Tuberculosis (TB) is an infectious disease transmitted by *Mycobacterium tuberculosis* and it was declared a global public health emergency in 1993 by the World Health Organization. In terms of deaths due to infectious disease, it ranks second only to HIV. Since 1990, the global incidence of TB has fallen, and has been associated with a 41% reduction in the TB mortality rate. However, the incidence of multi-drug-resistant TB (MDRTB — resistance to at least isoniazid and rifampicin) is increasing, which threatens global TB control because treatment then requires the use of combinations of less efficacious and potentially more toxic drugs.

**Epidemiology**

Despite improvements in TB surveillance, TB continues to be a major global health problem; in 2011, there were an estimated 8.7 million new cases and 1.4 million deaths worldwide.

In the UK, TB is a notifiable disease and cases are reported to Public Health England (formerly the Health Protection Agency), Health Protection Scotland or Public Health Wales. In 2011, the HPA said that there were 8,963 cases reported in the UK, where the incidence has risen steadily between 2000 and 2011 (6,724 to 8,963 cases). Three-quarters of UK TB cases are patients born outside the UK, and most of these are from South Asia and sub-Saharan Africa.

In 2011 in the UK, 8.4% of cases had resistance to at least one first-line antibiotic, most commonly to isoniazid, whereas MDRTB was found in 1.6% of cases.

Microbiology

TB is caused by the "*Mycobacterium tuberculosis* complex" (*M. tuberculosis, M. bovis* or *M. africanum*). It is usually spread by inhalation of airborne droplets expelled by infectious people while coughing or sneezing. When the mycobacteria are inhaled into the lungs, the body’s immune system is stimulated; *M. tuberculosis* antigens bind to Toll-like receptors on macrophages and activated T helper cells release interferon-gamma, and the mycobacteria are ingested by macrophages. Cytokines such as interferon-gamma and tumour necrosis factor (TNF)-alpha recruit other inflammatory cells, forming a

**SUMMARY**

Tuberculosis (TB) is a global health problem, with an estimated 8.7 million cases and 1.4 million deaths per year. Clinical manifestations of active TB disease are varied since *Mycobacterium tuberculosis* can infect any organ in the body, but common non-specific symptoms include malaise, weight loss, fever and night sweats.

Diagnosis of TB is based on the context of clinical signs and symptoms and investigations such as radiographic and microbiological results. Risk factors for TB include close contact with an infectious person, living in a country with a high incidence of TB, being immunocompromised due to medicines or disease and previous under-treatment of TB.
granuloma containing macrophages, T lymphocytes, B cells, dendritic cells, endothelial cells, fibroblasts and, probably, stromal cells.**

It is thought that in approximately 80% of people infected by TB, the immune system will successfully kill the bacteria, whereas in others the bacteria may persist within the granuloma (where they are not killed, but lie dormant). This is known as latent TB infection (LTBI) and such people are not infectious and do not have any active TB disease. It is estimated that a third of the world’s population has LTBI. Without treatment for LTBI, about 5–10% of people will progress to active TB in their lifetime.***

If the immune system fails to kill the bacteria, it fails to build the defensive barrier or the barrier fails some time later, then the *M tuberculosis* can start to divide and spread. This may be within the lungs (respiratory TB), or elsewhere if the bacteria have spread to other parts of the body (non-respiratory TB). Around half of all active TB cases develop within the first few years of the original infection.****

It has been postulated that vitamin D deficiency may have a role in the development of active TB and it has been shown that vitamin D levels are low in people who may have a role in the development of active TB and it has been shown that vitamin D levels are low in people with active TB*** and LTBI.**** However, although supplementation can correct vitamin D deficiency, improvements in TB treatment outcomes have yet to be demonstrated.***

**Clinical features**

TB most commonly manifests as respiratory disease, but a significant number of cases present at extra-pulmonary sites. Consequently, people with TB can have a wide range of symptoms, which can delay diagnosis.

