**GUIDELINES**

**Diagnosis of active and latent tuberculosis: summary of NICE guidance**

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Tuberculosis is a major preventable infectious cause of morbidity and mortality globally, which has re-emerged in high risk groups such as migrants, homeless people, problem drug users, and prisoners in the UK.¹ This article summarises the most recent recommendations (2011) from the National Institute for Health and Clinical Excellence (NICE)² on the diagnosis of latent tuberculosis (including the use of new tests) and of active tuberculosis. Although this summary focuses on diagnosis, the full guidelines cover the public health and clinical management of tuberculosis and replaced the guidelines published in 2006.³

**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. Evidence levels for the recommendations are in the full version of this article on bmj.com.

**Diagnosing latent tuberculosis (new/updated recommendations)**

**All contacts of tuberculosis cases, aged 5 years or older**

- Offer Mantoux testing in line with the Department of Health’s Green Book⁴ to:
  - Household contacts of all people with active tuberculosis
  - Non-household contacts (other close contacts, such as in workplaces and schools).
- A positive Mantoux test is an induration of ≥6 mm diameter for those who have not been vaccinated with BCG and ≥15 mm diameter for those who have been vaccinated.
- Consider interferon-γ release assay (IGRA) for people whose Mantoux test shows positive results, or in people for whom Mantoux testing may be less reliable (such as those who have been vaccinated with BCG).
- Refer people with a positive IGRA or an inconclusive Mantoux test to a tuberculosis specialist.

**Household contacts aged 2–5 years**

- Offer Mantoux testing.
- If the initial test is positive (taking into account BCG vaccination history), refer to a tuberculosis specialist to exclude active disease and consider treating latent tuberculosis.
- If the initial Mantoux test is negative but the child is a contact of a person with disease that is positive for acid fast bacilli on a sputum smear, offer an IGRA after six weeks and repeat the Mantoux test to reduce the rate of false negative results for latent infection.

**Household contacts younger than 2 years and older than 4 weeks**

- If contact was with a person whose sputum smear is positive for acid fast bacilli:
  - For children not vaccinated with BCG, perform a Mantoux test and offer isoniazid:
    - If the Mantoux test is positive, assess the child for active tuberculosis. If active tuberculosis is excluded, offer full treatment for latent infection
    - If the Mantoux test is negative (<6 mm induration), continue isoniazid for six weeks, and then repeat the Mantoux test together with an IGRA. If the repeat tests are negative, isoniazid may be stopped and BCG vaccination performed. If either repeat test is positive, assess the child for active tuberculosis and consider treating for latent tuberculosis.
  - For vaccinated children, perform a Mantoux test. If the Mantoux reaction is <15 mm, repeat the Mantoux test after six weeks, together with an IGRA. If both repeat tests are negative, no further action is needed. If either test is positive, exclude active tuberculosis and follow with treatment for latent tuberculosis.

**Contacts in outbreak**

- If large numbers of individuals need to be screened, consider a single IGRA for people aged ≥5 years.

**New entrants from countries with a high incidence of tuberculosis**

- For children under 5 years, offer a Mantoux test. If strongly positive, refer to consider treating latent tuberculosis.
- For children aged 5–15 years, offer a Mantoux test. If positive, follow with an IGRA.
- For people aged 16–35 years, offer either an IGRA alone or a dual strategy (Mantoux test followed by IGRA).
- For people over 35 years, consider the individual risks and benefits of likely subsequent treatment before offering testing.

**People who are immunocompromised**

- If latent tuberculosis is suspected in children who are immunocompromised, refer to a tuberculosis specialist.
- For people with HIV infection and CD4 counts <200 cells/mm³ (<200×10⁹/L), offer concurrent IGRA and Mantoux tests. If either test is positive, perform a
Assessment and diagnosis of tuberculosis

- Healthcare workers
  - Offer a Mantoux test to new NHS employees who will be in contact with patients or clinical materials if the employees are not new entrants from high incidence countries and have not had BCG vaccination (they do not have a vaccination scar, other documentation, or reliable history). If the Mantoux test is negative, refer to the Green Book for BCG immunisation guidance. If the Mantoux test is positive, offer an IGRA.
  - For new NHS employees who have recently arrived from high incidence countries or who have had contact with patients in settings where tuberculosis is highly prevalent, offer an IGRA.
  - Screen healthcare workers who are immunocompromised in the same way as other people who are immunocompromised.

