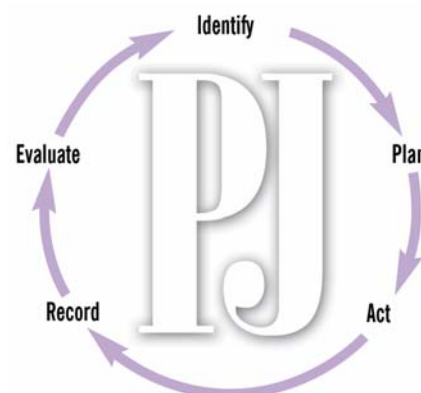


# Tuberculosis — a general introduction

In this first article in a series of four on tuberculosis, **Alistair Storey** presents the background to this resurgent infectious disease



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## ***Mycobacterium tuberculosis* can be transmitted in coughed or sneezed droplets**

Ten years ago, the World Health Organization declared tuberculosis (TB) a global health emergency. Today, TB ranks second to human immunodeficiency virus as the leading cause of death worldwide from an infectious disease.<sup>1</sup> Mycobacteria are ubiquitous. *Mycobacterium tuberculosis*, *M bovis*, *M africanum* and *M microti* can all cause TB in humans, but most cases are caused by *M tuberculosis*. Over 60 other species of mycobacteria have been identified, some of which are low-grade pathogens in man.

## **Global situation**

About two billion people (one third of the world's population) are infected with TB. The number of new cases each year (estimated at eight million) is rising, mainly as a result of the increasing burden of HIV infection.<sup>2</sup> Rates (incidence and prevalence) of TB are highest in sub-Saharan Africa but the total number of cases is highest in Asia. India, China, Indonesia, Bangladesh and Pakistan account for more than half of all cases.

All but 2 per cent of the estimated two million deaths annually caused by TB occur in developing countries, predominantly among young adults. Almost all of these deaths are preventable.

## **Transmission**

TB is transmitted almost exclusively by people with active pulmonary or laryngeal forms of the disease, who expectorate bacilli in droplet nuclei as they cough, sneeze or talk. In poorly ventilated, enclosed environ-

ments bacilli can remain airborne for several hours.

The tuberculosis bacillus is an intracellular pathogen. Transmission requires inhaled bacilli to reach the alveoli in the lung periphery and to be ingested by alveolar macrophages. Each macrophage then rapidly transports bacilli via the lymphatic system to the hilar lymph nodes and, if replication is not checked, infection can reach almost any other organ. Actively replicating bacilli destroy their host cell and are liberated into the blood and lymph to invade other macrophages.

## **Classification**

Depending on the host's immune response and the virulence of the invading bacilli, infection leads to eradication, containment resulting in latent infection (where the host is asymptomatic but continues to harbour small numbers of quiescent bacilli) or primary disease.

**Primary disease** Primary disease has been defined as progression from sub-clinical infection to active disease within five years after infection. The risk of primary disease follow-

## **Identify knowledge gaps**

1. What are the common symptoms of tuberculosis?
2. How is tuberculosis usually transmitted?
3. List three groups in the UK who are at most risk of becoming infected with tuberculosis.

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

ing infection is greatest in young children and immunocompromised adults. Most primary infections resolve rapidly because concentrations of macrophages containing replicating bacilli form epithelioid cells surrounded by layers of activated T lymphocytes and fibroblasts. These develop into a granulomatous lesion with a caseous and necrotic centre. In most cases this lesion effectively walls off the infection in fibrous scar tissue and can calcify.

**Latent disease** Infection usually evokes a strong T-helper type 1 cell-mediated immune response within three to eight weeks, when a tuberculin skin test will give a positive result. Cell-mediated immunity checks the progression from latent infection to active disease in 90 per cent of immunocompetent individuals. Of the 10 per cent who develop active TB, half will develop the disease within the first two years following infection.

