Tuberculosis is an infection caused by *Mycobacterium tuberculosis* which may affect any part of the body but most commonly affects the lungs. It is spread by a person inhaling the bacterium in droplets coughed or sneezed out by someone with infectious tuberculosis.

**Epidemiology**

The World Health Organisation estimates that 2 billion people (one-third of the world’s population) have latent infection with *Mycobacterium tuberculosis*, 15–20 million people have active disease and 3 million deaths occur each year from tuberculosis (95% in the developing world). One hundred years ago in the UK more than 30 000 people died from tuberculosis each year (about the same as for lung cancer at present). Mortality and notification rates declined steadily from 1900 onwards because of improvement in nutritional and social factors, with a sharper decline occurring from the late 1940s onwards after the introduction of effective treatment (Fig. 7.1). Notification rates in England and Wales reached a low point of about 5000 a year in 1987 but have increased again to about 6500 a year recently. This increased incidence of tuberculosis is mainly seen in inner city areas, particularly London, and the risk is highest in ethnic minority groups. The notification rates for tuberculosis are highest in the Black African (211 per 100 000 population), Pakistani (145 per 100 000) and Indian (104 per 100 000) ethnic groups and lowest in the white ethnic group (4 per 100 000). The recent increase in notification rates is partly due to patterns of immigration and increasing international travel. Other groups of people with a high incidence of tuberculosis are the homeless, those misusing drugs and alcohol and people co-infected with the human immunodeficiency virus (HIV). In younger age groups tuberculosis is often newly acquired infection whereas in the older age groups it is often reactivation of latent infection acquired many years previously. Factors which reduce resistance and precipitate reactivation include ageing, alcohol misuse, poor nutrition, debility from other diseases, use of immunosuppressive drug therapy and co-infection with HIV. In the UK, overlap between the population with HIV infection (mainly young white men) and the population with tuberculosis (mainly older white people and younger immigrants from the Indian subcontinent) is limited so that only 5% of patients with acquired immune deficiency syndrome (AIDS) have tuberculosis and about 3% of patients with tuberculosis are identified as having HIV infection. However, 4.5 million people worldwide are estimated to be co-infected with HIV and tuberculosis (98% in developing countries).

**Clinical course (Fig. 7.2)**

The clinical course of tuberculosis often evolves over many years and represents a complex interaction
between the infecting organism (*Mycobacterium tuberculosis*) and the person’s specific immune response and non-specific resistance to infection. Traditional descriptions of tuberculosis divide the disease into two main patterns, primary and post-primary tuberculosis, although these are mainly based upon the characteristic evolution of the disease in the days before effective chemotherapy.

**Primary tuberculosis**

Primary tuberculosis is the pattern of disease seen with first infection in a person (often a child) **without specific immunity** to tuberculosis. Infection is acquired by inhalation of organisms from an infected individual, and the initial lesion typically develops in the peripheral subpleural region of the lung followed by a reaction in the hilar lymph nodes. The **primary complex** appears on chest X-ray as a peripheral area of consolidation (Gohn focus) and hilar adenopathy. Occasionally, erythema nodosum develops at this stage. An immune response develops, the tuberculin test becomes positive and **healing** often takes place. This stage of the disease is often asymptomatic but may leave calcified nodules on chest X-rays representing the healed primary focus. Active **progression** of first infection may occur. Bronchial spread of infection may cause progressive consolidation and cavitlation of the lung parenchyma, and pleural effusions may develop. Lymphatic spread of infection may cause progressive lymph node enlargement, which in children may compress bronchi with obstruction, distal consolidation and the development of collapse and bronchiectasis. Bronchiectasis of the middle lobe is a very typical outcome of hilar node involvement by tuberculosis in childhood. Haematogenous spread of infection results in early generalisation of disease which may cause miliary tuberculosis, and the lethal complication of tuberculous meningitis (particularly in young children). Infection spread during

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**Figure 7.1** Notifications of tuberculosis and deaths in England and Wales, 1950–1995. Notifications of tuberculosis have declined from about 50,000 in 1950 to 5000 in 1987, since when notifications have increased to about 6500 per year. The recent increase is related to factors such as immigration, international travel and co-infection with HIV. (Reproduced with permission from *The Prevention and Control of Tuberculosis in the United Kingdom*, Department of Health, 1996.)
this initial illness may lie dormant in any organ of the body (e.g. bone, kidneys) for many years only to reactivate many years later.

