



**November 2007**

## **Tuberculosis**

### **Introduction**

The causative bacterial organisms for tuberculosis (TB) are included in the genus *Mycobacterium*. *Mycobacterium tuberculosis* is the most frequent cause of TB worldwide and affects only humans. *Mycobacterium bovis*, primarily a cattle organism, also can cause disease in humans.

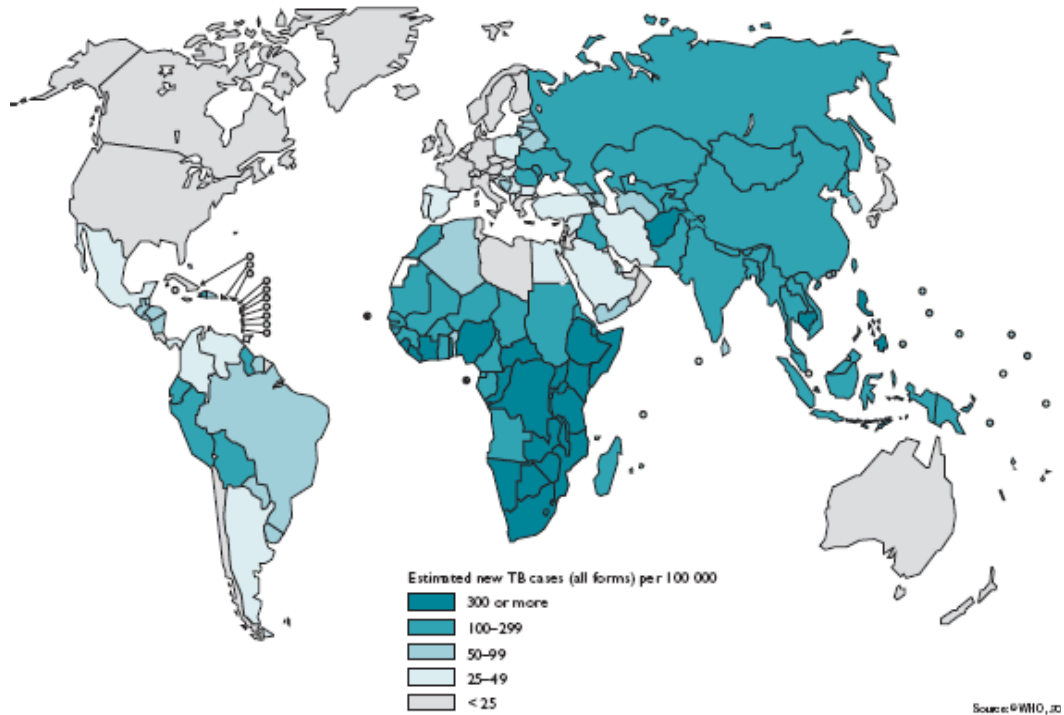
TB is a disease of worldwide importance, and in 1993 the World Health Organization (WHO) declared TB a 'Global Emergency' [1]. TB has afflicted the humans since the beginning of recorded history and today is the second leading cause of death from communicable disease [2]. TB and HIV/AIDS co-infection leads to substantial morbidity and mortality.

### **Epidemiology**

#### Global Epidemiology

TB is responsible for the death of nearly two million people worldwide each year [3]. sub-Saharan Africa has the highest incidence per capita (350 cases per 100,000), but the most number of cases occurs in the South and South East Asia regions [3]. Here there are an estimated 3 million new cases and 600,000 deaths annually, with the majority of cases in Bangladesh, India, Indonesia, Myanmar and Thailand [4]. A global rise in TB incidence is attributed to increasing global population and the vulnerability of those with HIV to TB infection, especially in Africa [3]. TB can enhance the progression of HIV, and vice versa, and is the leading cause of death amongst HIV positive individuals in low income regions of the world [3].

### Tuberculosis, 2004



### Risk for Travellers

The majority (>70%) of cases of TB reported in the UK occur in those born abroad, with most cases occurring in people born in sub-Saharan Africa and Asia. It is likely that many of these cases acquired infection in their country of origin. However, the complex natural history of TB means that the exact time and place of infection often cannot be determined, making it extremely difficult to estimate the incidence of TB as a travel related disease. The risk for travellers to highly endemic countries (TB incidence of  $\geq 40$  cases/100,000 population) is likely to be increased, particularly when the traveller undertakes activities such as health care work or where there is prolonged close contact with the local population such as travel for visiting friends and relations [5,6].

There has been concern about transmission of communicable diseases including TB during air flights. The Centers for Disease Control and Prevention (CDC) studied six separate incidents of airplane travel by a person subsequently found to be suffering from TB [7]. Evidence of transmission was found in two of these investigations [7,8,9]. In the first case, transmission took place between an infected flight attendant and other cabin crew, where the cumulative flight time exposure was greater than 12 hours [8]. In a second case TB was transmitted during a long flight to passengers seated in close proximity to the index case [9]. The WHO have also evaluated the risk of TB during air travel [10]. The CDC and WHO have concluded that the risk of TB transmission on an aircraft does not appear to be greater than in other confined spaces [7,10].



