Canadian Tuberculosis Standards

7th Edition

Chapter 16: Bacille Calmette-Guérin (BCG) Vaccination in Canada

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CHAPTER 16

BACILLE CALMETTE-GUÉRIN (BCG) VACCINATION IN CANADA

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KEY MESSAGES/POINTS

- BCG vaccination has historically been provided in several provinces/territories of Canada.
- With declining rates of TB in many settings and concern about the risk-benefit ratio associated with a live, attenuated vaccine, BCG is currently only recommended in certain high-incidence communities in Canada.
- BCG is currently recommended in Canada for infants in high-incidence settings and also may be administered to travellers returning for extended stays to a high TB incidence country where BCG is routinely given.

MAJOR SHIFTS IN RECOMMENDATIONS

- BCG is not recommended for adults, such as health care workers, before travel to high-incidence settings.

RECOMMENDATIONS

- BCG vaccination is recommended in high-incidence communities for infants in whom there is no evidence of HIV infection or immunodeficiency. If vaccination is delayed beyond 6 months of age, a TST (tuberculin skin test) should be done and documented as negative before vaccination. For infants aged between 2 months and 6 months, an individual assessment of the risks and benefits of tuberculin skin testing prior to BCG vaccination is indicated.
- For infants born in Canada who will be moving to and staying for extended periods of time in a country with high TB incidence and where BCG vaccination is still standard practice, vaccination is recommended soon after arrival in the high-incidence country.

INTRODUCTION

Bacille Calmette-Guérin (BCG) is the collective term applied to a family of live, attenuated vaccines derived from the passage of *Mycobacterium bovis* by Calmette and Guérin (hence the name Bacille Calmette-Guérin). The original strain was developed at the Pasteur Institute in Paris between 1908 and 1921. Subsequent strains have undergone further development through repeated subculturing in many laboratories around the world. These strains are now known to differ in terms of their genome and a number of biologically intriguing phenotypes, such as those with the ability to make virulence lipids and produce antigens.[1,2] While there are clear data showing that this variability translates into strains with different immunogenicity in humans[3] it remains unknown whether different BCG strains offer comparable or divergent protection against TB in humans. Three parent strains of the BCG collective – Danish, Tokyo and Pasteur – now account for more than 90% of the TB vaccines used. The Pasteur strain of BCG serves as the reference strain of the vaccine, and its complete genome sequence has been determined.[4] BCG is the only vaccine currently in use against tuberculosis (TB).

According to the World Health Organization (WHO), 161 member states have BCG on their vaccination schedule, such that in 2002 the global BCG coverage of infants less than 1 year of age was 81%.[5] A global registry of BCG usage, the BCG World Atlas (www.bcgatlas.org), was recently launched to provide detailed information on current and past BCG policies and practices in a searchable, on-line format.[6] In Canada there has been a longstanding interest in BCG.[7] Beginning in 1926 in Quebec[8] and 1933 in Saskatchewan,[9] the National Research Council sponsored controlled trials of the safety and efficacy of BCG. Thereafter, BCG vaccination, either universal or selective, was promoted throughout Canada. Gradually, as anti-TB drugs became available and incidence rates fell, BCG was discontinued in most populations. In recent years its use has been limited to the First Nations and Inuit populations, in which it has been part of a TB elimination strategy.[10] However, in the wake of reports of disseminated BCG in children born with congenital immunodeficiencies[11-13] and questions about its indication,[14,15] BCG is also being phased out in this group.

EFFICACY

The efficacy of BCG has been debated for many years, despite the fact that over 3 billion doses of the vaccine have been administered. The prevailing opinion, based upon epidemiologic and autopsy data, has been that BCG does not prevent the establishment of infection in an exposed subject.[16,17] However, data from interferon-γ release assays have challenged that opinion, suggesting that BCG, while not preventing the establishment of infection in everyone, may prevent it in some.[18] If infection does occur it is widely accepted that BCG increases the resistance to uncontrolled multiplication and dissemination of *M. tuberculosis* from the primary focus of infection to other parts of the lung and body. BCG will not prevent the development of active TB in individuals who are already infected with *M. tuberculosis*.

