Why	• Worldwide, TB continues to infect one-third of the population and is the second leading cause of death from an infectious disease. • The incidence of TB in Canada is among the lowest in the world. However, certain sub-populations in Canada remain at risk: Aboriginal persons in areas with a high prevalence of TB (particularly infants), Canadian-born elderly persons, immigrants, homeless persons and those infected with HIV.

Since the publication of the *2006 Canadian Immunization Guide:*

- Interferon gamma release assay (IGRA) testing has become available to assist in the diagnosis of TB
- New data have been obtained on the epidemiology of TB
- New recommendations have been developed on Tuberculin Skin Testing (TST) in infants

For additional information regarding tuberculosis and tuberculosis management in Canada, refer to the *Canadian Tuberculosis Standards (2007)*. (http://webqa.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php) For additional information regarding tuberculosis and travellers, refer to Committee to Advise on Tropical Medicine and Travel (CATMAT) *Risk assessment and prevention of tuberculosis among travellers*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-5/index-eng.php) For additional information regarding tuberculosis and HIV management, refer to *WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders.* (http://reliefweb.int/report/world/who-policy-collaborative-tbhiv-activities-guidelines-national-programmes-and-other)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

TB is an infectious, bacterial disease caused by the bacillus *Mycobacterium tuberculosis*. The bacteria typically infect the lungs (pulmonary) but can affect other sites as well (extra-pulmonary).

Reservoir

Humans

Transmission

M. tuberculosis infection is spread almost exclusively by the airborne route. The droplets may remain suspended in the air and are inhaled by a susceptible host. The duration of exposure required for infection to occur is generally prolonged (commonly weeks, months or even years). The risk of infection with *M. tuberculosis* varies with the duration and intensity of exposure, the infectivity of the source case, the susceptibility of the exposed person, and environmental factors. Although treatment courses are prolonged, effective treatment of the individual with active TB disease can reduce the infectiousness after two weeks. There are specific criteria for determining when isolation can be discontinued in cases of active TB disease. Refer to the *Canadian Tuberculosis Standards (2007)*. (http://webqa.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php)

Risk factors

A variety of factors influence the risk for *M. tuberculosis* infection, progression to active disease, and adverse outcomes from active disease:

- Risk factors for infection include proximity to a person with infectious TB, which may occur in a household setting where TB is present, in homeless shelters, in prisons and in certain occupations (e.g., working in a hospital or homeless shelter). In the household setting, over-crowding or living in large groups with a person with infectious TB increases the risk of infection.

- Progression from infection to active disease may be facilitated by co-morbidities such as HIV/AIDS and other immunodeficiencies, diabetes, silicosis, or malnutrition. Smoking is also associated with an increased risk for TB disease progression.

Adverse outcomes from disease are associated with delayed diagnosis and treatment of alcoholism, malnutrition, injection drug use and homelessness. Poverty, access to treatment, and compliance with treatment regimens may be related to these risk factors.

Spectrum of clinical illness

Most persons infected with TB do not develop active disease; the infection remains latent. The risk of developing active TB varies according to time since infection, age and other factors. The lifetime cumulative risk for the development of active TB disease is estimated to be 5% to10%. Approximately 50% of cases of active TB disease occur in the first 2 years following infection. In young children the risk of disease after infection is inversely related to age. There is a very high risk (up to 40%) in infants, who can have rapid progression and have a higher probability of miliary (disseminated) or meningeal disease. Rapid progression from infection to active TB disease is also more common in persons who are immunocompromised (e.g., HIV-infected, solid organ transplantation, receiving immunosuppressive therapy).

Classic symptoms of active disease include cough, fever, weight loss and night sweats. The clinical diagnosis of miliary TB is difficult because of variable presentation. Despite appropriate treatment, mortality from miliary TB remains as high as 20%. TB meningitis is associated frequently with devastating consequences: 25% morbidity (i.e., permanent neurologic deficit) and 15% to 40% mortality despite available treatment.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

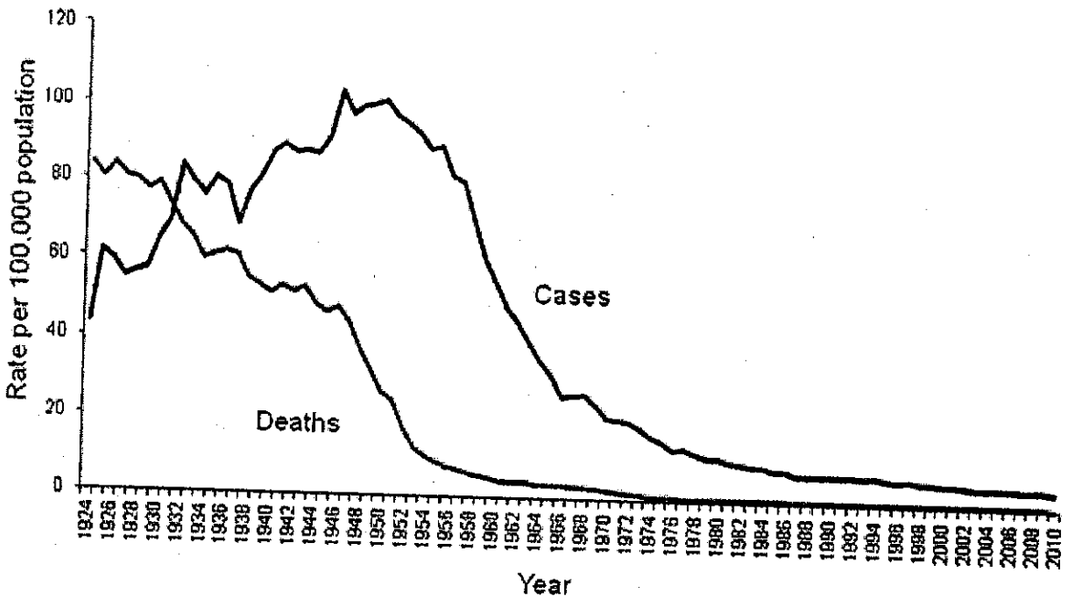
TB continues to be a leading cause of morbidity and mortality, especially in low and middle income countries. The global picture of TB is complicated by drug resistance and the HIV epidemic. About one-third of the world's population is infected with TB and TB is the second leading cause of death from an infectious disease worldwide. In 2010, there were an estimated 9 million cases of active TB disease and an estimated 1.4 million deaths from TB (1.1 million in non-HIV infected individuals and 0.35 million in HIV-infected individuals).

National

The reported incidence of TB in Canada is declining since a peak in the early 1940s (refer to *Figure 1*). In 2010, 1,577 cases of TB disease were provisionally reported, representing an incidence rate of 4.6 per 100,000 population. Most cases of active TB occurred in two groups: foreign-born individuals (66% of cases, rate of 13.3 per 100,000) and Aboriginal peoples (21% of cases, rate of 26.4 per 100,000). In 2010, Nunavut reported the highest incidence rate at 304 per 100,000 population followed by the Northwest Territories (25.1) and Yukon (17.4).

