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Guidelines

Tuberculosis—diagnosis, management, prevention, and control: summary of updated NICE guidance

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What you need to know

- Undertake tuberculosis (TB) testing in close contacts of people with pulmonary or laryngeal TB, people who are immunocompromised and at high risk of TB, and new entrants from high incidence countries who present to healthcare services
- Seek specialist input in the diagnosis and management of TB in children, and in the management of people with multidrug resistant TB or those with TB and comorbidities
- Consider enhanced case management, including directly observed therapy (DOT), in patients with clinically or socially complex needs
- Apply appropriate infection control measures if a person has suspected or confirmed infectious TB (pulmonary or laryngeal TB)

Tuberculosis (TB) incidence in the UK remains high compared with other Western European countries.[1] It disproportionately affects underserved groups, including homeless people, people in poor housing or affected by poverty, people with problem drug use, and people born in countries with a high incidence of TB.[2] However, many cases are preventable with public health measures, and, when disease does occur, most people can be cured. This article summarises the updated recommendations on diagnosing, managing, and preventing TB from the National Institute for Health and Care Excellence (NICE).[3] This guidance updates the 2011 clinical guideline[4] and incorporates the public health guidance on the identification and management of TB in under-served groups.[5]

What's new in this guidance [Note toA: This should be pithy and limited to what is new]

- Increase in the upper age limit for testing and treatment for latent TB from 35 years to 65 years
- A Mantoux test is considered positive at an induration of ≥5 mm regardless of BCG history
- How to re-establish treatment for active or latent TB after interruptions by adverse events from drug treatment

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

See glossary for definitions of terms used.

Glossary of terms

Active tuberculosis disease—Infection with mycobacteria of the *M tuberculosis* complex where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent infection, where mycobacteria are present but are not causing disease.

Directly observed therapy (DOT)—A trained health professional, or responsible lay person supported by a trained health professional, provides the prescribed medication and watches the person swallow every dose.

High incidence country—More than 40 cases of TB per 100 000 people per year[6]

Interferon γ release assay (IGRA)—A blood test used to diagnose latent TB (as an alternative or addition to tuberculin skin tests) based on detecting the response of white blood cells to TB antigens.

Latent infection—Infection with mycobacteria of the *M tuberculosis* complex where the bacteria are alive but not currently causing active disease.

Mantoux test—A type of tuberculin skin test in which tuberculin is injected intradermally. The injection site is examined for signs of a local skin reaction (induration) after 2-3 days. In any patient, regardless of BCG history, this guidance recommends that a Mantoux test is considered positive for TB infection if the transverse diameter of the area of induration is ≥5 mm.

Multidrug resistant TB—TB resistant to isoniazid and rifampicin, with or without any other resistance.

Nucleic acid amplification test (NAAT)—A test to detect fragments of nucleic acid, allowing rapid and specific diagnosis of *M tuberculosis* directly from different clinical samples.

TB case manager—A named individual, appointed as soon as a patient becomes known to the TB service, who takes responsibility for ensuring that diagnostic investigations are completed and outcomes documented, that an appropriate treatment regimen is monitored and completed, and that contacts are identified, evaluated, and treated.

Treatment interruption—A break in the prescribed antituberculosis regimen for ≥2 weeks in the initial phase, or more than 20% of prescribed doses missed intermittently.

Diagnosing latent infection

Box 1 provides general principles in identifying latent infection.

Box 1: Identification of latent infection *[Updated recommendations 2016]*

- Offer TB testing to close contacts of people with pulmonary or laryngeal TB, people who are immunocompromised and at high risk of TB, and new entrants from high incidence countries presenting for health care
- The upper age limit for offering to test and treat latent infection is 65 years
- In any patient, regardless of BCG history, consider a Mantoux test as positive if skin induration is ≥5 mm
- If any test for latent infection is positive, assess for active TB; if this assessment is negative, offer treatment for latent TB infection

Children and young people who have been in close contact with people with infectious TB

- For children aged less than 2 years who have been in close contact with people with pulmonary or laryngeal TB, see figure 1. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model, and the experience and opinion of the Guideline Development Group (GDG)]*

- For a child or young person aged between 2 and 17 years who has been in close contact with people with pulmonary or laryngeal TB, offer Mantoux testing. If negative, wait six weeks, offer an IGRA and repeat the Mantoux test. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model and the experience and opinion of the GDG]*
- Only consider using the IGRA alone in children and young people if Mantoux testing is not available or is impractical. This includes situations in which large numbers need to be tested. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model, and the experience and opinion of the GDG]*