Hard to reach groups

- Offer people from hard to reach groups a single IGRA (see NICE guidelines on the control of tuberculosis in hard to reach groups).

Diagnosis of active tuberculosis

Active respiratory tuberculosis

- Take a posterior-anterior chest x ray. If the x ray appearance suggests tuberculosis carry out further diagnostic investigation.
- Send multiple sputum samples (at least three, with one early morning sample) for tuberculosis microscopy and culture for suspected respiratory tuberculosis, before starting treatment if possible or, failing that, within seven days of starting.
- If possible obtain spontaneously produced sputum; otherwise use induction of sputum or bronchoscopy and lavage.
- In children unable to expectorate sputum, consider induction of sputum if it can be done safely; consider gastric washings as third line.
- Use rapid diagnostic tests for Mycobacterium tuberculosis complex (M tuberculosis, M bovis, M africanum) on specimens obtained from patients only if rapid confirmation of a tuberculosis diagnosis in a person whose sputum smear is positive would alter the patient’s care or before conducting a large contact tracing initiative. Do not use such tests for pleural fluid, cerebrospinal fluid, or urine to exclude the diagnosis of tuberculosis as they have a high false negative rate.

Active non-respiratory tuberculosis

- Discuss the advantages and disadvantages of both biopsy and needle aspiration with the patient, with the aim of obtaining adequate material for diagnosis.
- If non-respiratory tuberculosis is a possibility, place part or all of any of the following samples in a dry pot (do not place in formalin) and send for tuberculosis culture: 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 tuberculosis culture on the above samples (even if it is not requested).
- Take a chest x ray of all patients with non-respiratory tuberculosis to exclude or confirm coexisting respiratory tuberculosis. In addition, consider imaging, biopsy, and histopathology as well as bacterial culture depending on the affected organ.
- If clinical signs and other laboratory findings are consistent with tuberculosis meningitis, start treatment, even if a rapid diagnostic test is negative, because the potential consequences for the patient are severe.
- Carry out rapid diagnostic tests for M tuberculosis complex on biopsy material only if all the sample has been inappropriately placed in formalin and acid-fast bacilli are visible on microscopy.

Large scale contact investigation

- With a positive result by microscopy or tuberculosis culture, confirm the species of mycobacterium to be M tuberculosis complex by rapid diagnostic tests on material before starting large scale contact tracing (such as in a school or hospital). Use clinical judgment if tests are inconclusive or delayed.

Multiple drug resistant (MDR) tuberculosis

- Undertake a risk assessment for MDR tuberculosis. Risk factors for MDR tuberculosis include prior tuberculosis drug treatment; prior tuberculosis treatment failure; contact with a known case of drug resistant tuberculosis; birth in a foreign country, particularly one with a high incidence of tuberculosis as defined by the Health Protection Agency; HIV infection; residence in London; age profile (with highest rates between the ages of 25 and 44 years); and male sex.
- If a risk assessment suggests a patient has MDR tuberculosis, carry out rapid diagnostic tests for rifampicin resistance and start infection control measures and treatment for MDR tuberculosis pending the result of the tests.

Starting treatment

- If clinical signs and symptoms are consistent with a diagnosis of tuberculosis, start treatment without waiting for culture results. Continue the standard recommended regimen in patients whose subsequent culture results are negative.
Overcoming barriers
Primary care can and should play a key role in promoting early diagnosis of both active and latent tuberculosis through a systematic approach to screening for tuberculosis. Studies indicate that screening in primary care can contribute to the detection of latent tuberculosis in high risk groups. However, the resources available for the necessary tests are limited, with consequent variation in the extent to which interferon-γ release assays (IGRA) are implemented, as too often screening is not prioritised by commissioners. Demonstration of the potential impact of this intervention on local tuberculosis rates and of more pragmatic thresholds for screening migrants are the most effective ways to improve funding.

The application of the tests outlined in this article to achieve prompt diagnosis of active tuberculosis requires early recognition and referral of individuals with symptoms and signs of tuberculosis by general practitioners. Greater awareness of the clinical presentation of tuberculosis and risk factors among healthcare providers remains the primary route to achieve early diagnosis and avert transmission and adverse outcomes for the patient.