The Canadian-born non-Aboriginal population represents 12% of cases with an overall rate of 0.7 per 100,000. This rate is higher in the elderly, especially in those greater than 75 years of age. In 2010, only 4.9% of cases (77/1,577) were less than 15 years of age, and the corresponding age-specific incidence of these cases was 1.4 per 100,000.

Figure 1: Tuberculosis: Incidence and mortality rates, Canada 1924-2010



PREPARATIONS AUTHORIZED FOR USE IN CANADA

BCG VACCINE (Bacille Calmette-Guérin vaccine)(live, attenuated vaccine derived from *Mycobacterium bovis* (Connaught substrain)), sanofi pasteur Ltd. (BCG)

Lyophilized preparations of BCG for intravesical use in the treatment of carcinoma of the urinary bladder are formulated at a significantly higher strength and **must not** be used for TB vaccination.

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the *Drug Product Database*. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to *Table 1* in Contents of Immunizing Agents Availabable for Use in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

Clinical trials have demonstrated conflicting results regarding BCG vaccine efficacy. Meta-analytic reviews have estimated the vaccine efficacy in preventing any TB disease at approximately 51%. The protective effect of BCG vaccine against disseminated TB in the newborn is estimated to be 78%.

The duration of BCG vaccine protection is not well-established. Although generally thought to have declining protection over time, one follow up study demonstrated a protective effect for as long as 60 years. BCG vaccine will not prevent the development of active TB in individuals who are already infected with *M. tuberculosis*. TB disease should be considered as a possible diagnosis in any vaccinee who presents with a suggestive history, or signs or symptoms of TB, regardless of immunization history.

IMMUNOGENICITY

Immunological correlates of protection against TB infection or disease after BCG vaccination have not been identified.

RECOMMENDATIONS FOR USE

BCG vaccine is not recommended for routine use in any Canadian population. Following consideration of local TB epidemiology and if a program of early detection and treatment of latent TB infection cannot be implemented, BCG vaccination may be considered in exceptional circumstances such as infants in high risk communities, persons at high risk of repeated exposure, certain long term travellers to high prevalence countries, and in infants born to mothers with infectious TB disease. The Canadian Tuberculosis Standards (2007), (http://webqa.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php) including recommendations for use of BCG vaccine, are currently under review.

INFANTS IN HIGH RISK COMMUNITIES

If early identification and treatment of latent TB infection are not available, BCG vaccine may be considered for infants residing among groups of persons or in First Nations and Inuit communities with an average annual rate of smear-positive pulmonary TB greater than 15 per 100,000 population (all ages) during the previous 3 years, or for infants residing in populations with an annual risk of TB infection greater than 0.1%.

These criteria are based on the following:

- The rate of smear-positive pulmonary TB at 15 per 100,000 population represent a high incidence of infectious TB in designated geographic areas outside Canada. The Canadian Tuberculosis Committee and the Public Health Agency of Canada (PHAC) have adopted the same breakpoint for use in the Canadian population. For information on international smear-positive pulmonary TB incidence rates, refer to www.publichealth.gc.ca/tuberculosis.
- When the annual risk of TB infection is less than 0.1%, the International Union Against Tuberculosis and Lung Disease recommends that selective discontinuation of BCG vaccination programs be considered.

The goal of BCG vaccination in infants is to prevent miliary TB and TB meningitis. Infants in high risk communities should receive BCG vaccine as soon after birth as feasible and preferably before 6 weeks of post-natal age or discharge into the community. Refer to *Infants born prematurely*.

If BCG vaccination is offered currently to all infants in a community that does not meet one of the above criteria, the vaccination program should be discontinued as soon as a program of early detection and treatment of latent TB infection can be implemented.

If BCG vaccination is considered appropriate based on the above criteria, 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, including no family history of immunodeficiency. Indication that an inherited immunodeficiency may be present in a family includes a history of neonatal or infant deaths in the immediate or extended family. Such a history precludes BCG vaccination until immunodeficiency is excluded in the child. The optimal management of HIV exposed newborns living in communities meeting the above criteria is currently under National Advisory Committee on Immunization (NACI) review.

PERSONS AT HIGH RISK OF REPEATED EXPOSURE

If early identification and treatment of latent TB infection are not available, BCG vaccine may be considered for individuals who may be exposed repeatedly to persons with untreated, inadequately treated or drug-resistant active TB disease or tubercle bacilli in conditions where protective measures against infection are not feasible. Treatment of the source, removal from the source, and/or TB screening and chemoprophylaxis of the exposed person as indicated is generally preferred over the administration

of BCG vaccine. Consultation with a TB or infectious disease expert is recommended. Refer to *Workers* for additional information. In exceptional circumstances, BCG vaccine may be considered for long term travellers to countries with a high TB prevalence. Refer to *Travellers* for additional information.

BCG VACCINATION: PRE-IMMUNIZATION TUBERCULIN SKIN TESTING

The one-step tuberculin skin test (TST) is recommended as part of the assessment of some infants for BCG vaccine. Two-step tuberculin skin tests do not provide added value in this age group.

Tuberculin skin testing of infants prior to BCG vaccination

In infants who require BCG vaccine, the one-step TST may be needed as follows:

- If the **infant is less than 2 months of age**: give BCG vaccine without prior TST because the risk of prior TB exposure is low and the sensitivity of the TST at detecting latent TB infection is unknown.
- If the **infant is between 2 and 6 months of age**: complete an individual risk-benefit assessment because the validity of TST in infants under 6 months of age is unknown. In these infants, false negative TST results may occur; false positive TST results are rare. Tuberculin skin testing in this age group may lead to early diagnosis of latent TB infection. However, there is a risk that the infant may be lost to follow-up between the TST and receiving BCG vaccine.

Based on the outcome of the risk-benefit assessment either:

- Administer a one-step TST before BCG vaccine if there is a high risk of prior TB exposure OR
- Administer BCG vaccine without prior TST if the infant may not return after TST for BCG vaccine

If a TST is administered between 2 and 6 months of age, it should be recognized that the TST may be falsely negative, and therefore, despite a negative TST and BCG vaccination, active TB should still be considered if clinically compatible symptoms develop.

- If the **infant is more than 6 months of age**: complete a one-step TST. If the TST is negative, give BCG vaccine.

Refer to *Other considerations* for information regarding BCG vaccination and post-immunization tuberculin skin testing.

PREGNANCY AND BREASTFEEDING

BCG vaccine has not been studied in pregnant or lactating women. BCG vaccine should not be given during pregnancy although no harmful effects of BCG vaccination on the fetus have been observed. It is not known whether BCG vaccine is excreted in human milk. Because live vaccine may be excreted in human milk, caution should be exercised when considering BCG vaccine during lactation. Refer to *Immunization in Pregnancy and Breastfeeding* in Part 3 for additional general information.

