4.20 TUBERCULOSIS

4.20.1 Bacteriology

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex (M.TB complex), which are slow-growing, aerobic, acid-fast bacilli. The M.TB complex consists of *Mycobacterium tuberculosis*, *M. bovis*, *M. microti*, *M. canetti* and *M. africanum*, of which *M. tuberculosis* is the cause of almost all TB in Australia.2

4.20.2 Clinical features

As infection is usually air-borne, lung disease is the most common form of tuberculosis, accounting for approximately 60% of notified TB cases in Australia.3 Cough, fever, sweats, weight loss and haemoptysis are common symptoms of pulmonary TB. TB lymphadenitis is the most common extrapulmonary manifestation, but the disease can occur in any part of the body. Disseminated disease (miliary TB) and meningeal TB are more common in very young children, and are among the most serious manifestations of TB disease.1

Most persons infected with *M. tuberculosis* remain asymptomatic, but there is a 10% lifetime risk of developing clinical illness (although the risk can vary depending on age and immune status), sometimes many years after the original infection. Infants, the elderly and persons who are immunocompromised, due to drugs or disease or as a result of adverse socioeconomic circumstances (e.g. malnutrition, alcoholism), are more prone to rapidly progressive or generalised infection.1,4

4.20.3 Epidemiology

The World Health Organization (WHO) declared tuberculosis a global emergency in 1993, and recent reports have reaffirmed the threat to human health.5 It is estimated that in 2010 there were 8.8 million incident cases of TB globally. The majority of these cases (81%) were accounted for by 22 high-burden countries, which all have estimated TB incidences of greater than 40 per 100 000.6 Approximately 1200 cases of TB are notified to Australian health authorities each year. The annual notification rate for TB has been relatively stable at approximately 5 to 6 cases per 100 000 population since 1985.2,3 In the southern states, rates among Indigenous Australians overall are comparable with rates among Australian-born non-Indigenous Australians; however, in some specific settings (e.g. in the Northern Territory, Far North Queensland and northern South Australia) rates are higher in Indigenous Australians3 (refer to 3.1 Vaccination for Aboriginal and Torres Strait Islander people). Most TB cases in Australia (over 85%) occur in persons born overseas, particularly those born in Asia, southern and eastern European countries, Pacific island nations, and north and sub-Saharan Africa. The rate of TB in the overseas-born population has been slowly increasing over the past decade.3 The rate of multi-drug resistant (MDR) TB in Australia has been low (less than 2% of notified cases); however, the proportion of MDR-TB cases identified has increased in recent years.2,3,7-9 Tuberculosis in animals (*M. bovis*) has been eradicated by screening and culling programs.10

Patients who are immunocompromised are at high risk of developing active TB if they are infected with *M. tuberculosis*.5,11 Screening programs in Australia concentrate on contacts of notified cases and others at increased risk of TB infection, including refugees and healthcare workers.

4.20.4 Vaccine

The BCG vaccine currently registered for use in Australia is marketed by Sanofi-Aventis Australia Pty Ltd (refer below for more information). In circumstances where this product is in short supply, other BCG vaccine products may be made available in Australia. Advice on their use will be provided by state and territory health authorities. (Refer also to 4.20.12 Public health management of tuberculosis.)

- **BCG vaccine** – Sanofi-Aventis Australia Pty Ltd (live vaccine prepared from an attenuated strain of *Mycobacterium bovis*). 1.5 mg lyophilised powder in a multi-dose vial with separate diluent. Reconstituted vaccine contains 8–32 x 10^6 colony forming units per mL and monosodium glutamate 1.5% w/v. May contain trace amounts of polysorbate 80. Reconstituted volume provides about 10 adult or 20 infant doses.