Fig 1 Pathways for diagnosing latent TB infection in neonates and young children *[Updated recommendation 2016]*

People who are immunocompromised

- Refer children and young people who are immunocompromised and at risk for TB to a specialist. *[Updated recommendation 2016; based on the experience and opinion of the GDG]*
- For adults who are severely immunocompromised (including those with HIV and CD4 counts $<200\times10^6$ cells/L, or after solid organ or allogeneic stem cell transplant) and at risk for TB, offer an IGRA and a concurrent Mantoux test. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model, and the experience and opinion of the GDG]*
- For other adults who are immunocompromised and at risk for TB, consider an IGRA alone or with a concurrent Mantoux test. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model and the experience and opinion of the GDG]*

New entrants from high incidence countries who present to healthcare services

- Offer Mantoux testing to this group. If Mantoux testing is unavailable, offer an IGRA. *[Updated recommendation 2016; based on evidence ranging in quality from low to high, an original health economic model and the experience and opinion of the GDG]*

Diagnosing active disease (see table 1)

- Request rapid diagnostic nucleic acid amplification tests (NAATs) for the *M tuberculosis* complex on primary specimens if
  - There is clinical suspicion of TB disease
  - The person has HIV infection
  - Rapid information about mycobacterial species would alter the person's care
  - The need for a large contact tracing initiative is being explored.

  [New recommendation 2016; based on very low quality cross sectional studies and the experience and opinion of the GDG]
- In children and young people aged 15 years or younger, usually only one NAAT is needed per specimen type (for example, spontaneous sputum, induced sputum, or gastric lavage). *[New recommendation 2016; based on cross sectional studies ranging in quality from low to moderate and the experience and opinion of the GDG]*
- Once a person has been diagnosed with active TB, inform relevant colleagues so that the need for contact tracing can be assessed without delay, and assess the need for infection control measures (box 2). *[Reviewed, not amended, 2016; based on the experience and opinion of the GDG]*

Box 2: Infection control measures *[Updated recommendations 2016]*

- Minimise the number and duration of visits a person with TB makes to an outpatient department while they are still infectious

- Put people with suspected infectious or confirmed pulmonary or laryngeal TB who will remain in hospital in a single room. If this is not possible, keep the person's waiting times to a minimum. This may involve prioritising their care above that of other patients
- Do not admit people with suspected infectious or confirmed pulmonary TB to a ward containing people who are immunocompromised
- Explain to inpatients with suspected infectious or confirmed pulmonary or laryngeal TB that they will need to wear a face mask whenever they leave their room. Ask them to continue wearing it until they have had at least two weeks of treatment
- Offer patients advice on simple respiratory hygiene measures, such as covering the mouth and nose with a tissue when coughing or sneezing and disposing of the tissue in a waste basket
- For people deemed to be at high risk of multidrug resistance, provide care in a negative pressure room
- Staff and visitors should wear FFP3 face masks during contact with a person with suspected or known multidrug resistant TB while the person is thought to be infectious

Multidrug resistant TB

- Request rapid diagnostic NAATs for rifampicin resistance if risk factors for multidrug resistance are identified:
  - Previous TB drug treatment, particularly with poor adherence
  - Contact with a known case of multidrug resistant TB
  - Birth or residence in a country in which the World Health Organization reports that a high proportion (≥5%) of new TB cases are multidrug resistant (fig 2).[6]

  Start infection control measures (see box 2). *[Updated recommendation 2016; based on low quality cross sectional studies and the experience and opinion of the GDG]*
- If the NAAT for rifampicin resistance is positive
  - Continue infection control measures until pulmonary or laryngeal disease has been excluded
  - Manage treatment along with a multidisciplinary team with experience of managing multidrug resistant TB
  - Offer treatment with at least six drugs to which the mycobacterium is likely to be sensitive
  - Test for resistance to second line drugs.

  [New recommendation 2016; based on the experience and opinion of the GDG]

Fig 2 Estimated incidence of TB by country in 2014. (Adapted from WHO *Global Tuberculosis Report 2016*[6])

Treating latent infection

- For people with evidence of latent TB, including those with HIV infection or those under 65 years old, offer either
  - Three months of isoniazid (with pyridoxine) and rifampicin, *or*
  - Six months of isoniazid (with pyridoxine).