INFANTS BORN PREMATURELY

Infants born prematurely may receive BCG vaccine any time after 31 weeks of post-menstrual age. Infants born prematurely (especially those weighing less than 1,500 grams at birth) are at higher risk of apnea and bradycardia following vaccination. Hospitalized premature infants should have continuous cardiac and respiratory monitoring for 48 hours after their first immunization. Refer to *Immunization of Infants Born Prematurely* in Part 3 for additional information.

IMMUNOCOMPROMISED PERSONS

BCG immunization is contraindicated in most immunocompromised persons, including HIV infection, altered immune status due to malignant disease or transplant, and impaired immune function secondary to treatment with corticosteroids, chemotherapeutic agents or radiation. There is substantial risk of

disease due to dissemination of the vaccine bacille in immunocompromised people. Two exceptions to this contraindication are that BCG vaccine may be used, if indicated, in persons with complement deficiencies or isolated IgA deficiencies. Refer to *Contraindications and Precautions*. Refer to *Immunization of Immunocompromised Persons* in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Persons with chronic renal disease or undergoing dialysis, and those with hyposplenism or asplenia may receive BCG vaccine if indicated. Refer to *Immunization of Persons with Chronic Diseases* in Part 3 for additional general information.

TRAVELLERS

In general travellers do not need BCG vaccine. TB screening and chemoprophylaxis as indicated is the general approach to TB control in travellers.

BCG vaccine may be considered for long term travellers to countries with a high prevalence of TB in the following circumstances:

- Young children (under 5 years of age) who are anticipated to have no access to regular tuberculin skin testing
- Individuals who may have extensive occupational exposure to multidrug-resistant (MDR) tuberculosis
- Travellers who for reasons of logistics, drug toxicity or intolerance, or personal choice, are expected not to be able to utilize the recommended surveillance strategy or chemoprophylaxis regimens.

Travellers working in hospitals in high incidence countries have an increased risk of acquiring TB, especially where HIV is co-endemic. Canadian immigrants visiting friends and relatives in high prevalence countries are likely at higher risk than the average traveller, possibly due to their closer contact with the local population.

Consultation with an infectious disease or travel medicine specialist is recommended. For additional information regarding TB and travellers, refer to Committee to Advise on Tropical Medicine and Travel (CATMAT) *Risk assessment and prevention of tuberculosis among travellers*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-5/index-eng.php) Refer to *Immunization of Travellers* in Part 3 for additional general information.

WORKERS

In general, workers do not need BCG vaccine. Appropriate personal protection, environmental controls, treatment of the source, and TB screening and chemoprophylaxis of the exposed person as indicated are the typical approaches to TB control in workers. If early identification and treatment of latent TB infection are not available, BCG vaccine may be considered for workers (such as health care workers, laboratory workers, prison workers and those working in shelters for the homeless) who may be repeatedly exposed to persons with untreated, inadequately treated or drug-resistant active TB or tubercle bacilli in conditions where protective measures against infection are not feasible. Consultation with a TB or infectious disease expert is recommended. Refer to *Immunization of Workers* in Part 3 for additional general information.

VACCINE ADMINISTRATION

VACCINE RECONSTITUTION

BCG vaccine contains live, viable, attenuated mycobacteria. Handle as an infectious agent.

Gloves should be worn when reconstituting the contents of the vial and for withdrawing the dose. Dispose of the syringe, needle, vial with unused product, and all materials exposed to the product in a container for biohazardous waste.

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Infants (12 months of age and younger): 0.05 mL (0.05 mg)
Children (greater than 12 months of age) and adults: 0.1 mL (0.1 mg)

Route of administration

Reconstituted BCG vaccine should be administered by intradermal injection into the most superficial layers of the skin, in accordance with the instructions in the manufacturer's product leaflet. The area over the deltoid muscle is the preferred administration site. Refer to *Vaccine Administration Practices* in Part 1 for additional information.

Do NOT administer the product by the intravenous, intramuscular or subcutaneous routes. Intramuscular or subcutaneous administration may result in an abscess at the injection site.

Schedule

One dose of BCG vaccine should be administered.

BOOSTER DOSES AND RE-IMMUNIZATION

Re-immunization with BCG vaccine is not recommended. One study in school-aged children documented that re-immunization with BCG vaccine conferred no additional protection.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving BCG vaccine.

STORAGE REQUIREMENTS

Store BCG vaccine in a refrigerator at +2° C to +8° C. Do not freeze. Store the reconstituted product in a refrigerator at +2° C to +8° C and use within 8 hours. Protect from light. Refer to *Storage and Handling of Immunizing Agents* in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

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 intranasal live attenuated influenza vaccine (LAIV). 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) or a live parenteral vaccine and LAIV to reduce or eliminate potential interference from the vaccine given first on 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. In a blinded, randomized trial, neonates experienced less pain when the BCG vaccine was administered prior to concurrent intramuscular hepatitis B vaccine. Refer to *Timing of Vaccine Administration* in Part 1 for additional

general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to *Vaccine Safety* Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

Intradermal administration of BCG vaccine usually results in the development of erythema and either a papule or ulceration (in about 50%), followed by a scar at the immunization site. Keloid formation occurs in 2% to 4% of vaccine recipients. Non-suppurative regional lymphadenopathy occurs in 1% to 10%. Most reactions are generally mild and do not require treatment.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. Rare adverse events include local abscess formation and suppurative regional lymphadenitis (0.03% to 0.05% of vaccinees). These occur more frequently among infants less than 12 months of age than among older children and adults. There is some evidence in adults to suggest that subcutaneous administration of vaccine rather than the intended intradermal route is associated with more frequent abscess formation. Very rarely, disseminated BCG infection may occur and can be fatal in approximately 1 in 1 million vaccinations. Fatal cases almost always involve children with primary immunodeficiencies.

From 1993 to 1999, five cases of fatal disseminated BCG infection were reported by the Public Health Agency of Canada (PHAC)-Canadian Pediatric Society (CPS) Immunization Monitoring Program-Active (IMPACT) pediatric hospital surveillance network. This led to a thorough review by PHAC's Advisory Committee on Causality Assessment (ACCA) of the 5 deaths and 16 additional cases (1 non-fatal disseminated infection, 2 osteomyelitis, 8 abscesses, 4 lymphadenitis, 1 cellulitis) hospitalized for complications following BCG vaccination administered between 1993 and 2002. An additional fatal case of disseminated BCG was identified in 2003. All six fatal cases involved First Nations/Inuit infants with underlying immunodeficiency disorders that were not yet diagnosed at the time of immunization (vaccinated in the first week of life for 5 cases and at age 3 weeks for 1 case). All 6 cases were considered by ACCA as "very likely-certainly" associated with the vaccine. These events led to a change in NACI recommendations in 2004 and discontinuation of routine immunization of First Nations/Inuit infants in many Canadian provinces and territories.

