

3.22 TUBERCULOSIS

Bacteriology

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex (M.TB complex), that are slow-growing, aerobic, acid-fast bacilli. The M.TB complex consists of *Mycobacterium tuberculosis*, *M. bovis*, *M. microti*, *M. canetti* and *M. africanum*.¹ *M. tuberculosis* is the cause of almost all TB in Australia, whereas *M. bovis*, *M.canetti* and *M. africanum* are rare.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, including the meninges, bone and kidneys. Disseminated disease (miliary TB) and meningeal TB are the most serious forms, particularly in children.¹

Most individuals infected with *M. tuberculosis* remain asymptomatic, but there is a 10% lifetime risk of developing clinical illness, sometimes many years after the original infection. Infants, the elderly and patients with impaired immunity due to drugs or disease or as a result of adverse socioenvironmental circumstances (eg. malnutrition, alcoholism) are more prone to rapidly progressive or generalised infection.^{1,4}

Epidemiology

The World Health Organization (WHO) declared tuberculosis a global emergency in 1993, and recent reports have reaffirmed the threat to human health.⁵ About 1000 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, and multi-drug resistance remains rare, occurring in less than 2% of notified cases.² Tuberculosis in animals (*M. bovis*) has been eradicated by screening and culling programs. In Australia, most TB cases (greater than 80%) occur in people born overseas, particularly in Asia, southern and eastern European countries, the Pacific Islands, and north and sub-Saharan Africa. The rates of TB in the overseas-born population have been slowly increasing over the past decade.³ High TB rates seen in people from Ethiopia, Somalia and the Sudan reflect recent changes in the composition of Australia's migrant and refugee intake.^{3,6} Rates of TB are also high in Aboriginal and Torres Strait Islander people and in Papua New Guineans living in some parts of Australia.^{3,7}

Patients with impaired immunity are at high risk of developing active TB if they are infected with *M. tuberculosis*.^{4,5} Screening programs in Australia now concentrate on those at high risk, including contacts of notified patients.

Vaccine

- **BCG vaccine** – Sanofi Pasteur Pty Ltd (freeze-dried live vaccine prepared from an attenuated strain of *Mycobacterium bovis*). When reconstituted with accompanying buffered saline diluent, vaccine contains between 8–32 x 10⁶ colony forming units per mL and monosodium glutamate 1.5% w/v. Reconstituted vaccine provides about 10 adult or 20 infant doses.

BCG (Bacille Calmette-Guérin) vaccine is a suspension of live attenuated *M. bovis*. Worldwide, there are many BCG vaccines available but they are all derived from the strain propagated by the Institut Pasteur and first tested in humans in 1921.⁸ Protective efficacy ranges from 0 to 80% in controlled trials. The variation has been attributed to differences in vaccine strains, local prevalence of (protective) environmental mycobacteria, and host factors such as age at vaccination and nutritional status. Geographic latitude and vaccine strains explain most of the variation in efficacy. However, it should be noted that BCG is highly effective in children, particularly those <5 years of age, for whom it is primarily intended. The efficacy of BCG in adolescents and adults is less.

BCG is primarily intended for children as meta-analyses have found the protective efficacy for preventing serious forms of TB in this group is over 80%.⁹ Protective efficacy in all age groups is about 50%.^{10,11} An Australian study reported a protective efficacy of 30%, at best, in school-aged children.¹² Protective efficacy is difficult to quantify and may vary from 10 years to 50 years.^{13,14} The WHO does not recommend repeat vaccination.

In some studies, BCG has been shown to offer some protection against leprosy.¹⁵

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.¹⁶ Store reconstituted vaccine at +2°C to +8°C or *unreconstituted* (freeze-dried) vaccine in a freezer at -20°C. Protect vaccine from light (sunlight or fluorescent). Store diluent at +2°C to +8°C and do not freeze. Reconstituted BCG vaccine is very unstable and should be discarded after one working session of 8 hours. Do not freeze reconstituted BCG vaccine.

