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.

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 though 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. People infected with TB bacteria subsequently have a lifetime risk of progressing to active TB of about 10%. The risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is. 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 are 21 to 34 times more likely to develop active TB. 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, a total of 8963 cases of TB were reported (an increase of 6.6% from 2010) at a rate of 14.4 cases per 100,000 (an increase of 5.7%). Of the people reported to have TB in 2010, 436 (5.3%) died.

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 and 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 Health Protection Agency, 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 6.4% in 2010 to 7.6%), cases resistant to any first-line drug (7% in 2010 to 8.4%), and cases resistant to multiple drugs (from 1.3% in 2010 to 1.6%). In addition, 58% (47/81) of MDR-TB cases were resistant to at least one second-line drug.

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 clinical disease.

c)   Adults, young people and children at increased risk of infection with *Mycobacterium tuberculosis* complex.

d)   Consideration will also be given to specific subgroups for whom the diagnosis and management of TB may vary. Where appropriate and when reported by study authors these may include, but are not limited to:

- neonates, children and young people
- adults older than 35 years
- people with HIV.

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. For example:

- Primary, secondary and tertiary care NHS settings, including Accident and Emergency departments.
- Occupational health settings within the NHS, including those with responsibility for infection control and staff protection.
- Community settings.
- National and regional public health settings.
- Specific settings, including prisons and other detention facilities, educational settings, community-based centres and healthcare environments.

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 using Centre for Clinical Practice methodology

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)   Management of and referral for drug-resistant TB.

f)   Promoting adherence to treatment of active TB, including the effectiveness of DOT, reminder systems and counselling.

g)   Response to treatment interruptions.

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

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 using Centre for Public Health Excellence methodology

k)   BCG vaccination uptake within key groups.

l)   Promoting treatment – and adherence to treatment – among people with latent TB.

Areas not in the original guideline that will be included in the update

m)   Education and general awareness-raising about preventing, diagnosing, managing and controlling the spread of TB among key groups affected by TB.

n)   Information and support across the whole care pathway (from diagnosis to follow-up after completion of treatment) among key groups affected by TB. This includes people who have TB, their families and carers, and staff and healthcare workers.

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 product)

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 people 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 patient response to treatment, and follow-up after treatment completion.

d) Diagnosis of latent infection using Mantoux testing and interferon-gamma release assays in the context of case-finding activities, including:

- contact-tracing activities, including investigation of close contacts and outbreaks
- other proactive case-finding programmes among specific high-risk groups.

Areas not covered by the original guidelines or the update

e) Effectiveness of BCG vaccination.

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

g) Service models

5.4   Main outcomes

Main outcomes to be considered include:

a)   Diagnosis:

- diagnostic utility and accuracy of diagnostic strategies
- prognostic value of tests
- time to diagnosis of active TB
- 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 adherence to treatment for active TB:

- completion of treatment

- treatment success and symptom improvement, or treatment failure, relapse and emergence of drug resistance
- acceptability of approach
- other measures of adherence, for example pill-counting or blood tests
- health-related quality of life
- resource use and cost.

e)   Promoting adherence to, and uptake of, treatment for latent TB:

- uptake and completion of treatment.

f)   Vaccination of key groups:

- uptake of BCG vaccination among key groups across England and Wales
- barriers to uptake.

g)   Education, awareness: and support

- improved 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
- improved health, social and economic outcomes for people affected by TB.

5.5   Draft review questions

5.5.1   Areas to be developed using Centre for Clinical Practice methodology

Diagnosis of active TB

Respiratory TB

a)   While awaiting culture results in adults with suspected respiratory TB, what other tests are predictive of a positive diagnosis?

b)   While awaiting culture results in children and young people with suspected respiratory TB, what other tests are predictive of a positive diagnosis?

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

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

Non-respiratory TB

e)   What symptoms are suggestive of a diagnosis of active non-respiratory TB?

f)   While awaiting culture results in people with suspected active non-respiratory TB, what other tests are predictive of a positive diagnosis?

g)   In the presence of a negative culture, what other tests may support a positive diagnosis in people with suspected active non-respiratory TB?

Treatment of active TB

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

i)   In people co-infected with TB and HIV receiving drug treatment for both infections, what are the key drug interactions that affect the choice of treatment regimen for eradicating TB infection?

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

Respiratory TB

k)   In adults with active respiratory TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity? Are there circumstances in which a longer treatment period is indicated?

l)   In children with active respiratory TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity? Are there circumstances in which a longer treatment period is indicated?

m)   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?

n)   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

o)   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).

p)   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).

q)   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

r)   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?

s)   What other diagnostic methods should be used for the identification of drug resistance?

Treatment of drug-resistant TB

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

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

v)   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?

w)   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?

Management of and referral for drug-resistant TB

x)   Once a diagnosis is confirmed, to whom should people with drug-resistant TB be referred?

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

Promoting adherence to the treatment of active TB

z)   In people receiving drug treatment for active TB, which adherence-promoting strategies are effective in ensuring cure and/or treatment completion?

aa)   For which people receiving drug treatment for active TB is DOT effective in ensuring cure and/or treatment completion, compared with self-administered treatment? Who is the most effective observer and in what setting?

Response to treatment interruptions

bb)   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

cc)   For people in hospital who have active TB that is not suspected to be drug-resistant, what infection control measures are the most effective in preventing transmission of TB infection to others? Are additional measures necessary in settings where (i) people are immunocompromised, (ii) there are children, or (iii) healthcare workers may be particularly exposed?

dd) For people in hospital who have active TB that is suspected to be MDR-TB, what infection control measures are the most effective in preventing transmission of TB infection to others? Are additional measures necessary in settings where a) people are immunocompromised, b) there are children, or c) healthcare workers may be particularly exposed?

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

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

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

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 (in terms of the anti-TB drugs used and the duration of treatment) is the most effective in preventing the development of active TB?

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

regimen (in terms of the anti-TB drugs used and the duration of treatment) is the most effective in preventing the development of active TB?

5.5.2 Areas to be developed using Centre for Public Health Excellence methodology

Promoting the uptake of treatment for latent TB

kk) Which strategies and interventions are effective in promoting the uptake of prophylactic treatment for latent TB?

ll) What strategies are cost effective in promoting the uptake of prophylactic treatment among people with latent TB?

Promoting adherence to the treatment of latent TB

mm) Which strategies and interventions are effective in promoting and managing adherence to prophylactic treatment among people with latent TB?

nn) What strategies are cost effective in promoting adherence to prophylactic treatment among people with latent TB?

BCG vaccination uptake

oo) Which strategies and interventions are effective and cost effective at increasing the uptake of BCG vaccination in key groups?

pp) How effective and cost effective is BCG vaccination in terms of reducing the incidence of TB, in particular among key groups?

qq) What are the barriers to uptake of BCG vaccination?

Education and awareness

rr) Which strategies and interventions effectively (and cost effectively) raise awareness of TB, including symptoms and how to prevent,

diagnose and treat TB? Examples might include using peer education.

Information and support

ss)   Which strategies and interventions are effective and cost effective at providing and delivering information and support to people affected by TB, for example, the person, their families and/or carers, and staff?

tt)   What information and support (including access to support networks) should be given to people affected by TB?

5.6   Economic aspects

Developers will take into account both clinical and public health 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 consultation draft of the scope. The consultation dates are 27 November 2012 to 8 January 2013.

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).

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 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](#).