**Post-primary tuberculosis**

Post-primary tuberculosis is the pattern of disease seen after the development of specific immunity. It may occur following direct progression of the initial infection or result from endogenous reactivation of infection or from exogenous re-infection (inhalation of *Mycobacterium tuberculosis* from another infected individual) in a patient who has had previous contact with the organism and has developed a degree of specific immunity. Reactivation particularly occurs in old age and in circumstances where immunocompetence is impaired (e.g. illness, alcohol misuse, immunosuppressive drug treatment). The lungs are the most usual site of post-primary disease and the apices of the lungs are the most common pulmonary site.
Diagnosis

Clinical features

Definitive diagnosis requires identification of Mycobacterium tuberculosis because the clinical features of the disease are non-specific. The most typical chest symptoms are persistent cough, sputum production and haemoptysis. Systemic symptoms include fever, night sweats, anorexia and weight loss. A range of chest X-ray abnormalities occur (Figs 7.3 and 7.4). Cavitating apical lesions are characteristic of tuberculosis but such lesions may also be caused by lung cancer. Irregular mottled shadowing (particularly of the lung apices), streaky fibrosis, calcified granuloma, miliary mottling, pleural effusions and hilar gland enlargement may all be features of tuberculosis.

Diagnosis depends on the doctor having a high level of awareness of the many presentations of tuberculosis and undertaking appropriate investigations (e.g. sputum acid- and alcohol-fast bacilli (AAFB) staining and culture for tuberculosis) in patients with persistent chest symptoms or abnormal X-rays. A high index of suspicion is required in assessing patients who have recently immigrated from a high-prevalence area (e.g. Africa, Indian subcontinent), and in patients at risk for reactivation of infection because of factors which lower their resistance (age, alcohol misuse, debilitating disease, use of immunosuppressive drugs).

Although tuberculosis most commonly affects the lungs, any organ in the body may be involved and the diagnosis needs to be considered in patients with a pyrexia of unknown origin and in patients

Figure 7.3 This 24-year-old man presented with malaise, fever and weight loss without any respiratory symptoms. Six months previously he had immigrated to the UK from Pakistan. X-ray shows multiple 1–2 mm nodules throughout both lungs characteristic of miliary tuberculosis. Sputum and bronchoalveolar lavage did not show acid- and alcohol-fast bacilli (AAFB). Transbronchial biopsies, however, showed caseating granulomas characteristic of tuberculosis. His symptoms resolved and the chest X-ray appearances returned to normal after 6 months of anti-tuberculosis chemotherapy.
with a variety of indolent chronic lesions (e.g. in bone, kidney or lymph nodes). The term miliary tuberculosis refers to a situation where there has been widespread haematogenous dissemination of tuberculosis, usually with multiple ‘millet-seed’ size nodules evident on chest X-ray. Chest symptoms are often minimal and typically the patient is ill and pyrexial with anaemia and weight loss.

**Laboratory diagnosis**

Identification of *Mycobacterium tuberculosis* by laboratory tests may take some time and anti-tuberculosis treatment may have to be commenced based on clinical and radiological features while awaiting the results of laboratory tests. Once the diagnosis is suspected, repeated sputum samples should be examined by the Ziehl–Neelsen (ZN) method looking for AAFB which appear as red rods on a blue background. Sputum cultures require special media (e.g. Löwenstein–Jensen medium) and the tubercle bacillus grows slowly taking 4–7 weeks to give a positive culture and a further 3 weeks for the in vitro testing of antibiotic sensitivity. Biopsy of an affected site (e.g. pleura, lymph node, liver, bone marrow) may show the characteristic features of caseating granuloma (central cheesy necrosis of a lesion formed by macrophages, lymphocytes and epithelial cells). Biopsy specimens should also be submitted for mycobacterial cultures. Newer techniques are being developed to improve the speed, sensitivity and specificity of the laboratory diagnosis of tuberculosis. The Bactec radiometric system, for example, uses a liquid medium containing a radioactively labelled ¹⁴C-labelled substance which releases ¹⁴CO₂ when metabolised.