BCG (bacille Calmette-Guérin) vaccine is a suspension of a live attenuated strain of *M. bovis*. Worldwide, there are many BCG vaccines available, but they are all derived from the strain propagated by the Institute Pasteur, which was first tested in humans in 1921.12 BCG vaccination probably has little effect on preventing infection per se, or reactivation among those already infected with TB, so the role of BCG vaccination in preventing overall transmission is probably limited.13 However, there is strong evidence that BCG vaccination in infancy provides greater than 70% protection against severe disseminated forms of TB disease in young children, including miliary TB and TB meningitis.14,15 TB can be difficult to diagnose in young children and progression to disseminated TB can be rapid; they are therefore the primary target for the use of BCG vaccine. The efficacy of BCG vaccine against pulmonary disease in adults is less consistent and has ranged from no protection to 80% in controlled trials.19 The greatest protection has been
observed among skin test-negative adults in North America and Europe, and the lowest among skin test-positive persons in tropical settings. The reason for the wide variation in measured effectiveness is not clear, but has been attributed to variability in study quality, differences in BCG strains, host factors such as age at vaccination and nutritional status, and differences in the prevalence of infection with environmental mycobacteria. The duration of protection following BCG vaccination has been difficult to measure because the interval between infection and disease may extend to decades. Benefit from infant vaccination has been found in studies with follow-up of up to 12 years, but protection is commonly thought to decline over 10 to 20 years. There is evidence that memory responses persist for up to 10 to 50 years.

BCG vaccination has been shown to offer some protection against Mycobacterium leprae, the causative agent of leprosy.

BCG vaccine is not used in the treatment of tuberculosis disease. BCG may be used as a therapeutic modality for transitional cell carcinoma of the bladder.

4.20.5 Transport, storage and handling

Transport according to National vaccine storage guidelines: Strive for 5. Store at +2°C to +8°C. Do not freeze. Protect from light. BCG vaccine must be reconstituted by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine is very unstable and must be stored at +2°C to +8°C and used within one working session of 4 to 6 hours.

4.20.6 Dosage and administration

The dose of BCG vaccine in newborns and infants <12 months of age is 0.05 mL, given by intradermal injection. The dose of BCG vaccine in children ≥12 months of age and in adults is 0.1 mL, given by intradermal injection. BCG vaccine is given as a single dose. Due to the lack of evidence, BCG revaccination is not recommended in any person.

BCG vaccine is available from state/territory tuberculosis services.

Before vaccination

Tuberculin skin test (Mantoux)

All individuals, except infants <6 months of age, should undergo a tuberculin skin test (TST; Mantoux) before BCG vaccination. A hypersensitivity reaction to tuberculin purified protein derivative (PPD; Tubersol) used in the TST assists in the identification of those infected with M.TB. A hypersensitivity reaction may also occur in those infected with other mycobacteria and those previously vaccinated with BCG. Only immunocompetent persons who have induration <5 mm following correctly administered and interpreted TST should receive BCG vaccination. Guidelines to assist in the undertaking and interpretation of TST are available by contacting local state/territory tuberculosis services. It should be noted that live viral vaccines inhibit the response to tuberculin and tuberculin-positive persons may become tuberculin-negative for up to a month after measles infection. As such, tuberculin skin testing may be unreliable for at least 4 weeks after the administration of live viral vaccines.

Interferon-gamma (γ) release assays

Newly available blood tests (Interferon-gamma release assays; IGRAs) are available for the detection of tuberculosis infection. TST, however, remains the preferred method of screening for tuberculosis infection, pending further evaluation of IGRAs. Guidelines for the use of IGRAs in Australia have been developed by the National Tuberculosis Advisory Committee.

BCG vaccination procedures

BCG vaccination should only be given by medical or nursing staff who are trained in BCG vaccination procedures.

- Use a short (10 mm) 26–27 gauge needle with a short bevel. The risk of spillage can be minimised by using an insulin syringe to which the needle is already attached.
- Wear protective eye-wear. The person to be vaccinated (and the parent/carer holding a small child being vaccinated) should also wear protective eye-wear. Eye splashes may ulcerate; if an eye splash occurs, wash the eye with saline or water immediately.
- Identify the correct injection site. BCG vaccine should be injected into the skin over the region of insertion of the deltoid muscle into the humerus. This is just above the midpoint of the upper arm. This site is recommended to minimise the risk of keloid formation. By convention, the left upper arm is used wherever possible to assist those who subsequently look for evidence of BCG vaccination.
• Stretch the skin between a finger and thumb and insert the bevel into the dermis, bevel uppermost, to a distance of about 2 mm. The bevel should be visible through the transparent epidermis.