Dosage and administration

BCG vaccine is administered as a single dose by intradermal injection. It should be given only by specially trained medical or nursing staff who are fully conversant with the following procedures:

Tuberculin test all individuals, except infants <6 months of age, before vaccination. Read the test 48 to 72 hours later and, where 5 tuberculin units has been given, give BCG only to those who have <5 mm of induration.

- Give 0.1 mL of BCG to children and adults, and 0.05 mL to infants <12 months of age.
- 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 patient and parent holding the patient (if patient is a small child requiring restraint) should also wear protective eye-wear. Eye splashes may ulcerate, so if an eye splash occurs, wash the eye with saline or water immediately.
- Inject BCG into the skin over the region of the insertion of the deltoid muscle into the humerus. This is just above the mid-point 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. Considerable resistance will be felt as the injection is given. If this resistance is not felt, the needle may be in the subcutaneous tissues.
- Advise the subject of adverse events which may follow the injection.

A tuberculin reaction induced by BCG usually ranges from 0 to 15 mm, but clinical trials have not shown a consistent relationship between the size of tuberculin reactions and the protection provided. For this reason, tuberculin skin testing of BCG vaccinees is not routinely recommended. Because of waning hypersensitivity, most adults who were vaccinated with BCG in early childhood will have a negative tuberculin test.

BCG is available from State/Territory tuberculosis services.

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. Subjects who are given BCG despite previous tuberculosis infection will 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.

Recommendations

(i) Given the low incidence of TB in Australia and the variable efficacy in adults, BCG is not used in the general population.

(ii) BCG is recommended for the following:¹⁷

- Aboriginal and Torres Strait Island neonates living in regions of high TB incidence,
- neonates born to parents with leprosy or a family history of leprosy,
- children <5 years of age who will be travelling to live in countries of high TB prevalence for longer than 3 months (WHO defines 'high-risk' countries as those with an annual incidence of TB in excess of 100 per 100 000 population – see <http://www.who.int/tb/en/>),
- embalmers,
- healthcare workers involved in conducting autopsies.

(iii) State and Territory guidelines should be consulted for advice on vaccination of the following groups of individuals:¹⁷

- healthcare workers who may be at high risk of exposure to drug-resistant cases,
- neonates weighing <2.5 kg,
- children ≥5 years and <16 years of age who will be travelling or living for extended periods in countries with a high prevalence of tuberculosis.

Contraindications

The use of BCG vaccine is contraindicated in the following:

- individuals with impaired immunity due to HIV infection, corticosteroids or other immunosuppressive agents, congenital immunodeficiencies and malignancies involving bone marrow or lymphoid systems (because of the risk of disseminated BCG infection) (see also Chapter 2.3, *Groups with special vaccination requirements*),
- individuals with a high risk of HIV infection where HIV antibody status is unknown,
- individuals with any serious illness including the malnourished,
- individuals with generalised septic skin diseases and skin conditions such as eczema, dermatitis and psoriasis,
- pregnant women (BCG has never been shown to cause fetal damage, but use of live vaccines in pregnancy is not recommended),
- individuals who have previously had TB or a large (≥5 mm) tuberculin (Mantoux) reaction,
- individuals with significant febrile illness (administer 1 month from the time of recovery).

Precautions

BCG should be deferred in the following:

- neonates with a birth weight <2.5 kg or those who may be relatively malnourished,
- neonates of mothers who are HIV-positive,
- children who are currently on isoniazid preventive therapy for latent TB infection (as the therapy can inactivate the BCG),
- a 4-week interval should be allowed after administration of another live vaccine (MMR, varicella [and MMRV when available], yellow fever vaccine) unless given concurrently with the BCG.