The results of trials aimed at assessing the ability of BCG to prevent TB disease have been variable: protection has ranged from 0% to 80%. The reasons for this variability remain unclear, but there is some evidence that the more scientifically rigorous trials demonstrated higher efficacy rates, approaching 80%. The efficacy of BCG in adults is uncertain but is thought to be lower than that in children. There is good evidence that repeat BCG vaccination does not confer additional protection over a single dose. In addition to clinical trial data, there have been a number of case-controlled studies of BCG. A meta-analysis involving 10 case-controlled studies of BCG efficacy[19] provided a summary estimate of protection from BCG vaccination of 50%. Meta-analysis has also shown high rates of protection against meningeal and miliary TB in the vaccinated, as high as 85% in one clinical trial.[20]. More recently, there was a natural experiment of BCG discontinuation in Kazakhstan because of programmatic issues. In that setting, compared with infants not vaccinated, cohorts of infants vaccinated with different strains of BCG showed 50%-90% less culture-confirmed TB and 70%-90% less TB meningitis.[21]

The duration of the protective effect of BCG is disputed. A meta-analysis that examined protection over time demonstrated a decrease in efficacy of 5% to 14% in seven randomized controlled trials and an increase of 18% in three others.[22] A 55-year follow-up analysis of a study conducted in the 1930s found that BCG protective efficacy can persist for 50 to 60 years, indicating that a single dose might have a long-lasting effect.[23] In the recent study from Kazakhstan, the difference in TB rates between the non-vaccinated cohort and the vaccinated infants was largely confined to those aged 2 or less.

Unlike the high efficacy shown by vaccines against many viral infections, BCG vaccine does not provide a high degree of protection against TB. As a result, disease should still be considered in any vaccinee with a suggestive clinical presentation of TB, regardless of vaccination history.

ADMINISTRATION

BCG is available as a culture of live bacilli and is given intradermally. The manufacturer's instructions regarding administration should be carefully followed. The vaccine is supplied in a multidose vial, which is reconstituted using aseptic technique with a supplied diluent of sterile phosphate-buffered saline. The reconstituted product requires protection from heat and direct sunlight, and should be stored according to the manufacturer's instructions at 2 °C to 8 °C, and used within 8 hours. The dose in neonates is 0.05 mL, half the usual dose of 0.1 mL. The higher dose is recommended in children greater than 12 months of age. It is administered in a 1.0 mL syringe with a 26-gauge needle, the bevel facing upwards. BCG invokes the development of delayed-type hypersensitivity with a maximum response observed by 12 weeks, when the TST is usually positive. However, neither the presence nor the size of the TST response predicts protection: persistent skin test positivity is not correlated with continued protection.[24] Interpretation of the TST results of BCG-vaccinated individuals is problematic, but this issue is largely resolved with the introduction of interferon-γ release assays, which test for antigens that are not present in BCG. Details on evaluation for latent TB infection (LTBI) in the BCG-vaccinated individual are provided elsewhere (see Chapter 4, Diagnosis of Latent Tuberculosis Infection). Although for most children a scar develops after BCG vaccination, recent studies show that not all children with a record of receipt of BCG have a scar. In a series involving internationally adopted children, 27% of children with a record of BCG vaccination did not have a scar.[25]

Freeze-dried preparations of BCG for intravesical use in the treatment of primary and relapse carcinoma-*in-situ* of the urinary bladder are formulated at a much higher strength and must not be used for TB vaccination purposes.

RECOMMENDED USAGE

A summary of the provincial and territorial usage of BCG over time is provided by the Public Health Agency of Canada (http://www.publichealth.gc.ca/tuberulosis). In more recent years, BCG use in Canada has been limited to Inuit and on-reserve First Nations children born to mothers who tested negative for HIV prenatally. However, recommendations concerning the continued use of BCG in this and other Canadian populations have recently been revised. Currently, the National Advisory Committee on Immunization (NACI) does not recommend BCG vaccination for all Canadians. However, it allows that, in some settings, consideration of local TB epidemiology and access to diagnostic services may lead to the decision to offer BCG vaccination.[26,27]

- Vaccination in infants in First Nations and Inuit communities or groups of people with an average annual rate of smear-positive pulmonary TB greater than 15/100,000 population, or an annual rate of culture-positive pulmonary TB greater than 30/100,000 during the previous 3 years, or an annual risk of TB infection (ARI) greater than 0.1%, or if early identification and treatment of LTBI are not available. HIV testing in the mother of the child should be negative, and there should be no evidence or known risk factors for immunodeficiency in the child being vaccinated. Typically, BCG is given at birth, but if vaccination is delayed after birth a TST test is recommended in those over 6 months of age to ensure that the vaccine is only given to TST-negative infants. For infants aged between 2 months and 6 months, an individual assessment of the risks and benefits of tuberculin skin testing before BCG vaccination is indicated.