**Figure 7.4** This 68-year-old man was persuaded to consult a doctor because of a 6-month history of cough, haemoptysis, night sweats and weight loss. He suffered from alcoholism and lived in a hostel for homeless men. His chest X-ray shows cavitating consolidation throughout the right upper lobe with further areas of consolidation in the left upper and right lower lobes. Sputum acid- and alcohol-fast bacilli (AAFB) stains were positive and cultures yielded *Mycobacterium tuberculosis* sensitive to standard drugs. He was treated with directly observed anti-tuberculosis therapy. Six of 38 residents of the hostel were found to have active tuberculosis. DNA fingerprinting techniques showed that this cluster of six cases was caused by three different strains of *Mycobacterium tuberculosis* arising as a result of both reactivation of latent tuberculosis in debilitated elderly men and spread of infection within the hostel.
and detection of this reflects the growth of *Mycobacterium tuberculosis*. DNA techniques using the **polymerase chain reaction** are being developed and may, for example, prove useful in detecting evidence of infection in cerebrospinal fluid in tuberculous meningitis. DNA **fingerprint techniques** make it possible to distinguish different strains of *Mycobacterium tuberculosis*. This can give useful insights into the likely sources and spread of infection and help assess the relative contribution of newly acquired and reactivated infection in different populations.

**Treatment (Table 7.1)**

Before effective antibiotics became available in the late 1940s, about 50% of patients with sputum-positive tuberculosis died of the disease. Patients were admitted to sanatoria for bed rest, ‘sunshine and fresh air’ therapy and nutritional support in an attempt to enhance their own resistance to the disease. When large tuberculous cavities developed in the lungs attempts were made to collapse the cavities by inducing an artificial pneumothorax, crushing the phrenic nerve, instilling various materials outside the pleura to compress the lung (plombage) or performing thoracoplasty, whereby the ribs were excised and the lung compressed against the mediastinum (Fig. 7.5).

In the late 1940s **streptomycin** and **para-amino salicylic acid** (PAS) were introduced into clinical practice and the outlook for patients with tuberculosis was revolutionised. It soon became apparent that treatment had to be **prolonged** and **combinations** of antibiotics had to be used because of the capacity of the tubercle bacillus to lie dormant in lesions for long periods and to develop resistance to antibiotics.

The current standard treatment of tuberculosis consists of **6 months** of rifampicin and isoniazid,
supplemented by pyrazinamide and ethambutol for the first 2 months. All drugs are usually given in a single daily dose. Rifampicin and isoniazid are bactericidal drugs which kill extracellular bacilli which are actively metabolising. Both rifampicin and pyrazinamide are effective against intracellular bacilli, within macrophages. Prolonged treatment is needed to eradicate bacilli lying dormant. The use of the combination of drugs also prevents the emergence of resistance from the small number of bacilli which are naturally resistant to any one of the antibiotics. Ethambutol is bacteriostatic and is included in the treatment regimen to prevent the emergence of resistance to other drugs. It may be omitted in patients with a low risk of resistance to isoniazid (i.e. white patients who have not had previous anti-tuberculosis treatment and who do not have HIV infection). Patients from ethnic minority groups have a significantly higher risk of resistance to isoniazid and other drugs, and should be commenced on the four-drug combination. Meticulous supervision of treatment is essential and patients should be seen at least monthly for prescription of medication, checking of compliance with treatment and monitoring for side-effects (e.g. liver function tests). Errors in the prescription of medication or failure of the patient to comply with treatment may have serious consequences with the emergence of resistant organisms. Directly observed therapy should be instituted for patients who have difficulty complying with treatment, whereby the patient is observed to ensure that he or she swallows the medication. Sometimes this can be achieved by giving high doses of the anti-tuberculosis medication three times per week with the patient attending a hospital or general practice clinic to be given the medication under the supervision of a doctor or nurse. Flexible strategies are required to ensure compliance of patients with social (e.g. homelessness) or psychological (e.g. alcohol misuse, mental illness) problems and there is an important role for community health workers or trained laypersons in these circumstances.