Anaphylaxis following vaccination with BCG vaccine may occur but is very rare.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report, through local public health officials, any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due toimmunization, or a change in the frequency of a known AEFI. Refer to *Vaccine Safety* in Part 2 and other guidance for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

BCG vaccine is contraindicated in persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. In situations of suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.Refer to *Table 1* in *Contents of Immunizing Agents Available for Use in Canada* in Part 1 for lists of all vaccines available for use in Canada and their contents. For BCG vaccine, potential allergens include latex in the vial stopper.

BCG immunization is contraindicated in most immunocompromised persons, including HIV infection, altered immune status due to malignant disease or transplant, and impaired immune function secondary to treatment with corticosteroids, chemotherapeutic agents or radiation. Exceptions include both complement and isolated IgA deficiency. Before an infant is vaccinated with BCG vaccine the mother must be known to be HIV negative, and there should be no family history of immunodeficiency. Indications that an inherited immunodeficiency may be present in a family include a history of neonatal or infant deaths in the immediate or extended family. Such a history precludes BCG vaccination until immunodeficiency in the child is excluded.

If the BCG vaccine is administered accidently to an immunocompromised individual, consult an infectious diseases or TB specialist for treatment.

Immunization of pregnant women should be deferred until after delivery and generally should not be given if the mother is breastfeeding.

Extensive skin disease or burns are contraindications to BCG vaccination.

BCG is contraindicated for individuals with a positive TST, although immunization of tuberculin reactors has occurred frequently without complications.

Administration of BCG vaccine should be postponed in persons with moderate or severe acute illness. Persons with minor acute illness (with or without fever) may be vaccinated.

Refer to *General Contraindications and Precautions* in Part 2 for additional general information. Refer to *Immunization of Immunocompromised Persons* and *Immunization of Persons with Chronic Diseases* in Part 3 for additional general information.

DRUG INTERACTIONS

The BCG vaccine should not be administered to individuals receiving drugs with antituberculous activity, since these agents may be active against the vaccine strain.

OTHER CONSIDERATIONS

BCG VACCINATION: POST-IMMUNIZATION TUBERCULIN SKIN TESTING/INTERFERON GAMMA RELEASE ASSAY BLOOD TESTING

BCG immunization may result in a positive TST. The benefits gained by immunization must be weighed against the potential loss of the TST as a primary tool to identify infection with *M. tuberculosis*. The increasing availability of interferon gamma release assay (IGRA) blood testing may reduce this concern because the BCG vaccine does not produce a "false positive" result with the IGRA test. However, the IGRA test is expensive and not available in all jurisdictions in Canada. The usefulness of this test in children less than 5 years of age has been questioned due to only a moderate concordance (69% to 89%) with the TST, although the IGRA is considered more sensitive.

BCG vaccine is one of the mostly widely used vaccines in the world and is currently given at or soon after birth to children in over 100 countries. Vaccine may have been received by several population groups, including immigrants from many European countries and most developing countries. In Canada, many Aboriginal Canadians and persons born in Quebec and Newfoundland and Labrador from the 1940s until the late 1970s were vaccinated. For information on current and historical BCG vaccine usage in Canada by province/territory, refer to the *Canadian Tuberculosis Standards (2007)* Appendix F. (http://webqa.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php)

If BCG vaccine is received in the first year of life, it is very unlikely to cause TST reactions of 10 mm or more in persons 10 years of age and older because tuberculin reactivity acquired through BCG vaccination in infancy generally wanes over time. Therefore, a history of BCG immunization received in

infancy can be ignored in all persons 10 years of age and older when interpreting a TST result of 10 mm or greater.

If BCG vaccine was received between the ages of 1 and 5 years, persistent positive TST reactions may be observed in 10% to 15% of subjects even 20 to 25 years later. In persons vaccinated at 6 years of age and older, up to 40% will have persistent positive TST reactions. BCG-related TST reactions may be as large as 25 mm or more. Therefore, if BCG immunization was received after the first year of life, it can be an important cause of false-positive TST reactions, particularly in populations in which the expected prevalence of TB infection (i.e., true positive TST reactions) is less than 10%.

BCG immunization can be ignored as a cause of a positive TST under the following conditions:

- BCG vaccine was given during infancy, and the person tested is now 10 years of age or older. Although availability of the IGRA test is limited in Canada, IGRA testing has been shown to be a useful confirmatory test for latent tuberculosis infection in TST positive school children at low risk of TB infection who received BCG vaccine in infancy.
- The person is from a group with a high prevalence of TB infection (true positives), e.g., close contacts of an infectious TB case, Aboriginal Canadians from a high-risk community, immigrants from countries with a high incidence of TB.
- The person has a high risk of progression to disease if infected. Refer to *Canadian Tuberculosis Standards (2007)* for further information. (http://webqa.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php)

BCG vaccination should be considered the likely cause of a positive TST if:

- BCG vaccine was given after 12 months of age, AND
- there has been no known exposure to an active TB case or other risk factors, AND
- the person is either a Canadian-born non-Aboriginal OR an immigrant from a country with low TB incidence (e.g., Western Europe, United States).

Tuberculin skin testing should not be used as a method to determine whether previous BCG immunization was effective.

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PART 4

CHOLERA AND ENTEROTOXIGENIC ESCHERICHIA COLI (ETEC) TRAVELLERS' DIARRHEA VACCINE

KEY INFORMATION (refer to text for details)

What	• Cholera – o Is caused by *Vibrio cholerae* serogroups O1 and O139 o Is associated with poor sanitation; generally acquired from contaminated water or food o If untreated, severe fluid loss can lead to rapid dehydration and hypovolemic shock, which may be life-threatening • Enterotoxigenic *Escherichia coli* (ETEC) – o Accounts for 25% to 50% of travellers' diarrhea o Is transmitted by contaminated food and, less often, contaminated water o Most episodes are mild and self-limited • Cholera and travellers' diarrhea vaccine (DUKORAL®, Crucell Vaccines Inc.) efficacy is about 86% for epidemic cholera and approximately 25% for overall travellers' diarrhea. It protects against *Vibrio cholera* serogroup O1 but does not protect against cholera caused by *V. cholerae* O139 or other species of *Vibrio*. • Following the primary series, protection against cholera lasts for 2 years in persons 6 years of age and older and 6 months in children 2 to 5 years of age. Protection against ETEC travellers' diarrhea lasts for 3 months. • The most commonly reported adverse events following immunization are abdominal pain, diarrhea, nausea and vomiting.
Who	• For protection against cholera: Travellers to cholera-endemic countries who will be at significantly increased risk of exposure (e.g., humanitarian workers or health professionals working in endemic countries) may benefit from cholera and travellers' diarrhea vaccination. • For protection against travellers' diarrhea: Vaccination with cholera and travellers' diarrhea vaccine is of limited benefit and is not routinely recommended except for high risk travellers 2 years of age and older.