  [Updated recommendation 2016; based on network meta-analyses of very low quality randomised controlled trials, an original health economic model, and the experience and opinion of the GDG]
- Base the choice of regimen on the person's clinical circumstances. For example, offer three months of isoniazid (with pyridoxine) and rifampicin if hepatotoxicity is a concern, or offer six months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern (such as in people with HIV or after a transplant). *[Updated recommendation 2016; based on network meta-analyses of very low quality randomised controlled trials, an original health economic model, and the experience and opinion of the GDG]*

- If people at increased risk of developing active TB (box 3) do not have treatment for latent TB for any reason, advise them of the risks and symptoms of TB. *[Updated recommendation 2016; based on the experience and opinion of the GDG]*

Box 3: People at increased risk of developing active TB *[Updated recommendations 2016]*

- People with HIV, diabetes, chronic kidney disease, or silicosis, or receiving haemodialysis
- Children younger than 5 years old
- People with an excessive alcohol intake or who are injecting drug users
- People who have had solid organ transplantation
- People who have a haematological malignancy or are receiving chemotherapy
- People who have had a gastrectomy or jejunoileal bypass
- People who are having treatment with anti-tumour necrosis factor alpha or other biologic agents

Treating active disease

- If clinical features are consistent with a diagnosis of tuberculosis, start treatment (box 4) without waiting for culture results. Continue this regimen even if subsequent culture results are negative. *[Reviewed, not amended, 2016; based on the experience and opinion of the GDG]*

Box 4: Treatment regimen for active TB *[Reviewed, not amended, 2016]*

- For people with active TB without central nervous system involvement, offer
  - −Isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for two months, *then*
  - −Isoniazid (with pyridoxine) and rifampicin for a further four months
- For people with active TB of the central nervous system, offer
  - −Isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for two months, *then*
  - −Isoniazid (with pyridoxine) and rifampicin for a further 10 months
- Modify the treatment regimen according to drug susceptibility testing

Adherence

- TB case managers should work with the person diagnosed with TB to develop a health and social care plan, and support them to complete therapy successfully. They should
  - −Offer a risk assessment to every person with TB, to identify their needs and whether they should have enhanced case management (a package of tailored, supportive care, which may include directly observed therapy (DOT)) (see box 5)
  - −Educate the person about TB and the treatment
  - −Develop an individual care plan after discussion with the person
  - −Gain the person's consent to the plan and agree a review date
  - −Coordinate discharge planning, especially for people on DOT
  - −Explore appropriate ways that peers and voluntary organisations can provide support.

  [Updated recommendation 2016; based on evidence ranging in quality from low to high and the experience and opinion of the GDG]
- Multidisciplinary TB teams should also implement other strategies (see box 6) to encourage people to follow their treatment plan and prevent them stopping treatment early. *[Updated recommendation 2016; based on evidence ranging in quality from low to high and the experience and opinion of the GDG]*

Box 5: Enhanced case management for TB *[Updated recommendations 2016]*

- This comprises a package of supportive care tailored to the person's needs, for someone with clinically or socially complex needs

- DOT is offered as part of enhanced case management in people who
  - −Do not adhere to treatment (or have not in the past)
  - −Have been treated previously for TB
  - −Have a history of homelessness or drug or alcohol misuse
  - −Are in prison or have been in the past five years
  - −Have a major psychiatric, memory, or cognitive disorder
  - −Are in denial of the TB diagnosis
  - −Have multidrug resistant TB
  - −Request DOT after discussion with the clinical team
  - −Are too ill to administer the treatment themselves.

Box 6: Strategies to encourage people to follow their treatment plan *[Updated recommendations 2016]*

- Enhanced case management, including DOT
- Reminder letters, printed information, telephone calls, texts, and apps using an appropriate language
- Health education counselling and patient centred interviews
- Tailored health education booklets from quality sources
- Home visits
- Random urine tests and other monitoring (such as pill counts)
- Access to free TB treatment for everyone (irrespective of eligibility for other NHS care) and information about help with paying for prescriptions
- Social and psychological support (including cultural case management and broader social support)
- Advice and support for parents and carers
- Incentives and enablers to help people follow their treatment regimen

Re-establishing treatment after interruptions because of adverse events

- For people who have experienced a treatment interruption because of drug induced hepatotoxicity, investigate other causes of acute liver reactions. Wait until transaminase and bilirubin levels fall and hepatotoxic symptoms have resolved, then sequentially reintroduce each of the anti-TB drugs at full dose over a period of no more than 10 days, starting with ethambutol and either isoniazid or rifampicin. *[New recommendation 2016; based on very low quality evidence and the experience and opinion of the GDG]*
- In people with severe or highly infectious TB who need to interrupt standard therapy because of a reaction, consider continuing treatment with
  - −For those who have experienced a hepatotoxic reaction, a combination of at least two antituberculosis drugs of low hepatotoxicity and monitor with a liver specialist for further reactions
  - −For those who have experienced a cutaneous reaction, a combination of at least two antituberculosis drugs with a low risk of cutaneous reactions and monitor with a dermatologist for further reactions.