  (Strong recommendation, based on moderate evidence)

The annual risk of TB infection quoted, greater than 0.1%, is the ARI below which the International Union Against Tuberculosis and Lung Disease (IUATLD) recommends that selective discontinuation of BCG vaccination programs be considered.[11] If BCG vaccination is currently offered to all infants in a community that does not meet one of the criteria described, the vaccination program should be discontinued as soon as a program of early detection and treatment of LTBI can be implemented (see Chapter 9, Pediatric Tuberculosis).

- Vaccination of travellers planning extended stays in areas of high TB incidence, particularly when a program of serial TST and appropriate chemotherapy is not possible or where the prevalence of drug resistance, especially multidrug-resistant TB, is high. This recommendation largely pertains to infants born in Canada who will be moving to and staying for extended periods of time in a country with high TB incidence and where BCG vaccination is still standard practice.

  (Strong recommendation, based on moderate evidence)

In this situation, it is often more practical to recommend vaccination soon after arrival in the high-incidence country. For adults, such as health care workers, planning temporary travel to high-incidence countries, previous editions of these guidelines suggested that BCG vaccination should be considered. In the absence of evidence for the efficacy of BCG in such a situation, this is no longer recommended. Infection can be monitored using serial skin testing.

BCG vaccination of First Nations infants has now been discontinued in the Atlantic provinces, in Quebec and British Columbia. In Alberta, the rationale for continued use of the BCG has been challenged,[14] and a process of systematic withdrawal has begun. Elsewhere, on the prairies and in the territories, the benefits of BCG vaccination in preventing severe forms of TB in infants and young children may still outweigh any risks.

A consent form should be signed before vaccination. If BCG is discontinued in a community it should be replaced with a program of enhanced surveillance to ensure that TB disease and LTBI are detected early, particularly in high-risk communities. Delivery of enhanced surveillance and compliance with program recommendations may be challenging in some communities.

BOOSTER DOSES AND REVACCINATION

Revaccination with BCG is not recommended as there is no evidence that it confers additional protection. Because there is no correlation between skin test reactivity and protection, the TST is not recommended as a method to evaluate immunogenicity.[28]

ADMINISTRATION WITH OTHER VACCINES

The co-administration of BCG with other vaccines is not typically a problem in Canada, because when BCG is indicated it is given at birth. Infrequently, BCG is being given but other vaccines might also be scheduled, in which case the following is recommended. BCG vaccine may be administered concomitantly with inactivated vaccines (such as diphtheria/pertussis/tetanus /polio) and other live parenteral vaccines (such as measles/mumps/rubella) at different injection sites using separate syringes and needles. It may also be given with live intranasal influenza vaccine. If not given concomitantly, a minimum interval of 4 weeks is recommended between administration of two live parenteral vaccines (such as BCG and measles/mumps/rubella) to reduce or eliminate interference from the vaccine given first with the vaccine given later. Live *oral* vaccines, like rotavirus vaccine, may be given concomitantly with, or at any time before or after, live parenteral vaccines, such as BCG vaccine.

