

BCG vaccination: An update on current Australian practices



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Background

The Bacille Calmette–Guérin (BCG) vaccine is primarily used to prevent tuberculosis (TB) infection and disease in settings with high TB incidence.

Objective

The aim of this review article is to describe the current uses of BCG vaccination in Australia, including the indications and contraindications, efficacy and other off-target effects, and the role of the general practitioner.

Discussion

BCG vaccination in Australia is primarily used to prevent TB in neonates and children with a high risk of TB exposure. The BCG vaccine is most effective at preventing severe disseminated TB disease in young children and has variable efficacy in preventing adult disease. The BCG vaccine is usually well tolerated; however, given the small risk of adverse effects, vaccination should be undertaken by a practitioner experienced in its administration. When indicated, the BCG vaccine is available from specialist TB or travel medicine centres.

WHILE BACILLE CALMETTE–GUÉRIN (BCG) is among the oldest and most widely used vaccines globally, it is not routinely used in Australia because of the low prevalence of tuberculosis (TB). As a result, many practitioners have limited experience with the use and administration of this vaccine. In recent years, there has been increasing interest in BCG vaccination for both established and novel indications, including protection against COVID-19. The aim of this article is to review BCG vaccination in the Australian context, including consideration of potential therapeutic uses beyond prevention of mycobacterial infections. Some key definitions are outlined in Table 1.

What is the BCG vaccine?

The BCG vaccine was developed in the early 1900s to protect against *Mycobacterium tuberculosis*.^{1,2} It is a live-attenuated strain of *M. bovis*,³ and multiple strains exist, manufactured in different countries.⁴ When used as a vaccine to protect against TB, it is given intradermally.¹

Globally, BCG is one of the most widely administered vaccines. It is a major part of TB control programs in areas with high TB incidence.⁵ It has a significant role in preventing TB disease, especially

disseminated TB and TB meningitis in young children.⁶

Prior vaccination with BCG can sometimes result in a positive tuberculin skin test (TST; also known as Mantoux test). This cross-reactivity does not occur with interferon gamma release assays (IGRAs). Testing for latent TB infection (LTBI) throughout Australia commonly uses either TSTs or IGRAs, depending on patient characteristics, clinician preference and local availability. TB IGRAs are widely available in Australia; however, the Medicare Benefits Schedule only provides a rebate in certain circumstances (ie immunosuppression, human immunodeficiency virus [HIV] infection, exposure to a confirmed case of active TB, renal dialysis or silicosis).

Indications

The BCG vaccine was part of the Australian vaccination schedule until 1985 and was given to young adolescents through school-based programs.^{7,8} As the incidence of TB decreased below five per 100,000 population, and the risk of TB decreased, the vaccine was removed from the schedule in line with the International Union Against Tuberculosis and Lung Disease guidelines.⁵

Current indications for BCG vaccination in Australia are listed in Table 2. Current

recommendations focus on providing the BCG vaccine to neonates and young children at highest risk. These are children in some Aboriginal and Torres Strait Islander communities, children travelling to high-incidence countries,⁹ and household contacts of people with Hansen's disease (leprosy).¹ BCG vaccination is only recommended for those with occupational exposure if they have a high risk of exposure to drug-resistant TB, such as laboratory workers directly involved in culture of multi-drug resistant (MDR) TB.

The vast majority of clinical staff working in Australian healthcare settings do not require BCG vaccination.

BCG is not routinely recommended as a pre-travel vaccine for adults. However, for specific high-risk travellers (eg medical or nursing staff working with MDR TB programs internationally), specialist advice at a dedicated TB service should be sought.

BCG vaccination is not recommended for family members of people undergoing treatment for active or latent TB.

Investigation for LTBI (using a TB IGRA) and, if positive, consideration of treatment for LTBI is the preferred way of managing contacts of those with TB. Such investigations should be directed by state or territory jurisdictional TB programs.¹⁰

There have been shortages of BCG vaccine in recent years. The strain registered for use in Australia has been unavailable or subject to supply interruptions since 2012.¹¹ There are limited supplies of other BCG vaccine strains available for which special prescribing arrangements are required. As a result of these shortages, it is important to prioritise vaccine access to those who will benefit most from vaccination.

Where BCG vaccination is indicated, referral to a specialist TB or travel medicine centre with access to the BCG vaccine may be required in some jurisdictions. Table 3 includes contact information for state- and territory-specific TB services.

Efficacy

There is wide variability in the reported efficacy of the BCG vaccine in preventing TB. This partly stems from the different outcomes used (TB disease versus TB infection as measured with an IGRA or a TST), and partly from the difference in efficacy between subgroups. Some of the variability might also be attributable to different BCG vaccine strains⁴ and exposure to other environmental mycobacteria.¹² The greatest benefit of BCG vaccination is in the prevention of severe disseminated disease in young children.