The extraordinary ability of the bacillus to evade destruction and lie dormant poses an immense public health challenge. Any future defect in cell-mediated immunity could result in active disease and onward transmission, even decades after infection. HIV is now the most important risk factor for reactivation of latent TB infection. In people infected with HIV, the risk of disease following infection is 10 per cent per annum, equivalent to the life-

## **Topics in this series**

Tuberculosis in UK cities is an increasingly important threat to public health. The single most important way of controlling TB (especially sputum smear-positive cases) is early identification and treatment. Further articles in this series will look at:

- How TB is diagnosed and why culture and sensitivity tests are important
- Standard management of TB in the UK
- Prevention of TB and treatment of drug-resistant TB

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time risk seen in immunocompetent people with latent disease.

**Post primary disease** Of those who overcome primary infection, 5 per cent will eventually develop “post primary disease” either through reactivation or reinfection. Post primary TB usually affects the upper lung and is associated with a more aggressive immune response that can lead to extensive tissue destruction, liquefaction and the formation of cavities. Each cavity provides an ideal environment for the bacillus to replicate. Millions of bacilli are liberated from such cavities to seed infection to other parts of the lung, ascend the bronchial tree and gain access to the outside world.

### Clinical presentation

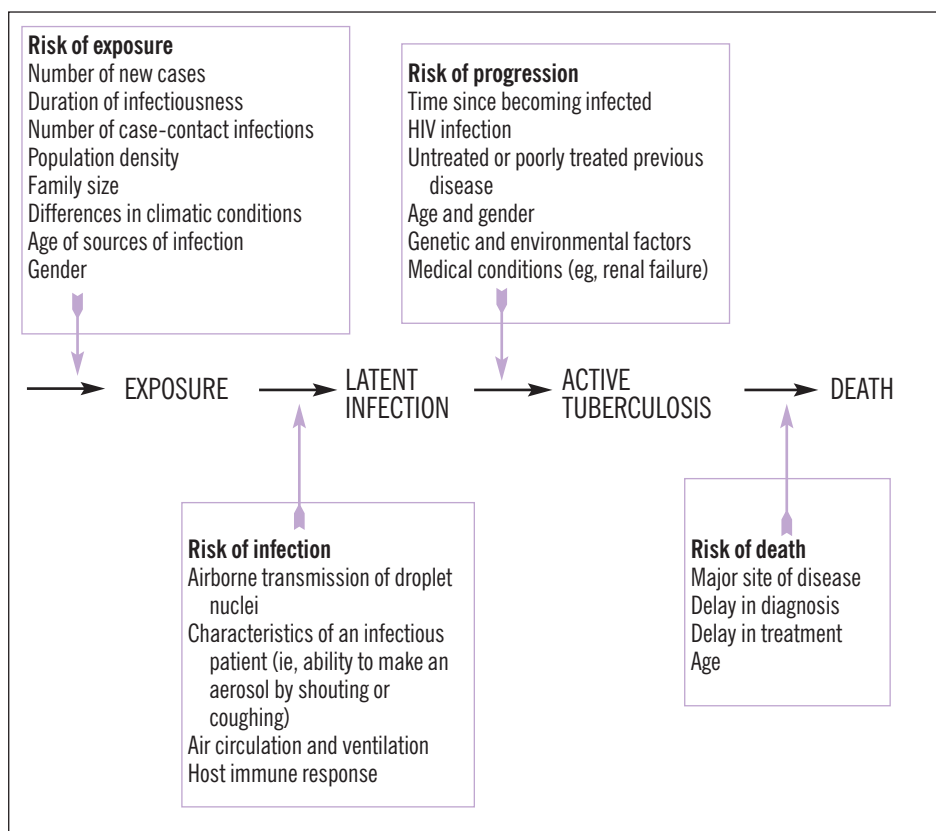
TB can affect almost any organ (most commonly the lymph nodes), bones and joints, and the central nervous, gastrointestinal and genitourinary systems. For this reason, the clinical presentation of active disease can take many forms depending on the site (or sites) affected, the severity of the infection and the immune status of the host.

Pulmonary disease is the most common clinical manifestation, accounting for around 80 per cent of cases. Only a proportion of these cases are infectious. Classically, patients with pulmonary TB present with the following symptoms:

- A cough of more than two weeks’ duration
- Weight loss
- Fever
- Night sweats
- Fatigue
- Shortness of breath
- Chest pain
- Haemoptysis (coughing up blood) in later stages

Tissue destruction can result in scarring and fibrosis and, if the infection is untreated or unchecked, erosion through blood vessels can occur leading to massive haemoptysis. Although the availability of effective chemotherapy meant that surgical intervention became a rarity, surgical excision is again being resorted to, especially in patients with multi-drug resistant forms of the disease, because the bioavailability of antituberculosis drugs within cavities is poor.