ADVERSE REACTIONS

Adverse events following BCG vaccination are reportable only in some provinces/territories, and thus their frequency may be underestimated. In order to provide accurate surveillance, the Public Health Agency of Canada (PHAC) collects case reports on adverse events following immunization from provincial and territorial health departments, health care professionals and the pharmaceutical industry. After intradermal injection of BCG an indurated papule forms within 2-3 weeks. A pustule or superficial ulcer develops by 6-8 weeks and heals within 3 months, leaving a 4-8 mm scar at the vaccination site in the majority of vaccinees. Regional adenopathy in the absence of erythema or vesicle formation should be considered an expected reaction to the vaccine.[29]

LOCAL REACTIONS

The majority of local reactions occurs within 5 months of vaccination and consists of prolonged skin ulceration, suppurative adenitis and localized abscess. *M. bovis* BCG can be cultured from approximately 5% of lymph nodes.[29] A European study found the mean risk of adenitis to be 0.387/100,000 in infants (i.e. children less than 1 year of age) and 0.25/100,000 in vaccinees aged 1 to 20.[30] Factors contributing to regional adenitis include the type of vaccine strain, the total number of viable and nonviable bacilli in the vaccine preparation and the dose of BCG given. The age of the person vaccinated is also important. Reducing the dose for newborns to 0.025 mL of vaccine further reduces the number of adverse reactions.[31] Treatment of suppurative adenitis is controversial. The WHO has suggested surgical drainage with direct installation of an anti-TB drug for adherent or fistulated glands, but no data exist to support this recommendation.[32] It appears that systemic treatment with anti-TB drugs is ineffective.[33]

SYSTEMIC REACTIONS

Osteitis is a rare complication of BCG vaccination developing within 4 to 144 months of vaccination. It appears to be associated with the administration of BCG in the gluteal region or thigh, and it has been reported most commonly from Scandinavian countries with a particular strain of BCG (BCG Swedish, also known as BCG Gothenberg). Less common reactions include fever, conjunctivitis, iritis and erythema multiforme. The most serious complication of BCG vaccination is disseminated BCG. It usually occurs within 6 months of vaccination, although long latent periods have been reported,[34] and it is usually fatal. In a study conducted by the IUATLD, disseminated BCG occurred in 3/1,000,000 recipients.[30] In studies conducted in Canada a different rate of occurrence of disseminated BCG is being reported.[11-13] Between 1993 and 2002, 21 BCG vaccine-related adverse events were reported, 15 of which were designated as serious, i.e. the patient died or was in hospital for longer than 3 days. There were six cases of disseminated BCG in immunocompromised infants, five in First Nations and Inuit children, all of whom subsequently died. There were also two cases of osteomyelitis, five abscesses and two cases of adenitis. All six disseminated cases were deemed very likely or certainly associated with the vaccination. An additional fatal case of disseminated BCG was identified in 2003.[13] Although the range estimates for adenitis and osteomyelitis appear to be consistent with global rates, the rate of disseminated BCG among First Nations children was much greater than the highest global rates.[35]

This high rate suggests that immunodeficiency states might be more common in First Nations and Inuit children, a possibility that is now being explored through Health Canada's First Nations and Inuit Health Branch and the Canadian Paediatric Surveillance Program, a collaborative initiative of the Canadian Paediatric Society and PHAC. As a consequence of these concerns related to disseminated BCG, NACI has revised its recommended usage of BCG.

CONTRAINDICATIONS TO BCG VACCINATION

BCG vaccination is contraindicated in people with immune deficiency diseases, including congenital immunodeficiency, HIV infection, altered immune status due to malignant disease, and impaired immune function secondary to treatment with corticosteroids, chemotherapeutic agents or radiation. Maternal HTLV-1 (human T-cell lymphotrophic virus type 1) infection and possible neonatal HTLV-1 infection are not a contraindication to BCG, as neonatal HTLV-1 infection does not result in significant immune suppression in the child. Extensive skin disease or burns are also contraindications. BCG is contraindicated for individuals with a positive TST result, although vaccination of tuberculin reactors has frequently occurred without incident. Before a newborn is vaccinated with BCG the mother should be known to be HIV negative, and there should be no family history of immunodeficiency. The vaccine should not be administered to individuals receiving drugs with anti-TB activity, since these agents have activity against the vaccine strain.

OTHER USES OF BCG VACCINE

Intravesical BCG is used for the treatment of transitional-cell bladder cancer, the most common form of bladder cancer. BCG immunotherapy has been associated with systemic side effects, including pneumonitis and miliary spread of the organism, which can be fatal.[36] Miliary spread occurs in patients who are otherwise deemed to be immunocompetent and responds to conventional anti-TB therapy, with the caveat that the organism is always resistant to pyrazinamide (PZA).

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