**Respiratory TB** Respiratory TB affects the lungs, pleural cavity, mediastinal lymph nodes or larynx, and is the most common site of TB disease in the UK — affecting 51.6% of cases in 2011.** Respiratory symptoms such as cough (initially dry but later possibly purulent with haemoptysis) and pleuritic chest pain may be present, and in advanced cases breathlessness can occur as a result of lung damage. Systemic symptoms such as malaise, weight loss, fever and night sweats are also common.****

**Lymph node TB** Lymph node TB is the most commonly reported site of non-respiratory disease in the UK, reported in 31% of all cases in 2011.** Cervical lymph nodes are most commonly affected; these become enlarged, but not always painful, and are usually asymmetrical in the neck. They usually start out firm, but often break down to form an abscess as necrosis occurs, which may discharge through the skin. Lymph nodes frequently enlarge at the start of anti-TB treatment because of a paradoxical immune reconstitution reaction.*****

**Bone and joint TB** Bone and joint TB accounts for approximately 10% of non-respiratory TB cases in the UK. Spinal TB may present with back pain, kyphosis or paraspinal abscesses, and can progress to vertebral collapse with resulting disability.******

**Disseminated TB** Disseminated (or miliary) TB occurs when tubercle bacilli spread through the bloodstream and may be associated with malaise, fever, anorexia and weight loss.****

**Central nervous system TB** Central nervous system TB accounted for only 2% of all TB cases reported in the UK in 2011, but is associated with chronic morbidity and high mortality. Early symptoms may be non-specific and include anorexia, malaise, headache, vomiting and altered behaviour. Typical symptoms of meningeal inflammation, such as fever and headache, may develop over days or weeks, then focal neurological signs, cognitive impairment or decreasing level of consciousness can occur.******

**Pericardial TB** TB pericarditis often has a gradual onset characterised by fatigue and dyspnoea. Systemic symptoms of pericardial TB include fever, malaise, sweats, cough and weight loss. A pericardial effusion is usually present initially, and this can progress to a constrictive pericarditis. Peripheral oedema, paradoxical pulse, raised venous pressure and hypotension can occur.******

**Diagnostic tests**

Exposure to and infection with *M tuberculosis* can be demonstrated by a positive tuberculin skin test or from a positive interferon-gamma release assay. However, these tests will not differentiate LTBI from active TB, nor distinguish those who have previously been treated for TB. Diagnosis of active TB is described in Box 1.

**Tuberculin skin test** For a tuberculin skin (Mantoux) test, tuberculin purified protein derivative (PPD) 2 units

Box 1: Diagnosis of active tuberculosis

A positive diagnosis of active tuberculosis (TB) can be made on the basis of clinical signs and symptoms, context and investigations. The following specific investigations can be used to confirm the diagnosis:

**Respiratory TB**

Chest X-ray plus at least three (with one early morning sample) sputum samples, sent for TB microscopy and culture. Sputum smear microscopy is a cheap and simple method of finding acid-fast bacilli (AFB) in the sputum. This quickly identifies mycobacteria, but will not discriminate between *Mycobacterium tuberculosis* and other mycobacterial infections. In the UK, all microbiological samples from people suspected to have a diagnosis of TB are cultured to allow positive identification of *M tuberculosis*; all positive cultures undergo sensitivity testing for resistance to first-line anti-TB drugs. Molecular amplification tests can quickly identify TB DNA and gene sequences that may code for drug resistance to rifampicin; however, these tests are faster than culture but tend to be less sensitive.

If the patient cannot produce a sputum sample, bronchoscopy and lavage or induced sputum (using hypertonic saline) can be used for adults. For children, induced sputum or gastric washings should be used.

**Non-respiratory TB**

Needle aspiration or biopsy from any site of suspected TB should be obtained where possible and sent to microbiology for culture. Examples of samples include lymph node biopsy, pus aspirated from lymph nodes, pleural biopsy and tissue from surgery.
in 0.1ml is injected intradermally and the skin examined after 48–72 hours (see Figure, adjacent). A strongly positive response is confirmed by an area of induration >15mm, indicating TB infection or disease. A positive response with an area of induration 6–15mm can indicate possible previous TB infection, bacille Calmette-Guèrin (BCG) immunisation or exposure to non-tuberculous mycobacteria, and may require further investigation.11

This test is cheap and easy to perform, but patients must return for the result to be interpreted. False positive results may occur due to exposure to environmental non-tuberculous mycobacteria, or to prior BCG vaccination. False negatives can occur in immunosuppressed patients whether due to drugs or disease and even in patients with extensive respiratory or disseminated TB, which can temporarily lower the immune system.