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A PATIENT’S JOURNEY

Tuberculosis

Mel Burden, Hugh Bakere

Ten months after returning home from working in a rural South African hospital, an infection prevention and control nurse developed tuberculosis. She describes the challenges of dealing with her treatment, her isolation, and the reactions of friends and colleagues.

I was 28 years old and newly married when I was diagnosed with pulmonary tuberculosis (TB). I had recently started a new job as an infection control nurse, and the irony of this was not lost on me or those around me. Ten months previously I had returned to Devon having spent six months working with my husband, Tom, in a rural South African hospital where drug resistant and sensitive TB were rife. With minimal hospital resources, we worked everyday without personal protective equipment. Several nurses there developed TB; some died.

Having had a persistent cough and mild breathlessness for about a month, I went to see my GP. I saw a locum who diagnosed a chest infection with exacerbation of my asthma. I told him this did not feel like asthma: my peak flow was normal and I had no expiratory wheeze. However, I provided a sputum sample for culture and sensitivity testing and took the prescribed amoxicillin.

My sputum grew a penicillin resistant Staphylococcus aureus, so my antibiotic was changed to erythromycin. The symptoms persisted. At this point, I could not walk up two flights of stairs without becoming breathless, and I joined our local gym in an attempt to improve my fitness.

After two weeks of antibiotics, continual coughing, and a negative sputum sample, I voiced the possibility of TB to my GP. However, asthma remained the working diagnosis.

Disbelief and guilt
My husband asked me if he could talk to his consultant, respiratory physician Hugh Bakere, and I agreed. After an informal chat, Dr Bakere saw me in clinic. My chest x ray appeared normal. He mentioned the possibility of bronchiectasis and the need to rule out TB, and said he didn’t think it was cancer. Over the following weekend I coughed up the usual thick green sputum and diligently dispatched more samples to microbiology. On the Wednesday I received a phone request to see Dr Bakere immediately. The sputum samples had tested positive for acid fast bacilli.
Mel presented to me through a slightly unusual route; her husband, a junior doctor, approached me with his concerns about her. I met Mel with her husband in my office. Mel had had a productive cough for seven weeks, had occasional night sweats, and felt generally lethargic. Her weight was stable. She was worried about tuberculosis as she had returned from working in a rural hospital with TB patients in South Africa, six months earlier. Mel had a history of asthma, normally well controlled, but her symptoms were different and more prolonged than those she had experienced with previous exacerbations of asthma.

I felt on initial assessment that pulmonary tuberculosis was a real possibility, along with perhaps bronchiectasis, and ordered a chest radiograph and three sets of sputum for microscopy culture and sensitivity analysis, examination for acid fast bacilli, and TB culture. The chest radiograph was clear but two sputum samples were acid fast bacilli positive, and *Mycobacterium tuberculosis* (fully sensitive) was later cultured. I was slightly surprised by the clear chest radiograph, but given her history and two confirmed sputum samples I was fairly happy with the diagnosis. A positive QuantiFeron test result provided further support. Endoscopy of the ear, nose, and throat showed no evidence of oropharangeal TB. I considered computed tomography of the thorax, which I expect would have shown a focus of disease, but decided against it as I did not want to expose this young woman to the associated radiation dose. Immediately after the positive sputum result, I started Mel on standard pulmonary mycobacterium TB therapy. This is six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol. I also gave her pyridoxine as prophylaxis against isoniazid induced neuropathy. We advised her to remain isolated at home avoiding new contacts for two weeks as a standard precaution. We were more concerned about this than usual as South Africa is an area with an increased incidence of multidrug resistant TB. Her case was notified and contact traced in the usual way. She has successfully completed her treatment.

The case highlights several points. Firstly, it is important to consider the diagnosis; key here was her travel and occupational history. As a respiratory physician in south west England, I am working in an area with a low incidence of TB (5.1 cases/100 000 in 2010) and see only a smattering of TB in the local population. Mel, however, was returning from a high incidence area (with significant exposure in the hospital she worked in) and her risk of contracting TB was therefore much higher. It was this history along with her clinical presentation that pushed TB up towards the top of my list of differential diagnoses. Secondly, a normal chest radiograph does not completely exclude TB. Thirdly, we should remember the value of good TB nurses, who delivered much of Mel’s ongoing care. Lastly, it is important to formalise care for our colleagues with an ongoing healthcare problem; Mel was slotted into the usual clinic set up quickly.