How	• Cholera prevention – o 6 years of age and older: give 2 doses orally, 1 to 6 weeks apart o 2 to 5 years of age: 3 doses orally, 1 to 6 weeks apart • ETEC travellers' diarrhea prevention: give 2 doses orally, 1 to 6 weeks apart • Booster doses should be administered, if indicated. The interval varies with age and indication. • Avoid oral administration of medicinal products or intake of food and/or drink for 1 hour before and 1 hour after vaccine administration. • Separate the administration of cholera and travellers' diarrhea vaccine and oral typhoid vaccine by at least 8 hours.
Why	• Most travellers following the usual tourist itineraries in countries affected by cholera are at extremely low risk of acquiring cholera infection; travellers' diarrhea is usually a mild and self-limited illness. • Not all recipients of this vaccine will be fully protected against cholera or travellers' diarrhea.

Since the publication of *2006 Canadian Immunization Guide*:

- New data have been obtained on the epidemiology of cholera.

For additional information, refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) *Statement on new oral cholera and travellers' diarrhea vaccination*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/asc-dcc-7/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Cholera is caused by the toxin-producing bacterium *Vibrio cholerae* serogroups O1 and O139. *V. cholerae* serogroup O1 causes the majority of cholera outbreaks and has two biotypes, Classical and El Tor. Each biotype has two serotypes, Inaba and Ogawa.

Enterotoxigenic *Escherichia coli* (ETEC) is the most common cause of travellers' diarrhea. Many ETEC strains produce a heat-labile enterotoxin that is similar to cholera toxin.

Reservoir

Humans and water sources are the main reservoirs of *V. cholerae*. Humans are the reservoir for ETEC.

Transmission

Cholera

Cholera is associated with poor sanitation and is generally acquired from contaminated water or food, particularly undercooked or raw shellfish and fish. The incubation period is 2 hours to 5 days and *V. cholerae* remain in the feces for 7 to 14 days after infection. Transmission from person to person is rare.

ETEC travellers' diarrhea

ETEC is transmitted by contaminated food and, less often, contaminated water. The incubation period is usually 24 to 72 hours and excretion of ETEC may be prolonged.

Risk factors

Cholera

Travellers at higher risk of cholera infection include those who drink or eat contaminated water or food, in particular undercooked or raw shellfish and fish. Humanitarian relief workers and those visiting areas of high risk with limited access to safe water and food are also at increased risk. The risk of cholera can increase following disaster situations due to the disruption of water and sanitation systems or the displacement of populations to overcrowded camps. Immunocompromised persons (such as malnourished children or HIV-infected persons) are at greater risk of morbidity if infected.

Travellers' diarrhea

The most important determinants of risk for travellers' diarrhea are the travel destination and the type of travel (e.g., five-star accommodations vs. backpacking). Factors associated with a higher probability of acquiring travellers' diarrhea include gastric hypochlorhydria and the relative lack of gut immunity seen in small children. In addition, specific groups of travellers are at an increased risk of serious consequences of travellers' diarrhea:

- persons with chronic illnesses, such as immunodeficiency diseases
- individuals with chronic renal failure
- persons with congestive heart failure
- individuals with insulin-dependent diabetes mellitus
  persons with inflammatory bowel disease

Spectrum of clinical illness

Cholera

Cholera presents as profuse, watery diarrhea. If left untreated, severe fluid loss can lead to rapid dehydration and occasionally hypovolemic shock, which may be life-threatening. Case fatality ranges from 50% or more without treatment to less than 1% among adequately treated patients. The spectrum of disease is wide, with mild and asymptomatic illness occurring more frequently than severe disease. The ratio of symptomatic to asymptomatic cases varies from strain to strain.

Travellers' diarrhea

Most episodes of travellers' diarrhea are mild and self-limited although the illness can be debilitating and particularly difficult to manage in remote or unfamiliar surroundings. Some travellers experiencing more severe acute inflammatory gastroenteritis may develop persistent gastrointestinal symptoms, but long term sequelae resulting from non-inflammatory gastroenteritis such as that caused by ETEC are very uncommon.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

Cholera: The World Health Organization (WHO) estimates that approximately 3 to 5 million cholera cases occur annually, with up to 120,000 deaths. Cholera is endemic in many countries. A map of the areas reporting cholera outbreaks is available from the World Health Organization (WHO). (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_CholeraCases0709_20091008.png)

Travellers' diarrhea: It is estimated that up to 50% of travellers from developed countries who visit developing countries will have traveller's diarrhea, depending on the destination. The highest rates are seen in Latin America, Africa and the Indian subcontinent, while intermediate rates of 8% to 15% are seen for travellers to China, Russia, the Middle East and southeastern Asia.

National

In Canada, cholera cases are very uncommon. There have been 19 cases of cholera reported between 2005 and 2008. There are no Canadian data on ETEC and travellers' diarrhea.

RECENT OUTBREAKS

Since the 19th century, cholera pandemics have killed millions of people across all continents. The current cholera pandemic began in South Asia in 1961, reached Africa in 1971 and the Americas in 1991. In recent years there has been multiple cholera outbreaks related to mass population movement, especially at times of strife, such as within refugee camps in resource-poor countries. Recently, two large scale outbreaks included Zimbabwe in 2009 and Haiti in 2010. In Haiti, over a one year period, almost half a million cases were reported, with over 6,200 deaths.

PREPARATIONS AVAILABLE FOR USE IN CANADA

CHOLERA AND TRAVELLERS' DIARRHEA VACCINE

- **DUKORAL®:** inactivated, oral, travellers' diarrhea and cholera vaccine containing heat inactivated *V. cholerae* O1 Inaba classic strain, formalin inactivated *V. cholerae* O1 Inaba El Tor strain, and heat and formalin inactivated *V. cholerae* O1 Ogawa classic strain with recombinant non-toxic cholera toxin B subunit, Crucell Sweden AB (manufacturer), Crucell Vaccines Inc.(distributor)

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Table 1 in Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

Cholera

A clinical trial using an early formulation of cholera and travellers' diarrhea vaccine demonstrated an overall efficacy against *V. cholerae* O1 El Tor of 64% and complete protection against moderate to severe diarrhea. A large field trial using an early formulation of this vaccine demonstrated efficacy of 85% against *V. cholerae* O1 El Tor disease for the initial 6 months and 50% for the 3-year follow-up period. A field trial using the current cholera and travellers' diarrhea vaccine demonstrated an efficacy of 86% against epidemic cholera. Cholera and travellers' diarrhea vaccine does not protect against cholera caused by *V. cholerae* O139 or other species of *Vibrio*.