  [New recommendation 2016; based on the experience and opinion of the GDG]

Uptake of BCG vaccination in people from eligible groups

- To improve the uptake of vaccination, identify eligible groups[7] opportunistically, such as through new registrations in primary care, with antenatal services, or other points of contact with secondary or tertiary care; people entering education; links with statutory and voluntary groups; or contact investigations. *[New recommendation 2016; based on evidence ranging in quality from low to high and the experience and opinion of the GDG]*
- In primary care

- −Educate and support practice staff, such as by raising awareness of guidelines and who is at risk and promoting BCG and TB testing in eligible groups;
- −Incorporate reminders for staff on practice computers
- −Consider financial incentives for practices
- −Use written reminders, telephone calls, text messages, or a combination of these for reminders ("immunisations due") and recall ("immunisations overdue").

[New recommendation 2016; based on evidence ranging in quality from low to high and the experience and opinion of the GDG]

- Incorporate compute r reminders into maternity service (obstetrics) IT systems for staff. *[New recommendation 2016; based on low quality evidence and the experience and opinion of the GDG]*
- Vaccinate babies at increased risk of TB before discharge from hospital or before handover from midwifery to primary care, if possible. Otherwise, vaccinate soon afterwards (for example, at the 6 week postnatal check). *[New recommendation 2016; based on the experience and opinion of the GDG]*
- Trained lay health workers, community based healthcare staff, or nurses should use home visits to give information and advice to disadvantaged people on the importance of immunisation. *[New recommendation 2016; on evidence ranging in quality from moderate to high and the experience and opinion of the GDG]*

Overcoming barriers

More routine use of NAATs means that laboratories may need to review their practices for TB diagnosis, as well as invest in the training and facilities required. Where this is not possible, it will be necessary to arrange partnerships with other centres for external testing.

The updated guidance also puts a greater emphasis on the role of "specialists," whether they are individual clinicians or the multidisciplinary team. This is particularly important for treatment of children, co-management of TB with other conditions, and the management of multidrug resistant TB. Partnerships with other centres or specialist advisory services (such as the national advisory service for multidrug-resistant TB currently provided by the British Thoracic Society (http://forums.brit-thoracic.org.uk/ for further information)) may be necessary to ensure that specialist input is available for all patients.

Guidelines into practice

Does the patient have signs, symptoms, or risk factors for TB, and, therefore, should diagnostic efforts be initiated?

Should infection control measures be initiated, and to what degree? Do rapid diagnostic tests for drug resistance need to be ordered?

How patients were involved in the creation of this article

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

Further information on the guidance

Methods

The Guideline Development Group (GDG) and Service Delivery Group (SDG) followed standard National Institute for Health and Care Excellence (NICE) methods to produce this updated guidance.[8 9] The GDG included two infectious disease epidemiologists, a physician in global health and tuberculosis (TB), two general practitioners, two consultants in communicable disease control, two TB nurses, one respiratory pharmacist, two infectious diseases physicians, two respiratory physicians (one co-opted), one paediatrician, two medical microbiologists, and four patient or lay members. The SDG included two infectious disease epidemiologists, one infectious diseases physician, one director of public health, one consultant in public health, two respiratory physicians, one consultant in health protection, one consultant in communicable

disease control, one TB nurse, one general practitioner, one community development officer, and three patient or lay members.

The GDG and SDG developed the review questions. To answer these questions, the NICE systematic reviewing team identified and analysed the clinical and health economic evidence. Meta-analysis, network meta-analysis, narrative analysis, and health economic modelling were undertaken when appropriate. GRADE methodology was also applied to develop quality ratings for the body of evidence. The development groups appraised and interpreted the evidence to develop the recommendations and research recommendations. A draft guideline, which went through a quality assurance process, was developed. The draft guideline was consulted on by a range of stakeholders who were invited to comment, and all comments were considered by the GDG when producing the final version of the guideline.