At present, drug-resistant tuberculosis is rare in the initial treatment of patients from the white ethnic group in the UK, but is more common in patients who have had previous treatment or who come from Africa or the Indian subcontinent. Overall about 7.8% of isolates of Mycobacterium tuberculosis are resistant to isoniazid, 1.7% are resistant to rifampicin and 1.2% have multiple drug resistance. Multidrug-resistant tuberculosis results from inadequate previous treatment. The development of resistant organisms in a patient failing to comply with treatment may make the tuberculosis very difficult to treat, and such a patient poses a risk to public health because he or she may infect others with drug-resistant tuberculosis. Some outbreaks of multidrug-resistant tuberculosis have occurred in prisons and hospitals with high mortality rates.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adult</th>
<th>Duration</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10 mg/kg</td>
<td>300 mg</td>
<td>6 months</td>
<td>Hepatitis, neuropathy</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg</td>
<td>&lt;50 kg</td>
<td>6 months</td>
<td>Hepatitis, rashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>450 mg</td>
<td></td>
<td>Enzyme induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>35 mg/kg</td>
<td>&gt;50 kg</td>
<td>Initial</td>
<td>Hepatitis, rashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg</td>
<td>15 mg/kg</td>
<td>2 months</td>
<td>Elevated uric acid</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- 6 months of rifampicin and isoniazid, with pyrazinamide and ethambutol for first 2 months
- Monitor treatment meticulously (e.g. monthly review)
- Check compliance
- Use directly observed therapy if problems with compliance
- Notify the diagnosis to Public Health Authorities
- Contact tracing of close family contacts.
The most dangerous of the adverse reactions to anti-tuberculosis treatment is hepatotoxicity, and patients should be advised to stop treatment and report for medical advice if they develop fever, vomiting, malaise or jaundice. Isoniazid, rifampicin and pyrazinamide may all cause hepatitis and allergic reactions such as rashes. Isoniazid may cause a peripheral neuropathy and this is preventable by pyridoxine 10 mg/day, which is given routinely to those at risk of neuropathy (e.g. patients with diabetes or alcohol misuse). Intermittent rifampicin may cause ‘flu-like’ symptoms, and the induction of microsomal hepatic enzymes reduces the serum half-life of drugs such as warfarin, steroids, phenytoin and oestrogen contraceptives so that patients may need adjustment in dosage of medications and may need to use alternative contraceptive measures. Rifampicin produces a reddish discoloration of urine (which may be used to monitor compliance) and may cause staining of soft contact lenses. Pyrazinamide sometimes causes initial facial flushing, and may cause an elevation of uric acid levels with arthralgia. Ethambutol causes a dose-related optic neuropathy, which is rare at doses below 15 mg/kg/day. Patients should have their visual acuity checked before starting treatment and should be warned to stop the drug if visual symptoms occur, and the drug should be avoided if possible in patients with impaired renal function or pre-existing visual problems.

Latent tuberculosis

The term ‘latent tuberculosis’ refers to the situation where a person has been infected with Mycobacterium tuberculosis at some time but does not currently have active disease. The immune response has controlled the primary infection but all viable organisms might not have been eliminated. It is estimated that there is a 5–10% risk of a person with latent tuberculosis developing active disease at some stage over the course of their life. The greatest risk of progression to disease is within 2 years of the initial infection and this is particularly relevant when undertaking contact tracing procedures of people who may have acquired infection recently from a patient with active tuberculosis. Factors which increase the risk of reactivation of latent infection include ageing, alcohol misuse, poor nutrition, co-infection with HIV and use of immunosuppressive drugs. Recently, for example, tumour necrosis factor alpha antagonists are being used in the treatment of Crohn’s disease and rheumatoid arthritis, and these immunosuppressive treatments are associated with a significant risk of reactivation of latent tuberculous infection such that latent infection should be sought and treated before starting such treatments. People with latent tuberculosis are asymptomatic and usually have a normal chest X-ray. Detection of latent infection depends on demonstrating an immune response to Mycobacterium tuberculosis using a tuberculin test or an interferon-gamma-based blood test.