Protection against cholera can be expected approximately one week after completion of primary immunization and lasts for 2 years in persons 6 years of age and older, and 6 months in children 2 to 5 years of age.

ETEC travellers' diarrhea

Cholera and travellers' diarrhea vaccine provides moderate, short-term protection against diarrhea caused by ETEC. Given that less than 50% (range, 25% to 50%) of cases of travellers' diarrhea are caused by ETEC, the overall protection provided by cholera and travellers' diarrhea vaccine against travellers' diarrhea is estimated to be approximately 25%. A large field trial using an early formulation of this vaccine demonstrated 67% protection against ETEC for 3 months, with the number needed to vaccinate to prevent one case of ETEC calculated as over 2,600 from the published data. Another study demonstrated that the vaccine had a protective efficacy of approximately 50% against ETEC

diarrhea. A third study showed efficacy against ETEC diarrhea of 52% and an overall protection against travellers' diarrhea of 23%.

Protection against ETEC travellers' diarrhea can be expected approximately one week after completion of primary immunization and lasts for 3 months.

IMMUNOGENICITY

Immunological correlates of protection against cholera after oral vaccination have not been identified. There is a poor correlation between serum antibody responses and protection. IgA antibodies produced in the intestine probably mediate protective immunity.

Cholera and travellers' diarrhea vaccine induces intestinal IgA responses in 70% to 100% of vaccinated subjects and serum antibodies have also been detected. A booster dose elicits an anamnestic response indicative of an immune memory. The duration of the immunological memory is estimated to be at least 2 years in adults.

RECOMMENDATIONS FOR USE

TRAVELLERS (2 years of age and older)

Vaccination with cholera and travellers' diarrhea vaccine is of limited benefit and is not routinely recommended for most travellers. For travellers, prevention of cholera or travellers' diarrhea relies primarily on care in the choice of food and water supply and in the use of good hygienic measures rather than on immunization. A detailed, travel-related risk assessment should be made to determine which travellers are most likely to benefit from vaccination.

Cholera and travellers' diarrhea vaccine is not recommended in children less than 2 years of age because efficacy has not been studied in this age group.

Cholera

Travellers to cholera-endemic countries who may be at significantly increased risk of exposure (e.g., humanitarian workers or health professionals working in endemic countries) may benefit from immunization with cholera and travellers' diarrhea vaccine. Most travellers following the usual tourist itineraries in countries affected by cholera are at extremely low risk of acquiring cholera infection.

Travellers should take all the necessary precautions to avoid contact with or ingestion of potentially contaminated food or water since not all recipients of cholera and travellers' diarrhea vaccine will be fully protected against cholera. This is particularly true for travellers to areas where the *V. cholerae* O139 is endemic.

No country or territory requires vaccination against cholera as a condition for entry.

Travellers' diarrhea

Cholera and travellers' diarrhea vaccine may be considered for prevention of travellers' diarrhea in the following short-term travellers, 2 years of age and older:

- Persons with chronic illnesses (e.g., chronic renal failure, congestive heart failure, insulin-dependent diabetes mellitus, inflammatory bowel disease) for whom there is an increased risk of serious consequences from travellers' diarrhea
- Persons at increased risk of acquiring travellers' diarrhea (e.g., children 2 to 5 years of age; people with gastric hypochlorhydria)
- Persons who are immunosuppressed because of human immunodeficiency virus (HIV) infection or other immunodeficiency states
- Persons with a history of repeated severe travellers' diarrhea

Indications for cholera and travellers' diarrhea vaccine to prevent travellers' diarrhea are limited because:

- Most episodes of travellers' diarrhea are mild and self-limited.
- Therapeutic options (oral rehydration, dietary management, anti-motility and antibiotic treatment) are available if prevention fails.
- The overall protection provided by cholera and travellers' diarrhea vaccine against travellers' diarrhea is expected to be approximately 25%.
- Vaccinated travellers may have a false sense of security and may not be as strict in observing food and water precautions.

Refer to *Booster doses and re-immunization* and *Schedule*.

PREGNANCY AND BREASTFEEDING

Cholera and travellers' diarrhea vaccine has not been studied in pregnant or lactating women. Administration of this vaccine to pregnant women may be considered in high-risk situations only (e.g., outbreak) after evaluation of the benefits and risks. This vaccine may be given to lactating women. Refer to *Immunization in Pregnancy and Breastfeeding* in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

Immunocompromised persons, included HIV-infected persons, may be immunized with cholera and travellers' diarrhea vaccine; however, the antibody response may be suboptimal. Refer to *Immunization of Immunocompromised Persons* in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Cholera and travellers' diarrhea vaccine consists of a single-dose vial of vaccine and a sachet of sodium hydrogen carbonate effervescent buffer granules. Prepare the buffer solution and vaccine in accordance with the instructions in the manufacturer's product leaflet.

Route of administration

Cholera and travellers' diarrhea vaccine is for oral administration only. It can be self-administered. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Table 1 summarizes the schedule for cholera or ETEC travellers' diarrhea immunization, by age.

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Table 1: Immunization Schedule for cholera and travellers' diarrhea and cholera vaccine, by indication and age

	Cholera		ETEC Travellers' Diarrhea	General Instructions
	2 to 5 years of age	6 years of age and older	2 years of age and older	
Primary Immunization	3 doses orally, 1-6 weeks apart	2 doses orally, 1-6 weeks apart	2 doses orally, 1-6 weeks apart	If more than 6 weeks elapses between doses, re-peat primary series Give final dose at least 1 week before departure
Booster	1 dose every 6 months	1 dose every 2 years	1 dose every 3 months	If more than 5 years have passed since primary immunization or last booster dose, repeat primary series.

BOOSTER DOSES AND RE-IMMUNIZATION

Cholera

An optimal booster dose or interval has not been established; however, if indicated based on ongoing risk:

- For children 2 to 5 years of age - a booster dose is recommended every 6 months
- For people 6 years of age and older - a booster dose is recommended every 2 years; a complete primary series (2 doses) is recommended if the last dose was received more than 5 years previously.

ETEC travellers' diarrhea

Cholera and travellers' diarrhea vaccine provides short-term protection (approximately 3 months) against ETEC diarrhea; therefore, if the traveller will be at ongoing risk, booster doses should be considered. An optimal booster dose or interval has not been established; however, if there is an ongoing risk:

- For people 2 years of age and older - a booster dose is recommended every 3 months.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving cholera and travellers' diarrhea vaccine.