Children with TB can be asymptomatic and, more commonly, other organs are involved, particularly those of the CNS.<sup>3</sup> If not treated promptly tuberculosis meningitis carries a high mortality and a high incidence of serious neurological sequelae. Miliary TB is most common in infants and young children and occurs if the bacilli become bloodborne and disease becomes established in the lungs and other sites simultaneously. The term “miliary” is derived from the Latin word *milium* meaning millet seed and describes the characteristic multiple small lesions. Miliary disease can occur shortly after initial infection or as a result of post primary disease many years



**Figure 1: Epidemiology of tuberculosis — factors affecting risk of exposure, infection, progression to disease and death**

later. Often, the onset of miliary disease is insidious with a gradual development of weight loss, malaise, anorexia and low grade fever.

People with advanced HIV infection are also at increased risk of disseminated disease involving multiple organs and, similarly, present a significant diagnostic challenge.

### Epidemiology

Where TB is common and cases have long infectious periods, exposure to the pathogen is almost unavoidable. This results in high rates of infection and reinfection in children and a high morbidity and mortality from TB among young adults (who are the most economically productive sector of society) and those caring for and supporting young children and extended families. In this way, TB hinders development and impoverishes those parts of the world that are worst affected.

The risk of infection and progression to active disease is decreased by improvements in the social and physical environment. A reduction in overcrowding leads to reduced transmission. Better nutrition and reduced concurrent morbidities, stress and exposure to environmental pollutants all lessen the risk of progression to active disease.

As transmission rates decline, the average age of cases increases until the majority of young people are not infected and the burden of TB is predominantly associated with reactivated disease in the elderly. This epidemiological transition has been seen across most of the industrialised world.

Without treatment, sputum smear-positive TB is fatal in between 30 and 40 per cent of

cases within one year and cumulatively kills about 50 to 70 per cent within five to seven years. The remainders either spontaneously remit without treatment or remain chronically ill.<sup>4</sup> It is estimated that an infectious untreated person with TB infects about 10 people each year.<sup>5</sup> Although exposure to and infection with the bacillus are prerequisite to the development of disease the fact that not all contacts become infected and only one in 10 of infected contacts ever develops disease indicates that the causal chain of processes influencing the epidemiology of TB is not straightforward. Figure 1 shows the principal factors determining risk of exposure, infection, progression to disease and death.

In the UK, the epidemiology of TB changed markedly in the latter half of the last

### Summary

- One third of the world’s population is infected with tuberculosis
- Incidence of TB in UK cities is increasing (40 per cent of UK cases now occur in London)
- TB most commonly affects the lungs but can cause disease in almost any organ
- Disease can occur decades after initial infection
- TB is transmitted almost exclusively by people with active pulmonary or laryngeal forms of the disease
- Disease is concentrated in socially deprived subgroups within the urban population, many of whom experience poor access to health and social care

Adapted from Rieder HL. Opportunity for exposure and risk of infection: the fuel for the tuberculosis pandemic. *Infection* 1995;23:1-4.

## Tuberculosis in the UK — a brief history

Tuberculosis has been around since 8,000BC (skeletal deformities caused by TB have been identified), but the disease reached epidemic proportions in western Europe in the early 19th century when industrialisation fuelled a massive growth in the urban poor population. It is estimated that one-third of all deaths in London during the first 40 years of the 19th century were as a result of TB. Although it was most rampant among the poor, TB also infected the more privileged.

At the time, the disease (known as “the white plague”) was little understood and greatly feared. Theories of the day attributed the disease to moral turpitude, to the foul emanations of contaminated water, air, and soil or to social causes at a local level. Despite the fact that today TB is curable in almost all cases, the disease retains much of its stigma.