Tuberculin testing (Fig. 7.6)

Hypersensitivity to the tubercle bacillus can be detected by the intradermal injection of a purified protein derivative (PPD) of the organism. The response is of the type IV cell-mediated variety and results in a raised area of induration and redening of the skin. In the Mantoux test 0.1 mL of tuberculin solution is injected intradermally (not subcutaneously) and the test is read at 48–72 hours. A positive result is indicated by redness and induration at least 10 mm in diameter. If active tuberculosis is suspected the lowest dilution may be used initially to prevent a severe reaction, and higher concentrations used if there is no reaction. The Heaf test is performed with a spring-loaded needled ‘gun’. A drop of undiluted PPD (100 000 TU/mL) is placed on the volar surface of the forearm and the ‘gun’ is used to puncture through the PPD solution. The reaction is graded from I to IV according to the formation of papules and the extent of induration. A positive tuberculin test indicates the presence of hypersensitivity to tuberculin resulting from either previous infection with tubercle bacillus or from bacillus Calmette–Guérin (BCG) vaccination. A weak reaction may be non-specific and indicate contact with other non-tuberculous environmental mycobacteria. A strongly positive test in a child who has
not received BCG vaccination is likely to indicate primary infection. If there is evidence of active disease, full anti-tuberculosis treatment is required; if there is no evidence of active disease chemoprophylaxis is advisable. A source amongst adult contacts of the child must be carefully sought. A negative tuberculin test makes active tuberculosis unlikely and indicates a lack of immunity so that BCG vaccination is recommended.

**Interferon-gamma blood tests**

Tuberculin skin tests lack specificity in diagnosing *Mycobacterium tuberculosis* infection since a positive reaction may be due to previous BCG vaccination or to exposure to non-tuberculous mycobacteria. In recent years laboratory assays have been developed which measure the release of interferon gamma from a patient’s T-cells when exposed to specific antigens from *Mycobacterium tuberculosis*.

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**Figure 7.6 Tuberculin testing.** In order to standardise procedures the Mantoux test is nowadays preferred to the previous Heaf test.
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There are currently two such assays available in the UK: the Quantiferon Gold assay (Cellestis Limited, Australia) and the T-spot TB assay (Oxford Immunotec, Oxford, UK). These tests require only a single blood test but it needs to be analysed in the laboratory within a few hours. These interferon-gamma blood tests are likely to be most useful in more specific diagnosis of latent *Mycobacterium tuberculosis* infection.

Control

Treating active disease

Prompt identification and treatment of patients with active tuberculosis limits the spread of infection. Sputum-positive patients (AAFB positive) should be considered as potentially infectious until they have completed 2 weeks of treatment. The patient’s family will already have been exposed to the risk of infection so that segregation of the patient from contact with his or her family at the time of diagnosis is not useful, and most patients can be treated as outpatients. Where patients with suspected or confirmed tuberculosis are admitted to hospital they should be kept in a single room. Particular care is required if the patient has multidrug-resistant tuberculosis and these patients should be treated in a negative pressure ventilation room to prevent transmission of infection to other patients or health-care workers.

Contact tracing

When a diagnosis of tuberculosis is made there is a statutory requirement in the UK for the doctor to notify the patient to the public health authorities who are then responsible for undertaking screening of contacts. The index patient may have acquired infection from, or transmitted infection to, someone in his or her close environment. It is usual to limit contact tracing to household contacts and to close friends sharing a similar level of contact with the index patient. If initial investigations reveal a large number of contacts with tuberculosis, consideration should be given to widening the circle of contacts who are offered screening. Typically about 1–3% of close contacts of smear-positive cases are found to have active disease, and many more have latent infection.