Adverse events

About 5% (common) of vaccinees experience adverse events. 2.5% develop injection site abscesses and 1% lymphadenitis. About 1% (uncommon) may need medical attention including surgery as a result of the adverse event.¹⁸ Anaphylactoid reactions have also been reported. Gross local or generalised infection can be treated with antituberculous drugs. Keloid formation can occur, but the risk is minimised if the injection is not given higher than the level of the insertion of the deltoid muscle into the humerus.

Use in pregnancy

Use of BCG in pregnancy is not recommended. BCG has never been shown to cause fetal damage, but use of live vaccines in pregnancy is contraindicated.

The tuberculin skin test (TST)

(i) Hypersensitivity to tuberculin Purified Protein Derivative (PPD) follows either natural infection with either *M. tuberculosis* or with other mycobacteria that induce cross-reactivity, or BCG vaccination. The skin test is used (a) to detect past infection for epidemiological purposes, (b) to detect latent TB infection (LTBI), especially in contacts of TB patients, (c) as an aid in diagnosing disease due to TB, and (d) as a pre-vaccination screen before BCG to prevent vaccine reactions.

(ii) Most tuberculin testing in Australia is performed using the Mantoux technique. The PPD preparation for this test is currently supplied by Sanofi Pasteur Pty Ltd. The product, Tubersol, comes in multidose vials and has 5 Tuberculin units (TU)/0.1 mL (10 doses per 1 mL vial). For routine testing, 0.1 mL of PPD (ie. a dose of 5 TU) is injected intradermally into the skin of the upper third of the flexor surface of the left forearm, producing a peau d'orange bleb 4 to 10 mm in diameter. The reaction is examined 48 to 72 hours later, and the diameter of the palpably indurated skin is measured across the long axis of the forearm and recorded in millimetres. In certain circumstances, 2-step skin testing may be required. It is used to detect individuals previously infected who may

test negative to tuberculin testing initially, but who show a strong reaction to tuberculin if the same procedure is repeated 1 to 2 weeks later. The 2-step test is important to establish the baseline reaction when future tuberculin testing is required as part of contact tracing or monitoring of high-risk groups. Detailed information can be accessed in the Tubersol product information and relevant State/Territory guidelines.

(iii) Erythema *without* induration should be disregarded. Strongly positive reactions may be accompanied by skin necrosis, lymphangitis and regional adenitis. Patients with a history of such strongly positive reactions to previous testing should not be retested.

(iv) The reaction to PPD may be suppressed by recent surgery, sarcoidosis, immunosuppressant drugs and illnesses, such as Hodgkin's disease, lymphoma and HIV infection that result in impaired immunity. The reaction also wanes with increasing age, so that most adults vaccinated with BCG in childhood have negative tuberculin reactions.

(v) The reaction to PPD may be unreliable for 4 weeks after administration of other live vaccines including MMR, varicella and yellow fever vaccines unless given concurrently. The tuberculin skin test should be deferred for patients with major viral infections or live-virus vaccination in the past month. Oral typhoid and oral polio (OPV is no longer used in Australia but may have been received overseas) vaccines do not necessitate a delay in testing.

(vi) The use of the Heaf gun, a multiple puncture apparatus primed with highly concentrated PPD, is not recommended.

(vii) Although BCG is not routinely recommended, it may be offered by some States and Territories to their healthcare staff who should be made aware that subsequent tuberculin skin testing may be difficult to interpret.

(viii) New interferon-gamma release assays (blood tests) using specific antigens for *M. tuberculosis* are now available in some laboratories. Interferon-gamma based assays are increasingly being used to diagnose latent TB and, particularly, to distinguish latent TB from post-BCG vaccine skin reactivity. There are relatively few data on the sensitivity and specificity of these tests in children, particularly those <2 years of age, or in people with impaired immunity.¹⁹

Variations from product information

The product information states that BCG should not be frozen. NHMRC advises that BCG can be stored unconstituted (freeze-dried) in a freezer at -20°C.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.