• If the injection is not intradermal, withdraw the needle and try again at a new site. A truly intradermal injection should raise a blanched bleb of about 7 mm in diameter with the features of peau d’orange (the appearance of orange peel). Considerable resistance will be felt as the injection is given. If this resistance is not felt, the needle may be in the subcutaneous tissues.

Response to BCG vaccination

In response to BCG vaccination, a small red papule forms and eventually ulcerates, usually within 2 to 3 weeks of vaccination. The ulcer heals with minimal scarring over several weeks. There may be swelling and tenderness in local lymph nodes. While a local reaction represents a normal response to BCG vaccination, more extensive local reactions are less common (refer to 4.20.11 Adverse events below). Subjects who are given BCG vaccine despite latent or previous TB infection are likely to experience an accelerated response characterised by induration within 24 to 48 hours, pustule formation in 5 to 7 days, and healing within 10 to 15 days.

Clinical trials have not shown a consistent relationship between the size of tuberculin reactions after BCG vaccination and the level of protection provided. TST is not recommended to demonstrate immunity after BCG vaccination.\(^{28,29}\)

Co-administration with other vaccines

BCG can be administered at the same time as, or at any time following receipt of, other inactivated vaccines (e.g. tetanus-containing vaccines), if required.

If administration of both BCG and another live parenteral vaccine (e.g. MMR or yellow fever) is indicated, the vaccines should be given either on the same day or at least 4 weeks apart.

There are no restrictions on the timing of BCG vaccine in relation to oral live vaccines, including rotavirus and oral poliomyelitis vaccine (OPV) (e.g. in infants who have received OPV overseas).

4.20.7 Recommendations

BCG is not recommended for routine use in the general population, given the low incidence of TB in Australia and the variable efficacy reported in adults. However, some groups are at increased of tuberculosis and BCG vaccination may be warranted for these persons, based on a risk assessment. BCG should be specifically considered for the following groups.

Aboriginal and Torres Strait Islander neonates

In some parts of Australia, the incidence of TB is appreciably higher among Aboriginal and Torres Strait Islander people than Australian-born non-Indigenous Australians, and BCG is recommended for neonates living in those regions.\(^{30}\) State and territory guidelines should be consulted for local recommendations and the geographic areas where BCG vaccination of Aboriginal and Torres Strait Islander neonates is conducted (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control). (Refer also to 3.1 Vaccination for Aboriginal and Torres Strait Islander people.)

Infants born in Australia to migrant parents

TB is rare in infants and young children born in Australia, but infants born to parents who have migrated from countries with a high TB incidence (i.e. >40 cases per 100 000 population per year – refer to 4.20.3 Epidemiology above) may be at higher risk of TB exposure in their early life.\(^{31}\) BCG vaccination of these infants is not routinely recommended because of the uncertainty of the risks and benefits.

Children who will be travelling to high TB incidence settings

The risk of TB disease in children travelling to countries with a high TB incidence (i.e. >40 cases per 100 000 population per year – refer to 4.20.3 Epidemiology above) depends on the age of the child, the duration of stay, and the TB incidence at the destination. Country-specific incidence data are available from the World Health Organization.\(^{32}\)

The need for BCG vaccination should be assessed for young children, particularly those aged <5 years, who will be travelling to a country with high TB incidence for an extended period. This is best discussed with local state/territory TB services or with a paediatric infectious diseases specialist. BCG vaccination should ideally occur at least 3 months before departure and therefore consideration should be given to future travel plans at birth.

Neonates born to parents with leprosy or a family history of leprosy

There is strong evidence that BCG provides some protection against Mycobacterium leprae.\(^{23}\)

Occupational groups

There is some evidence that specific occupational groups are at increased risk of TB, including embalmers, and healthcare workers likely to encounter patients with TB (e.g. chest clinic staff) or those involved in conducting
autopsies. Due to the limited evidence of benefit of BCG vaccination in adults and interference of vaccination with interpretation of TST, routine BCG vaccination of persons within these occupations is not recommended. In occupational settings, TB prevention and control should be focused around infection control measures, employment-based TST screening and therapy for latent TB infection. However, BCG vaccination should be considered for TST-negative healthcare workers who are at high risk of exposure to drug-resistant TB, due to the difficulty in treating drug-resistant infection.