In 1882, Robert Koch identified the tubercle bacillus. The realisation that TB was transmissible prompted a strategy of confinement either in the patients’ homes, hospitals or purpose-built sanatoriums where a strict regimen of bed rest and fresh air was often imposed. Radical surgical interventions, which aimed to halt the disease process by removing affected areas of lung through thoracoplasty, or starving the bacillus of oxygen through artificial pneumothorax (often repeated) were tried. Phrenicotomy (division of the phrenic nerve), scalenectomy (division of the scalene muscle) and plombage (the extrapleural insertion of fat, soft paraffin wax, sponges or lucite spheres) were also attempted.

century. Rates of disease now vary greatly between different areas and between subgroups within a population. London now accounts for more than 40 per cent of cases nationally and rates are increasing.<sup>6</sup> The retreat of disease into specific risk groups within the population poses new challenges to the control of TB in the UK.

**Migrants** Migration from countries with strong historical links with the UK, an aging population and a continued shortfall in the labour market has resulted in an increasing proportion of cases occurring among people from countries where TB remains highly endemic. Around 60 per cent of all cases in the UK now occur in foreign-born persons. Half of these cases occur among migrants who have been resident in the UK for more than five years and 40 per cent of these cases have been resident for 10 years or longer. Rates of disease are highest among the most recent migrants.

In England and Wales between 1980 and 1992 TB incidence increased by 35 per cent among the poorest 10 per cent of the population, by 13 per cent among the next poorest 20 per cent, with no increase among the remaining 70 per cent of the population.<sup>7</sup> TB notification rates in London increased by 12 per cent for each 1 per cent increase in

Despite the absence of effective chemotherapy the prevalence of disease across the UK and Europe declined dramatically throughout the late 19th and early 20th centuries. This happened as a result of public health reforms that improved the nutritional status and social and physical environment of the urban poor. Such reforms stemmed from the realisation that insanitary conditions cause disease epidemics and the enlightened notion of interdependence between social and biological conditions. In addition, in 1913, provision was made to make notification of all suspected cases of TB a statutory requirement across England and Wales. This legal requirement was consolidated in the 1921 National Public Health Tuberculosis Act.

The onset of effective drug therapy and the prospect of ambulatory treatment signalled the end of the sanatoriums. With the exception of during the two world wars, TB rates continued to decline. The introduction of radiological services for screening, improved surveillance, milk pasteurisation (before the widespread practice of pasteurisation the ingestion of *M bovis* in milk from cows with tuberculous mastitis was a significant source of infection in young children), treatment of contacts and the widespread use of the Bacillus Calmette–Guérin vaccine accelerated the rate of decline and led to hope that TB might soon be eradicated. However, the late 1980s saw a resurgence of the disease. The reasons for resurgence in the UK are multifactorial but include increased social deprivation, HIV co-infection and a failure of control. Better systems to detect and notify the disease has increased the numbers reported.

the number of persons living under overcrowded conditions, irrespective of their ethnic origin.<sup>8</sup>

**Homeless people** Chest radiography screening programmes have repeatedly demonstrated high rates of TB among homeless people in London, particularly among those sleeping rough or using direct access hostels.<sup>9</sup> High risk of infection and compromised immunity due to malnutrition, poor physical health and substance misuse make the homeless population particularly vulnerable to TB. These people are also at high risk of poor outcomes to treatment because their lifestyles are often at odds with the routine of daily medication and regular hospital follow up.

**HIV** The extent to which HIV has impacted on the epidemiology of TB in the UK remains unclear. It has been estimated that between 1993 and 1998, 11 per cent of the rise in London’s TB cases could be attributed to HIV.<sup>10</sup> Recent estimates suggest that the proportion of new TB cases with HIV co-infection is increasing.

**Prison populations** WHO identifies prison populations as high-risk for the occurrence and transmission of TB because people entering the prison system are likely to come from

high-risk backgrounds and prison environments facilitate the spread of the disease. The prison population in England and Wales is increasing and, compared with the general population, includes a higher proportion of persons with a history of homelessness and drug and alcohol problems. The first documented occurrence of TB transmission in a UK prison was recently reported.<sup>11</sup>

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### Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Find out how prevalent tuberculosis is in your community.
2. Think about how you could provide health promotion on tuberculosis awareness.
3. Look out for the tuberculosis action plan to be published by the Department of Health.

### Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)  
What will you do now and how will this be achieved?