Interferon-gamma release assays Two blood tests are commonly used in the UK: QuantiFERON-TB Gold and T-SPOT.TB. These immunological tests are more specific for M tuberculosis because they use antigens that are present in M tuberculosis and in only a few species of environmental mycobacteria, and not in BCG.4

Risk factors

Becoming infected with M tuberculosis is dependent on the intensity and duration of exposure to a infectious source. Accordingly, the greatest risk is to those people who live in close proximity (ie, within the same household), for prolonged periods, to someone with infectious respiratory TB.3,5 Other risk factors for TB include:

- Close contact with infectious people
- Birth in, previous residence in, travel to or receiving visitors from a country considered to have a high incidence of TB (incidence rate of 40 per 100,000 or greater); specific countries that meet this definition can be found on the Public Health England website or in the latest WHO global tuberculosis report1
- Being immunocompromised due to disease (eg, HIV infection) or medication (eg, prolonged corticosteroid use, chemotherapy, TNF inhibitors)
- Specific clinical conditions associated with an increased risk — diabetes mellitus, chronic kidney disease, solid organ transplantation, jejuno-ileal bypass, silicosis, gastrectomy
- Being very young or elderly (immune systems less robust)
- Chronic poor health or nutrition, eg, due to homelessness, drug abuse, alcoholism
- People living in poor or crowded housing conditions, including those living in hostels
- Previous under-treatment of TB

Preventing spread

An essential component of the control of global TB is to prevent further cases of TB infection through actions such as vaccination and tracing contacts.1

BCG vaccination The BCG vaccine contains a live attenuated strain of M bovis. It is 70–80% effective against the most severe forms of TB (such as TB meningitis in children) but is less effective in adults. Current UK vaccination strategies are designed to target the at-risk population rather than to vaccinate the entire UK population. The immunisation “green book” should be consulted for current recommendations regarding the UK BCG immunisation programme.6

In brief, BCG immunisation should be offered to: infants living in areas of the UK with a high annual incidence of TB (40 per 100,000 or greater); infants or young children with a parent or grandparent who was born in a country with a high incidence of TB; children (where TB infection is excluded) who are contacts of people diagnosed with respiratory TB; and people under the age of 35 years at occupational risk of TB (eg, healthcare workers, veterinary staff, prison staff, staff of hostels for homeless people).

Screening

After a person has been diagnosed with active TB, it is important that contact tracing plus screening of household or close contacts is performed, particularly where the index case has infectious TB (sputum smear-positive). This will determine the extent of transmission and allow identification of other potential cases of active TB or LTBI.

Current UK guidelines recommend tuberculin skin (Mantoux) testing to diagnose latent TB infection in people who are household or non-household contacts of people with active TB. Interferon-gamma testing is advised for people who have positive tuberculin skin tests, or in patients where tuberculin skin tests may be unreliable (eg, those who have received the BCG vaccine).1
Additional contact tracing may be required where people with sputum smear-positive TB are diagnosed if they:

- Are hospital inpatients, because other patients may need to be screened if they have spent more than eight hours in the same bay.
- Are school pupils or members of staff, because students and teachers may need to be screened.
- Have recently travelled on a flight longer than eight hours, which may require contact tracing of other passengers.

Screening for TB may also be performed if:

- New entrants from countries with a high incidence of TB.
- Healthcare workers who have not had a BCG vaccination and will have contact with patients or clinical specimens, who are new entrants from a country with a high incidence of TB, or who have had contact with patients in settings with a high incidence of TB.
- Patients who require immunosuppressive medicines such as TNF inhibitors.

**Infection control**

Patients with sputum smear-positive TB are potentially infectious. Those with drug-sensitive TB can usually be treated as outpatients and do not require hospital admission unless there is a clear clinical or socioeconomic need. The risk of transmission to household contacts will be no greater during treatment than before diagnosis and treatment, and infectiousness will reduce rapidly after treatment starts.

However, if patients with sputum smear-positive TB are admitted to hospital, they should be accommodated in a single side room until either discharge from hospital or after two weeks of anti-TB drug treatment. This should be a negative-pressure isolation room if the ward is also caring for immunocompromised patients, such as those with HIV.

Staff are not required to wear masks or gowns, or use barrier nursing techniques, unless MDRTB is suspected or aerosol-generating procedures (eg, bronchoscopy, sputum induction or nebuliser treatment) are being performed. Conversely, patients should be asked to wear a surgical mask whenever they leave their rooms until they have received at least two weeks of anti-TB drug treatment.

Although there is no evidence that drug-resistant M. tuberculosis is more virulent than drug-sensitive M. tuberculosis, the consequences of transmission of MDRTB disease are greater than the spread of drug-sensitive TB, since the complexity, cost and duration of treatment are significantly greater. Therefore, patients with suspected or proven MDRTB should be isolated in a negative-pressure room and staff should wear FFP3 masks during patient contact while the patient is considered infectious.

**References**