4.20.8 Pregnancy and breastfeeding

BCG vaccine is contraindicated in pregnant women.

BCG vaccine can be given to breastfeeding women. Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

4.20.9 Contraindications

BCG is a live vaccine and its use is contraindicated in the following groups:

- Persons with known or suspected HIV infection, even if asymptomatic or with normal immune function, because of the risk of disseminated BCG infection.
- Persons treated with corticosteroids or other immunosuppressive therapy, including monoclonal antibodies against tumour necrosis factor-alpha (TNF-alpha) (e.g. infliximab, etanercept, adalimumab) (refer to 3.3 Groups with special vaccination requirements).
- Infants born to mothers treated with bDMARDS (e.g. TNF-alpha blocking monoclonal antibodies) in the third trimester of pregnancy frequently have detectable antibodies for several months and they should not be vaccinated with BCG. (Refer also to ‘Use of immunosuppressive therapy during pregnancy’ in 3.3.2 Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants.)
- Persons with congenital cellular immunodeficiencies, including specific deficiencies of the interferon-gamma pathway.
- Persons with malignancies involving bone marrow or lymphoid systems (refer also to 3.3 Groups with special vaccination requirements).
- Persons with any serious underlying illness, including severe malnutrition.
- Pregnant women (BCG vaccine has not been shown to cause fetal damage, but use of live vaccines in pregnancy is not recommended).
- Persons who have previously had TB or a large (≥5 mm) reaction to a tuberculin skin test.

4.20.10 Precautions

For those who would otherwise be candidates for BCG, vaccination should be deferred in the following groups:

- Neonates who are medically unstable, until the neonate is in good medical condition and ready for discharge from hospital.
- Infants born to mothers who are suspected or known to be HIV-positive, until HIV infection of the infant can be confidently excluded.
- Persons with active skin disease such as eczema, dermatitis or psoriasis at or near the site of vaccination.
- Persons being treated for latent TB infection, as the therapy is likely to inactivate the BCG vaccine.
- Persons with significant febrile illness, until 1 month after recovery.

Vaccination before or after immunoglobulin or blood product administration

BCG vaccine can be given at any time before or after administration of immunoglobulin or any antibody-containing blood product as there is minimal interaction between these preparations and BCG vaccine. (Refer also to 3.3.4 Vaccination of recent recipients of normal human immunoglobulin and other blood products.)

4.20.11 Adverse events

The normal reaction to BCG vaccination has been described above (refer to 4.20.6 Dosage and administration). About 5% of vaccinated persons experience adverse events. Injection site abscesses occur in 2.5% of vaccinated persons and lymphadenitis in 1%, while up to 1% require medical attention. Gross suppurative or generalised complications of BCG vaccination have been treated with anti-tuberculosis drugs; however, there is no consensus on the management of
these complications and specialist advice should be sought from local state/territory tuberculosis services. Anaphylactic reactions have also been reported. Keloid formation can occur, but the risk is minimised if the injection is not given higher than the level of insertion of the deltoid muscle into the humerus. The overall risk of fatal disseminated infection is extremely low (approximately 1 case per million vaccinated persons).\(^\text{13}\)

### 4.20.12 Public health management of tuberculosis

Tuberculosis is a notifiable disease in all states and territories in Australia. Further instructions about the public health management of tuberculosis, including management of cases of tuberculosis and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

In special circumstances, such as during shortages of the currently registered vaccine, state and territory public health authorities can also provide advice on the use of alternative vaccine products.

### 4.20.13 Variations from product information

Although the product information for BCG vaccine specifies that vaccine must be used within 8 hours of reconstitution, the National Tuberculosis Advisory Committee (NTAC) guidelines recommend that any unused vaccine is discarded after a working period of 4 to 6 hours.

The product information for BCG vaccine states that the vaccine is contraindicated in individuals with generalised skin disease such as eczema, furunculosis, atopic dermatitis or other exudative or inflammatory dermatologic conditions. The ATAGI recommends instead that, BCG vaccination should be deferred in persons with active skin disease at or near the site of vaccination.

### References

A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