STORAGE REQUIREMENTS

Store cholera and travellers' diarrhea vaccine in a refrigerator at +2°C to +8°C. Do not freeze. The vaccine can be stored at room temperature (less than +27°C) for up to 2 weeks on one occasion only. The buffer sachet may be stored at room temperature. If the vaccine and buffer mixture is not used immediately, it can be stored at room temperature (less than +27°C) for up to 2 hours. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

The administration of cholera and travellers' diarrhea vaccine and oral typhoid vaccine capsules should be separated by at least 8 hours. Oral administration of other vaccines should be avoided 1 hour before and 1 hour after vaccination with cholera and travellers' diarrhea. There are limited data, but there is no known interaction between cholera and travellers' diarrhea vaccine and other commonly used travel vaccines, such as hepatitis A, hepatitis B, meningococcal and yellow fever vaccines. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

In a clinical trial, the most commonly reported adverse events following immunization with cholera and travellers' diarrhea vaccine were: abdominal pain (16%), diarrhea (12%), nausea (4%) and vomiting (3%). These events are most likely due to the bicarbonate buffer used with the vaccine since they occurred with similar frequency when vaccine and buffer or buffer alone were given.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Anaphylaxis following vaccination with cholera and travellers' diarrhea vaccine may occur but is very rare.

Globally over 7 million vaccine doses have been distributed. Events such as paraesthesia, dyspnea, urticaria, pruritus, angioedema, gastroenteritis, lymphadenitis, flu-like syndrome and hypertension have been reported very rarely (less than 1 per 10,000 doses distributed), and no causal relation has been established.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report, through local public health officials, any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php) and Vaccine Safety in Part 2 for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS

Cholera and travellers' diarrhea vaccine is contraindicated in persons with history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer to Table 1 in Contents of Immunizing Agents Available for Use in Canada in Part 1 for lists of all vaccines available for use in Canada and their contents.

Administration of Cholera and travellers' diarrhea vaccine should be postponed in persons with moderate or severe acute illness or acute gastrointestinal illness. Persons with minor acute illness (with or without fever) may be vaccinated.

Refer to General Contraindications and Precautions in Part 2 for additional general information.

DRUG-DRUG AND DRUG-FOOD INTERACTIONS

Avoid oral administration of medicinal products or intake of food and/or drink for 1 hour before and 1 hour after Cholera and travellers' diarrhea vaccine administration. Food and/or drink may increase acid production in the stomach and impair the effect of the vaccine.

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PART 4

DIPHTHERIA TOXOID

KEY INFORMATION (refer to text for details)

What	• Diphtheria is rare in Canada. It occurs worldwide and is endemic in many developing countries. • Case-fatality rate is about 5% to 10%; highest death rates occur in the very young and the elderly, and in non-endemic countries because diagnosis is often late. • Diphtheria toxoid-containing vaccines are only available as a combination vaccine. • Diphtheria toxoid-containing vaccines may be used for diphtheria post-exposure immunization in non-immune persons. • Diphtheria antitoxin for treatment of diphtheria is available on an emergency basis through local public health officials. • After a complete primary series (at least 3 doses) more than 97% of vaccinees develop antibody concentrations that are protective against diphtheria. • Redness, swelling and pain at the injection site are the most common adverse reactions to diphtheria toxoid-containing vaccines.
Who	• Diphtheria toxoid-containing vaccine is recommended for: o routine immunization of infants and children o immunization of children who missed diphtheria immunization on the routine schedule o immunization of previously unvaccinated or incompletely vaccinated adults o routine booster immunization of adolescents and adults
How	• **Routine diphtheria immunization of infants and children:** administer DTaP-IPV-Hib* vaccine at 2, 4, 6 and 12 to 23 months of age (generally given at 18 months of age). If infant immunization for hepatitis B is undertaken, DTaP-HB-IPV-Hib* vaccine may be used. Subsequently administer a booster dose of either DTaP-IPV* or Tdap-IPV* vaccine at 4 to 6 years of age (school entry) and a booster dose of Tdap* vaccine 10 years later at 14 to 16 years of age. • **Adults previously immunized with diphtheria-toxoid containing vaccine:** administer one dose of Tdap vaccine if not previously received in adulthood (18 years of age and older) and give a booster dose of Td* vaccine every 10 years. • Diphtheria toxoid-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes.

Why	• Diphtheria occurs worldwide and is endemic in many developing countries. • Inadequately or unimmunized travellers to areas with endemic diphtheria are at higher risk of acquiring disease. • Occasional cases of imported diphtheria are identified in developed countries, like Canada. • Death occurs in 5% to 10% of diphtheria cases.

* Refer to *Diphtheria toxoid-containing vaccines* for complete vaccine description.

Since the publication of the *2006 Canadian Immunization Guide*:

- A new combination vaccine containing tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) has become available.
- Two new combination vaccines containing tetanus toxoid, reduced diphtheria toxoid, reduced acellular pertussis and inactivated poliomyelitis vaccine (Tdap-IPV) have become available.
- A new combination vaccine containing diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine (DTaP-HB-IPV-Hib) has become available for primary immunization of infants and young children.
- The combination vaccine containing diphtheria and tetanus toxoids, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine (DTaP-IPV-Hib) has become available in a pre-mixed format.

For additional information, refer to the National Advisory Committee on Immunization (NACI) Statement on the recommended use of pentavalent and hexavalent vaccines. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-01/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Diphtheria is caused by exotoxin-producing strains of the bacterium *Corynebacterium diphtheriae*.

Reservoir

Humans

Transmission

Diphtheria is transmitted by person-to-person spread from the respiratory tract or, rarely, by contact with articles soiled with excretions of infected persons. The incubation period is about 2 to 5 days (range, 1 to 10 days). The infectious period in untreated persons is usually 2 weeks or less and, rarely, more than 4 weeks. Chronic carriers are asymptomatically colonized with *C. diphtheriae* on the skin or in the nasopharynx and may shed organisms for 6 months or more.

Risk factors

Inadequately or unimmunized travellers to areas with endemic diphtheria are at higher risk of acquiring disease. A list of countries where diphtheria is endemic is available from the United States Centers for Disease Control and Prevention (CDC) (http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/diphtheria.htm) or the current version of the CDC's Health Information for International Travel Yellow Book. (http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm)

Seasonal/temporal pattern

Diphtheria occurs most frequently in winter and spring months in temperate climates.

Spectrum of clinical illness

Respiratory diphtheria affects the mucous membrane of the upper respiratory tract. Symptoms include a mild fever, sore throat, difficulty swallowing, malaise and loss of appetite. It can progress to acute respiratory distress, upper airway obstruction and asphyxia in young children. An adherent, asymmetrical, grayish white membrane visible on the tonsils and oropharynx typically appears within 2 to 3 days of illness. Dissemination of diphtheria toxin can result in systemic complications such as myocarditis and central nervous system effects. The case-fatality rate is about 5% to 10%; the highest rates occur among the unvaccinated very young, and elderly, and in non-endemic countries because diagnosis is often late. Localized infection of the skin (cutaneous diphtheria) may occur but is rarely associated with systemic complications.