Estimates of the efficacy of BCG vaccination in preventing adult pulmonary disease vary widely in different settings (0–80%),⁵ with an average protection rate of 50%.³ A meta-analysis of BCG trials showed a relative risk of 0.49 (95% confidence interval: 0.34, 0.64) for TB disease in those who had received the BCG vaccine.¹³

The availability of TB IGRAs has provided an opportunity to consider whether the BCG vaccine provides protection against TB acquisition rather than simply reducing risk of progression to active disease. A meta-analysis of studies

Table 1. Abbreviations and terms used

Abbreviation/term	Meaning
TST	Tuberculin skin test, also known as the Mantoux test Tuberculin (protein derived from <i>Mycobacterium tuberculosis</i>) is injected intradermally and the site monitored to establish if there is immune recognition of tuberculin suggesting prior exposure
IGRA	Interferon gamma release assay Antigen is presented to the patient's blood in vitro to measure interferon gamma release; response to the antigen suggests immune recognition
TB IGRA	An IGRA using TB antigen to test for immune recognition of TB, suggesting prior exposure
LTBI	Latent tuberculosis infection
MDR-TB	Multi-drug resistant TB
Miliary TB	A characteristic appearance on chest imaging suggestive of disseminated tuberculosis disease

TB, tuberculosis

Table 2. Current Bacille Calmette–Guérin vaccination indications in Australia¹

Population	Recommendations
Aboriginal and Torres Strait Islander people	Recommended for neonates in some areas of NT, Qld and northern SA
Occupational groups	Consider only in workers with a high risk of exposure to drug-resistant TB
Travellers	Recommended for child travellers at increased risk of acquiring TB, such as those: <ul style="list-style-type: none"> <5 years of age travelling to a high-incidence country (>40 cases of TB per 100,000 population/year) with a cumulative duration of travel to a high incidence area of >1 month during early childhood
People with exposure to Hansen's disease	Recommended for young children and household contacts of people who have Hansen's disease

TB, tuberculosis

of TB IGRA positivity in children who were recently exposed to TB found a protective efficacy of 19% in BCG-vaccinated children.¹⁴ The same study looked at progression to active disease in exposed children and found a protective effect of 71% against active disease; of those infected, there was a protective effect of 58% against progression to active disease.¹⁴

The BCG vaccine's protective effect against TB meningitis and miliary TB is consistently estimated at between 70% and 90%.^{14,6} This may be due to the younger age of people usually affected by TB meningitis or miliary TB and waning of the vaccine's protective effect, or due to a different pathogenesis of pulmonary disease. BCG vaccination has been shown to be highly cost effective for children in high-incidence TB settings.⁶

Other uses and off-target effects

BCG vaccination also provides protection against nontuberculous mycobacteria. BCG vaccination protects against Hansen's disease, caused by *M. leprae*, with an overall protective effect of approximately 25%.¹⁵ There are also observational data

from European studies suggesting that BCG vaccination provides some protection against nontuberculous mycobacterial lymphadenitis in children.¹⁶ Of interest to those living in south-eastern Australia, the BCG vaccine is not thought to provide significant protection against *M. ulcerans* infection, although it may protect against *M. ulcerans* osteomyelitis.^{15,17,18}

BCG vaccination also has 'off-target' effects beyond preventing TB.¹⁹ In the Australian context, the BCG vaccine is most recognised for its use in treating bladder cancer. In this situation, it is administered through multiple intravesicular instillations and acts as an immunomodulatory agent.²⁰ The preparation of BCG vaccine for this purpose contains roughly 1000-fold the concentration of organisms in a BCG vaccine used for TB prevention, and serious adverse effects can occur if administered inappropriately.

It has also been reported from randomised controlled trials conducted in settings with high infant mortality that BCG vaccination provides survival benefit for infants independent of its TB protective effect. BCG vaccination has been shown

to reduce all-cause neonatal mortality by preventing deaths from sepsis and rates of respiratory infections other than pulmonary TB.²¹ This off-target (or 'non-specific') effect of BCG vaccination is attributed to the ability of this vaccine to induce trained immunity in the innate immune system.²²

There is a range of exploratory uses of BCG vaccine currently under investigation in Australia. A trial of BCG vaccine for the treatment of multifocal motor neuropathy and multifocal acquired demyelinating sensory and motor neuropathy is underway (ACTRN12618001936213). Topically, there has also been interest in the role of BCG vaccination in protecting vulnerable populations from severe COVID-19 disease. It has been postulated that the effect of BCG vaccination on innate immunity may reduce SARS-CoV-2 viraemia following exposure, with subsequent lessened risk of severe COVID-19 disease.²³ This hypothesis is being investigated in a number of trials internationally, including the Australian 'BCG vaccination to Reduce the impact of COVID-19 in Australian healthcare workers following Coronavirus Exposure' (BRACE) trial (NCT04327206).