Screening of contacts consists of a combination of checking for symptoms of tuberculosis, chest X-ray, tuberculin testing, interferon-gamma tests and assessment of BCG status. Most cases of active tuberculosis are found at the first clinic visit in unvaccinated close contacts of smear-positive disease. If the contact has not had BCG vaccination a tuberculin test is performed and if this is negative vaccination is recommended. For children a tuberculin test is the usual initial screening test. Children with a strongly positive tuberculin test should have a chest X-ray. A strongly positive tuberculin test with a normal chest X-ray suggests that the child has been infected with tuberculosis bacillus has not developed active disease but remains at risk of doing so in the future. The risk of future activation of such latent infection is reduced by chemoprophylaxis which consists of treatment for 6 months with isoniazid alone, or for 3 months with isoniazid and rifampicin. In latent tuberculosis there are many thousand times fewer bacteria than in active tuberculosis and treatment with a single drug for 6 months or two drugs for 3 months is sufficient to kill dormant bacteria. Those with a negative tuberculin test should have it repeated 6 weeks later (to ensure they are not in the process of developing immunity to recently acquired infection), and if they remain tuberculin-negative BCG vaccination is advisable.

Screening of immigrants

Immigrants from areas with a high prevalence of tuberculosis (e.g. Africa, Indian subcontinent) should be screened for tuberculosis on arrival in a country of low prevalence such as the UK. Adults should have a chest X-ray and children should have a tuberculin test. Thereafter the procedure is as for close contacts, with treatment of active disease, chemoprophylaxis of latent infection or BCG vaccination as appropriate.


BCG vaccination

BCG is a live attenuated strain of tuberculosis which provides about 75% protection against tuberculosis for about 15 years. It is given by intradermal injection (not subcutaneous injection) and produces a local skin reaction. In the UK BCG vaccination used to be offered to children at the age of 13 years. This policy has now been changed from routine to targeted vaccination whereby BCG vaccination is offered to infants in communities with a high incidence of tuberculosis (>40 per 100,000) and to unvaccinated individuals who come from, or whose parents come from, countries with a high prevalence of tuberculosis.

Non-tuberculous mycobacteria (atypical opportunistic mycobacteria)

There are a number of other mycobacteria that can cause pulmonary disease and that do not belong to the Mycobacterium tuberculosis complex. These are called ‘atypical’ or ‘opportunist’ mycobacteria and the most common of these are Mycobacterium kansasii, Mycobacterium avium-intracellulare complex, Mycobacterium malmoense and Mycobacterium xenopi. They are widespread in nature and can be found in water and soil so that sometimes contamination of clinical specimens occurs from environmental sources. They act as low-grade pathogens which do not usually pose a risk to normal individuals. Infections occur mainly in patients with impaired immunity (e.g. AIDS, see Chapter 8) or in those with damaged lungs (e.g. advanced emphysema or lung cavities from previous Mycobacterium tuberculosis infection). They are often associated with chronic symptoms such as cough, sputum production, haemoptysis and weight loss. Diagnosis is made on the basis of their characteristics on laboratory culture tests. Treatment is often difficult requiring prolonged (e.g. 2 years) treatment with rifampicin and ethambutol because these organisms often show resistance to some standard anti-tuberculosis antibiotics. Some more recently developed antibiotics (e.g. clarithromycin or ciprofloxacin) may be useful in treatment. These organisms are low-grade pathogens and do not pose a threat to contacts of infected patients so that there is no need for contact tracing procedures.

Keypoints

- Worldwide, 2 billion people have latent infection with Mycobacterium tuberculosis and 15–20 million people have active tuberculosis.
- In the UK the incidence of tuberculosis is highest in the African, Pakistani and Indian ethnic groups, in homeless people and in people with reduced immunity because of ageing, alcohol misuse, poor nutrition, immunosuppressive drug treatments and co-infection with HIV.
- Diagnosis depends on having a high level of awareness of the presentations of tuberculosis and undertaking appropriate investigations (e.g. sputum AAFB staining) to identify Mycobacterium tuberculosis.
- Treatment consists of 6 months of rifampicin and isoniazid with pyrazinamide and ethambutol for the first 2 months.
- Control of tuberculosis involves detection and meticulous treatment of cases of active tuberculosis, notification of the diagnosis to the public health authorities, contact tracing to detect active or latent infection in contacts of the index case, and targeted vaccination of groups with a high incidence of tuberculosis.

Further reading


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