## Transmission

Almost all TB infections are transmitted through inhalation of infected respiratory droplets passed on when a person with open pulmonary tuberculosis is coughing. Prolonged exposure to the infective organism is usually required and brief contact carries little risk.

Uncommonly TB can be contracted through consumption of milk or food contaminated with *M. bovis*.

Laboratory personnel and pathologists are at risk of inoculation of bacilli through cuts and scratches.

## Signs and Symptoms

In most cases, primary TB infection is either asymptomatic or a febrile respiratory illness of short duration. The infection is usually contained by the host's immune system and becomes dormant, termed latent tuberculosis infection (LTBI). Therefore, the vast majority (90%) of immunocompetent people infected will never develop disease. Development of disease is most likely to occur in the first few years after infection; those most at risk are young children and persons with an underlying medical condition (e.g. poorly controlled diabetes, renal failure, transplantation, malignant disease or HIV infection and AIDS), or with other predisposing risk factors such as malnutrition.

LTBI can reactivate many years after the initial exposure. Reactivation often occurs in settings of advanced age or immune compromise such as corticosteroid therapy, cancer treatment or HIV infection.

TB disease can affect any part of the body. Primary TB infection most commonly occurs in the mid and lower lung, with regional spread to the hilar lymph nodes. Reactivation pulmonary disease often occurs with cavitation in the upper lung zones. Disease may also be extrapulmonary. The most common sites are the lymph nodes, pleura, genitourinary system, bones and joints, and central nervous system (CNS); disseminated or military disease also occurs. CNS involvement includes inflammation of the meninges (TB meningitis) or space occupying lesions of the brain (tuberculoma).

Patients with pulmonary TB may have a productive cough with purulent sputum, breathlessness and chest wall pain. Additional symptoms are often non-specific: weight loss, malaise and night sweats. However, some patients even those with extensive disease may have no symptoms at all. Diagnosis is made by radiological examination and sputum smear microscopy. Those with pulmonary TB are infectious for as long as the bacteria remain in the sputum.

Extra pulmonary disease can present in a variety of ways depending upon the site (e.g. CNS symptoms include cranial nerve palsies, motor and sensory defects, seizures and coma), though weight loss and malaise are often key features. Diagnosis may require tissue sampling. Those with extrapulmonary TB are generally not infectious to others.



## Treatment

The standard initial treatment of TB is the use of first-line anti-TB medications: isoniazid, rifampicin, pyrazinamide and ethambutol [11]. TB that is resistant to isoniazid and rifampicin is defined as multi-drug resistant TB (MDR-TB) and second-line drugs are required. In the late 1980s and early 1990s low income countries as well as the United States and Europe had outbreaks of MDR-TB [12]. More recently, extensively drug resistant strains of TB (XDR-TB) have emerged globally, and present a serious public health threat [12,13]. Most cases of XDR-TB have occurred in eastern Europe, western Asia and South Africa. Vulnerable groups include the immunocompromised, particularly those living with HIV [14] and those living in poverty. In response to the emergence of XDR-TB, the WHO has published recommendations for its prevention and control [15].

In 1991 the World Health Organization (WHO) implemented the Directly Observed Treatment Short Course (DOTS) strategy for treatment and control of TB globally [16]. This strategy aims to maximise completion of treatment and reduce the incidence of drug resistant strains. The strategy's recommendations include government commitment to TB control, prompt case detection by sputum smear microscopy, and a standardised treatment regime with directly observed treatment for at least the first two months. Although there have been successes with the DOTS strategy, in areas with high HIV prevalence the approach has been less effective and additional strategies are needed to achieve a reduction in tuberculosis morbidity and mortality [17].

Drug treatment needs to be continued for several months; usually six months for pulmonary TB and often longer for bone or meningeal TB. Lack of compliance with medications is a major contributing factor to development of drug resistant strains of TB, a problem that the DOTS strategy aims to reduce.

## Prevention

Primary prevention against tuberculosis is by vaccination with BCG (Bacillus Calmette-Guérin) vaccine. In the United Kingdom, vaccination against TB (BCG vaccine) forms part of the UK national immunisation programme and is targeted to high risk individuals that includes some travellers [18].

In addition to vaccination, those caring for TB infected individuals should be advised to adhere to local protocols, that may include isolation and barrier nursing procedures. The use of FFP3 masks is recommended for healthcare workers where risk of infection is high (i.e. during cough-inducing procedures such as intubation or suction on individuals with active, untreated TB) and when they are caring for patients MDR-TB for as long as the patient remains infectious [11,18,19].

## Vaccine Information

### Tuberculin skin testing prior to BCG vaccination – Mantoux test

In the UK, tuberculin skin testing (TST or Mantoux) is used either prior to BCG, in order to determine whether there has been previous infection with *Mycobacterium tuberculosis*



(BCG should not be given if TST indicates previous exposure), or as an aid to diagnosis [18,20].