Hugh Bakere

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**Psychological effects**

Overriding all of this was stigma. I was infectious. I was to be confined to my house, unable to socialise. I had to make phone calls and explain to people why I could not see them, or why they had to be screened.

Part of me was disbelieving—I felt relatively well; it couldn’t be right. I was apprehensive about treatment, the side effects, and prognosis after treatment. There was also a part of me that felt bitter that I hadn’t been listened to. This passed after I realised how quickly I was diagnosed in the grand scheme of things, but I sometimes wonder what could have happened.

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**Fatigue in primary non-small cell lung cancer (BMJ) 2012;345:e7004**

**Neuromuscular degeneration (BMJ) 2012;345:e6880**

**Non-small cell lung cancer (BMJ) 2012;345:e6443**

**How no one acted when they should have (BMJ) 2012;345:e5366**

**Irreversible renal damage from accidental mushroom poisoning (BMJ) 2012;345:e5262**

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**A DOCTOR’S PERSPECTIVE**
Tom was a great support, and appointments with the respiratory team soon made me more positive. I was also fortunate to be working within the infection control team, who provided a huge amount of support. Regular contact from my GP added to the support. On the advice of the TB nurses, I researched several organisations (see resources box) to gain a deeper understanding of TB. Reading other peoples’ stories was helpful, and I started to keep a diary, which, in part, motivated me to write this article.

Now treatment is complete I am back at work full time—my manager and colleagues have been instrumental in my graduated return to work. The medication and side effects are no more, and I can enjoy food again. I have regained weight, have no cough, and my stamina has increased. My family and friends have all been screened with encouraging results. The huge worry and guilt regarding infecting others has gone. Did this contribute to my feeling better?

My patient journey has shown me that TB is not just a medical disease—so many emotional and social factors interplay, making it paramount that a TB patient gets appropriate care and support for these issues as well as medical treatment.

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USEFUL RESOURCES FOR PATIENTS AND CLINICIANS
Health Protection Agency—Provides useful and comprehensive information on TB (www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis)
World Health Organization’s observations on the observance of World TB Day in 2010 are available at www.who.int/dg/speeches/2010/world_tb_day_20100324/en/index.html
TB Alert (www.tbalert.org)—The only British charity working solely on fighting TB in the UK and overseas
British Lung Foundation (www.lunguk.org)—Resources are focused on providing support for people affected by lung disease. The foundation funds world class research, campaigns to bring about positive change in lung health, and aims to improve treatment, care, and support for those affected by lung disease
The truth about TB (www.thetruthabouttb.org) contains information on symptoms and risks of TB, treatment, and information and stories about people who have had TB in the UK

for children seemed cruel, with some of them too young to understand; x ray radiation to adults concerned me. Others were self employed and could have lost earnings while attending appointments, and all because of my desire to experience healthcare in a developing country.

ANSWERS TO ENDGAMES, p 50 For long answers go to the Education channel on bmj.com

PICTURE QUIZ Neonatal seizure: what is the cause?
1 Common causes of neonatal seizures include hypoxic ischaemic encephalopathy, intracranial haemorrhage, intracranial infections, congenital cerebral malformations, metabolic disorders, and focal ischaemic stroke.
2 Jitteriness and benign neonatal sleep myoclonus are the two most common conditions that mimic seizure in neonates.
3 The MRI of the brain shows extensive venous thrombosis.
4 Neonatal cerebral sinovenous thrombosis.
5 Management involves anticoagulation with low molecular weight heparin, ultrafractionated heparin, or warfarin and management of seizures and any identified acquired causes of cerebral sinovenous thrombosis.

STATISTICAL QUESTION
Analysis of outcome measures within treatment groups
Statements a, b, and c are all false.

ANATOMY QUIZ
Anatomy of the pituitary region
A: Optic chiasm
B: Hypothalamus
C: Pituitary stalk
D: Posterior lobe of pituitary gland
E: Anterior lobe of pituitary gland
F: Suprasellar cistern