Table 3. State- and territory-specific tuberculosis services

State/territory	Tuberculosis service
Australian Capital Territory	Canberra Hospital Respiratory and Sleep Medicine, http://findahealthservice.act.gov.au/c/fahs?a=sp&pid=1316133581&site=52990&servicecategory=28
New South Wales	NSW Health – Tuberculosis, www.health.nsw.gov.au/Infectious/tuberculosis/Pages/default.aspx
Northern Australia	Darwin Tuberculosis and Leprosy Unit, https://nt.gov.au/wellbeing/health-conditions-treatments/bacterial/tuberculosis-tb/tb-clinic
Queensland	Queensland Health – Contact a tuberculosis service, www.health.qld.gov.au/clinical-practice/guidelines-procedures/diseases-infection/diseases/tuberculosis/contact-a-service
South Australia	SA Health – SA Tuberculosis Services in Central Adelaide Local Health Network, www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/services/hospitals/outpatient+services/outpatient+clinics/central+adelaide+lhn+specialist+and+outpatient+clinics/sa+tuberculosis+services+in+calhn
Tasmania	Tasmanian Health Service – Respiratory and Sleep Medicine, http://outpatients.tas.gov.au/clinics/respiratory_and_sleep_medicine
Victoria	The Royal Melbourne Hospital – Victorian Tuberculosis Program, www.thermh.org.au/health-professionals/clinical-services/victorian-tuberculosis-program
Western Australia	Department of Health – Western Australia Tuberculosis Control Program, https://www2.health.wa.gov.au/Articles/A_E/About-the-Western-Australia-Tuberculosis-Control-Program

While clinical trials for novel indications are critical, the efficacy of BCG vaccination for these conditions remains uncertain. Because of the potential side effects and limited access to the vaccine, BCG vaccination should not be used for these indications outside of clinical trials.²³

Adverse effects and contraindications

The BCG vaccine is generally safe and well tolerated. Most people who receive the BCG vaccine experience mild local reactions at the injection site,¹ with serious adverse effects being rare. The rate of adverse events following immunisation in a study conducted in Victoria was approximately 15 per 10,000 doses administered.²⁴ The most common adverse reactions are injection site abscesses (which may be prolonged in some cases and require local wound care), lymphadenitis and severe local reactions.²⁵ Osteomyelitis can occur, likely through haematogenous spread, and can be difficult to treat.²⁶ Disseminated BCG disease can occur, almost exclusively in patients who are severely immunocompromised.²⁵⁻²⁷

BCG vaccination should be undertaken by practitioners with appropriate training in administration and adverse effect monitoring.

There are multiple contraindications to BCG vaccine administration (Table 4). It is a live vaccine and therefore should

not be administered to individuals who are immunocompromised. This includes people living with HIV infection²⁸ and infants born to mothers treated with biological disease-modifying antirheumatic drugs in the third trimester of pregnancy.¹ BCG vaccination should also not be given to those who have had TB previously or those with a large reaction to the TST.¹

There are also some groups for whom precaution should be exercised when administering the BCG vaccine. These include unwell infants, people with a significant febrile illness and people with skin disease at the site of injection. People on treatment for LTBI should not receive the BCG vaccine as the treatment is likely to inactivate the vaccine. Infants born to mothers living with HIV should be shown to be HIV negative prior to receiving the BCG vaccine.

Conclusion

Even in the era of SARS-CoV-2, TB is the leading infective cause of death worldwide. The BCG vaccine is a safe, effective and cost-effective method of preventing many TB-related deaths, especially in young children. While it is important to investigate and understand the role of the BCG vaccine in other areas, this should not be at the expense of its proven use for TB protection. Further evidence on safety and efficacy is required to assess the role of BCG vaccination for indications other than TB prevention.

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Table 4. Contraindications to Bacille Calmette-Guérin vaccination

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> • Individuals who are immunocompromised, including those with <ul style="list-style-type: none"> - HIV - biological disease-modifying antirheumatic drugs (and infants born to mothers treated with same during the third trimester of pregnancy) - other significant immunocompromise • Previous TB infection • Large reaction to TST 	<ul style="list-style-type: none"> • Unwell infants • Current febrile illness • Skin disease at proposed site of infection • Current treatment for LTBI • Infants born to mothers living with HIV, unless shown to be HIV negative

HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test

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