TST testing prior to BCG is necessary for:

- Those aged 6 years and over
- Children aged under 6 years who have lived in a country with an annual TB incidence of 40/100,000 or greater for longer than 3 months
- Close contacts with a known TB case
- Those with a family history of TB infection in the last 5 years

### **Bacillus Calmette-Guérin (BCG)**

#### **Indications for use of vaccine**

BCG vaccine offers protection in children against the most severe forms of the disease, including meningeal and miliary TB [21].

Vaccination requires intra-dermal injection and should be carried out by healthcare professionals skilled in this technique.

In the UK, vaccination against TB forms part of the UK national immunisation programme and is targeted to high risk individuals [18]. BCG vaccination is recommended for:

- All infants (aged 0-12 months) living in areas of the UK where the annual incidence of TB is 40 cases/100,000 population or greater
- All infants (aged 0-12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater
- Previously unvaccinated children aged one to five years with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater
- Previously unvaccinated, tuberculin-negative children aged from six to under sixteen years of age with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater
- Previously unvaccinated tuberculin-negative contacts of cases of respiratory TB (following recommended contact management advice) [11,18]
- Previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least 3 months) in a country with an annual TB incidence of 40/100,000 or greater

In addition, TB vaccination is recommended for the following two groups of travellers:

- Previously unvaccinated tuberculin-negative travellers under 16 years of age, going to live or work with local populations for three or more months in a country where the annual incidence is 40/100,000 or greater



- Individuals at occupational risk including healthcare workers aged less than 35 years of age, irrespective of duration of stay.

There is a little evidence of vaccine efficacy in adults (i.e. those aged 16 years and older) and vaccination is only recommended for such individuals in special circumstances [18,22]. Repeated BCG vaccination is not recommended as there is no evidence that re-vaccination confers additional protection [18].

### Pre and post travel screening for tuberculosis

For travellers for whom BCG vaccination is not an option, pre and post travel tuberculin skin testing may be considered, either as a screening test for latent or recent infection or as an aid to diagnosis of active disease [11,22].

The measurement of interferon gamma (IFN-gamma), as means to identify active or LTBI, may be used as an alternative to TST in some countries [23,24]. In the UK, the acceptability and efficacy of IFN-gamma testing is still under evaluation [11,25].

### Availability of vaccine

BCG vaccine contains a live attenuated strain of the tuberculin bacillus (Danish strain 1331). BCG Vaccine manufactured by the Statens Serum Institute (SSI) is the only vaccine available in the UK.

### BCG Vaccine

Vaccine	Manufacturer	Schedule	Age range
BCG Vaccine "SSI"	Statens Serum Institut	Single dose following negative tuberculin testing*	Infants below 12 months: 0.05ml  Children aged 12 months and over and adults: 0.1ml

### Tuberculin PPD SSI

Tuberculin	Manufacturer	Schedule	Age range
Tuberculin PPD 2TU per 0.1ml solution for injection	Statens Serum Institut	Single test for tuberculin skin testing  Repeat testing should be avoided within one year	Not specified in SmPC  Refer to Green Book for guidance regarding indication for testing



\* Full details of tuberculin testing and interpretation can be found in the Department of Health publications [18,20].

The specific Summary of Product Characteristics (SmPC) for should be consulted prior to the administration of any vaccine [26,27].

### **Vaccine schedules**

BCG vaccine is administered as a single intradermal dose. Although immunity may wane over time, reinforcing doses are not recommended due to uncertainty about their efficacy and the risk of adverse reactions [18].

### **Contraindications**

BCG vaccination should not be given to:

- Those who have evidence of a previous BCG vaccination
- Those with a past history of TB
- Those with an induration of 6mm or more following TST or Mantoux (SSI)
- Those with confirmed anaphylaxis to a component of the vaccine
- Pyrexia or generalised infected skin conditions
- Neonates in a household where an active TB case is suspected or confirmed
- Immune suppression including systemic corticosteroid therapy, radiotherapy, malignant conditions, known or suspected HIV infection

### **Precautions**

- Postpone in those who are acutely unwell
- Pregnancy. Although the risk of vaccination is theoretical, it is advisable to delay vaccination until after delivery [18].

### **Adverse events**

The expected reaction to a successfully administered BCG vaccine is induration at the vaccine site followed by development of a lesion that may ulcerate before it heals, leaving a small, round, flat scar.

No other vaccines should be administered in the arm used for BCG vaccination for 3 months due to the risk of regional lymphadenitis.

BCG vaccine should be administered strictly intradermally at the insertion of the deltoid muscle, or lateral thigh. Inadvertent subcutaneous administration or administration higher on the arm has been associated with an increased risk of local reaction and keloid formation.



Undesirable adverse events include:

- Uncommon: headache, fever, enlargement of regional lymph node, ulceration with discharge at the site of vaccination
- Rare (<1/1,000): Disseminated BCG complications including osteomyelitis or osteitis, allergic reactions including anaphylaxis, lymphadenitis, abscess formation

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## Reading list

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## Links

Health Protection Agency [www.hpa.org.uk/infections/topics\\_az/tb/menu.htm](http://www.hpa.org.uk/infections/topics_az/tb/menu.htm)

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