see 'Further information').

5.7   Status

5.7.1   Scope

This is the final scope.

5.7.2   Timing

The development of the guidance recommendations will begin in February 2013.

6   Related NICE guidance

6.1   Published guidance

6.1.1   NICE guidance to be updated

This guidance will update and replace the following NICE guidance.

- Tuberculosis. NICE clinical guideline 117 (2011).

6.1.2   Other related NICE guidance

- Tuberculosis - hard-to-reach groups. NICE public health guidance 37 (2012).
- Infection control. NICE clinical guideline 139 (2012).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).

6.2   *Guidance under development*

NICE is currently developing the following related guidance (details available from the NICE website).

- Xpert MTB/RIF assay (and alternative technologies identified during scoping). NICE Diagnostics Assessment Programme guidance. Status: this topic has been paused. The Health Technology Assessment (HTA) programme at the National Institute for Health Research (NIHR) has commissioned a project in which there is significant overlap with the planned scope of the Diagnostic Guidance. The topic has therefore been paused and any decision to proceed with the topic will depend on the outcome of the NIHR project.

7   Further information

Information on the guidance development process is provided in the following documents, available from the NICE website.

The Centre for Clinical Practice's guideline development process and methods.

The Centre for Clinical Practice's interim methods guide for developing service guidance 2013.

The Centre for Public Health Excellence's methods are described in Methods for development of NICE public health guidance (third edition, 2012).

Information on the progress of the guidance will also be available from the NICE website.