Available versions of this guidance

NICE has produced four different versions of the guidance:

- A full version (http://www.nice.org.uk/guidance/ng33/evidence);
- A summary version known as the "NICE guidance" (http://www.nice.org.uk/guidance/ng33);
- A pathway (http://pathways.nice.org.uk/pathways/tuberculosis); and
- A version for people using NHS services, their families and carers, and the public (http://www.nice.org.uk/guidance/NG33/ifp/chapter/about-this-information).

All these versions, together with a suite of tools to help with implementation of the guidance (http://www.nice.org.uk/guidance/ng33/resources), are available from the NICE website (http://www.nice.org.uk). Further updates of the guidance will be produced as part of NICE's guideline development programme.

Future research

- In people with suspected TB, what is the relative clinical and cost effectiveness of universal and risk-based use of rapid nucleic acid amplification tests?
- Apart from culture, what other diagnostic tests or combinations of tests can establish an accurate diagnosis of active respiratory TB in children and young people with suspected active TB?
- For isoniazid-resistant TB, what is the most effective regimen for reducing mortality and morbidity?
- What effects does isolation have on the quality of life of people being treated for TB?
- For people with active, drug susceptible TB who experience treatment interruptions because of adverse events, particularly hepatotoxicity, what approach to re-establishing treatment most effectively reduces mortality and morbidity?

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Table 1 Tests to diagnose active TB *[Updated recommendations 2016; based on very low quality cross-sectional studies and the experience and opinion of the GDG]*

Suspected site of disease	Possible imaging techniques*	Specimen	Routine test	Additional tests (if they would alter management)
Pulmonary (people aged ≥16 years)	X ray† CT thorax	3 respiratory samples (preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or bronchoscopy and lavage; preferably 1 early morning sample)	Microscopy Culture Histology	NAAT
Pulmonary (children aged ≤15 years)	X ray† CT thorax	3 respiratory samples (preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or bronchoscopy and lavage; preferably 1 early morning sample)	Microscopy Culture Histology NAATs (1 per specimen type)	IGRA and/or Mantoux test (with expert input)
Pleural	X ray Bronchoscopy	3 respiratory samples (preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or bronchoscopy and lavage; preferably 1 early morning sample)	Microscopy Culture Histology	—
		Pleural fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Central nervous system	CT† MRI†	Biopsy of suspected tuberculoma	Microscopy Culture Histology	—
		Cerebrospinal fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Meningeal	CT† MRI†	Cerebrospinal fluid	Microscopy Culture Cytology	NAAT Adenosine deaminase assay
Lymph node (including intrathoracic mediastinal adenopathy)	Ultrasound CT MRI	Biopsy	Microscopy Culture Histology	NAAT
		Aspirate	Microscopy Culture Cytology	NAAT
Pericardial	Echocardiogram	Biopsy of pericardium	Microscopy Culture Histology	—
		Pericardial fluid	Microscopy Culture Cytology	NAAT Adenosine deaminase assay
Gastrointestinal	Ultrasound CT Laparoscopy	Biopsy of omentum Biopsy of bowel Biopsy of liver	Microscopy Culture Histology	—
		Ascitic fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Genitourinary	Ultrasound	Early morning urine	Culture	—
	Intravenous urography Laparoscopy	Biopsy from site of disease, such as endometrial curettings or renal biopsy	Microscopy Culture Histology	—
Bone or joint TB	X ray CT MRI	Biopsy or aspirate of paraspinal abscess Biopsy of joint	Culture	—

		Aspiration of joint fluid		
Disseminated	CT thorax and head MRI Ultrasound of abdomen	Biopsy of site of disease, including lung, liver, and bone marrow	Microscopy Culture Histology	Additional tests appropriate to site
		Aspirate bone marrow	Microscopy (if sample available)	
		Bronchial wash	Culture	
		Cerebrospinal fluid	Cytology	
		Blood	Culture	
Skin	—	Biopsy	Microscopy Culture Histology	—
Abscess outside of lymph nodes	Ultrasound or other appropriate imaging	Aspirate	Microscopy Culture Cytology	—
		Biopsy	Microscopy Culture Histology	—

CT=computed tomography. NAAT= Nucleic acid amplification test. MRI=magnetic resonance imaging.
*Taking into account, for example, the exact site of suspected disease and the availability of the test at the time of assessment.
†Routine imaging.