DISEASE DISTRIBUTION

Incidence/prevalence

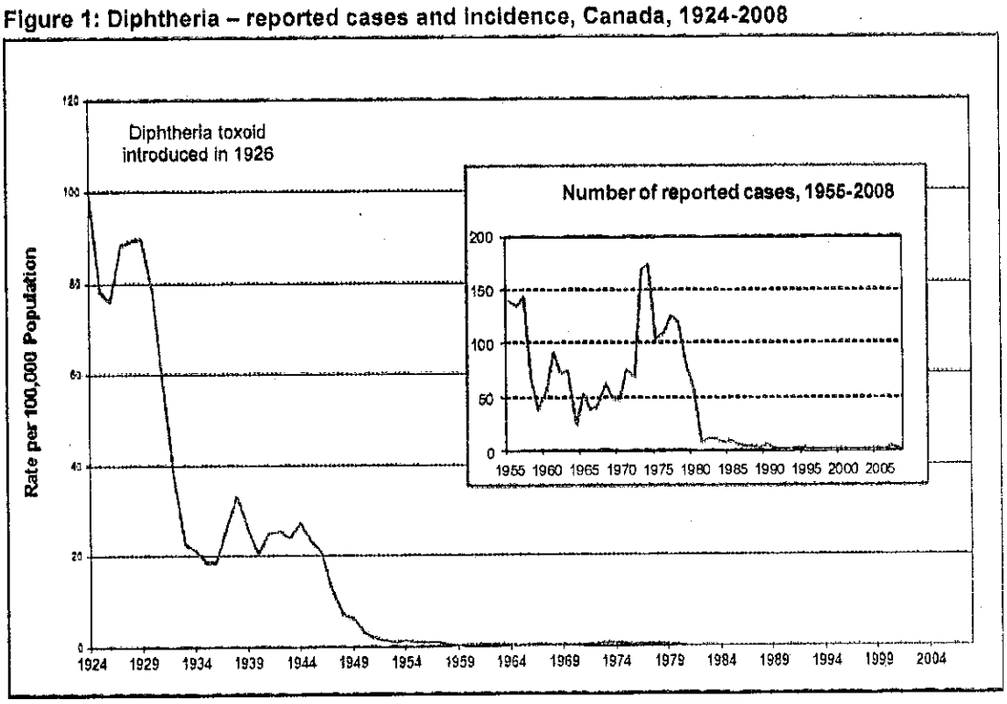
Global

Diphtheria occurs worldwide and is endemic in many developing countries as well as in Albania, Russia and other countries of the former Soviet Union. In other countries, occasional cases of imported diphtheria are identified. Resurgence of diphtheria has been reported in countries with low vaccine coverage. A total of 4,187 cases of diphtheria were reported to the World Health Organization (WHO) in 2010.

National

Routine infant and childhood diphtheria immunization has resulted in a dramatic decline in reported cases of diphtheria (refer to *Figure 1*). A small number of toxigenic strains of diphtheria bacilli are detected each year (0 to 5 isolates), although classic diphtheria is rare. Serosurveys of healthy adult populations in Canada indicate that approximately 20% (higher in some age groups) do not have protective concentrations of antibody to diphtheria; adult booster doses are required.

Figure 1: Diphtheria – reported cases and incidence, Canada, 1924-2008



Population data sources: Statistics Canada, Population by Sex and Age, 1921-1971, revised annual estimates of population, Canada and the provinces, (Catalogue 91-512)
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RECENT OUTBREAKS

The potential for re-emergence of diphtheria if immunization levels decline was demonstrated during the 1990s in the Commonwealth of Independent States (former Soviet Union) when over 140,000 cases and 4,000 deaths were reported.

PREPARATIONS AVAILABLE FOR USE IN CANADA

DIPHTHERIA TOXOID-CONTAINING VACCINES

- **ADACEL®** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine), sanofi pasteur Ltd. (Tdap).
- **ADACEL®-POLIO** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine combined with inactivated poliomyelitis vaccine), sanofi pasteur Ltd. (Tdap-IPV).
- **BOOSTRIX®** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine), GlaxoSmithKline Inc. (Tdap).
- **BOOSTRIX®-POLIO** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine combined with inactivated poliomyelitis vaccine), GlaxoSmithKline Inc. (Tdap-IPV).
- **INFANRIX hexa™** (adsorbed vaccine containing diphtheria and tetanus toxoids, acellular pertussis, hepatitis B (recombinant), inactivated poliomyelitis and conjugated *Haemophilus influenzae* type b vaccine), GlaxoSmithKline Inc. (DTaP-HB-IPV-Hib).
- **PEDIACEL®** (adsorbed vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine and *Haemophilus influenzae* type b

conjugate vaccine), sanofi pasteur Ltd. (DTaP-IPV-Hib).
- **QUADRACEL®** (adsorbed vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine), sanofi pasteur Ltd. (DTaP-IPV).
- **Td ADSORBED** (adsorbed vaccine containing tetanus and reduced diphtheria toxoids), sanofi pasteur Ltd. (Td).
- **Td POLIO ADSORBED** (adsorbed vaccine containing tetanus and reduced diphtheria toxoids and inactivated poliomyelitis vaccine), sanofi pasteur Ltd. (Td-IPV).

Diphtheria toxoid is only available as a combination vaccine. The amount of diphtheria toxoid present varies by product. Preparations containing higher concentrations of diphtheria toxoid (designated as "D") are administered for primary immunization of infants and young children less than 7 years of age (pediatric formulation). Preparations containing a lower concentration (designated as "d" and referred to as "reduced") may be administered as a booster dose to children 4 years to less than 7 years of age and are the recommended product for older children, adolescents and adults (adolescent/adult formulation).

DIPHTHERIA ANTITOXIN

- **ANTIDIPHTHERIA SERUM:** purified immunoglobulins obtained from the plasma of horses hyper-immunized with diphtheria toxoid, Instituto Butantan, (DAtx)

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Table 1 and Table 2 in Contents of Immunizing Agents Available for Use in Canada in Part 1 for lists of all vaccines and passive immunizing agents available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

Diphtheria toxoid protects against the systemic effects of diphtheria toxin but does not directly protect against infection. Carriage of *C. diphtheriae* can occur in immunized individuals, but the rate of carriage is lower in immunized populations. After a complete primary series, more than 97% of vaccinees develop antibody concentrations that are protective against diphtheria toxin. In studies assessing booster response, 100% of vaccinees had a protective antibody titre one month after the booster dose. Antitoxin is believed to persist at protective concentrations for 10 years or more.

RECOMMENDATIONS FOR USE

INFANTS AND CHILDREN (2 months to 17 years of age)

Diphtheria toxoid-containing vaccine is recommended for routine infant immunization beginning at 2 months of age. DTaP-IPV (with or without Hib) vaccine is authorized for use in children less than 7 years of age. DTaP-HB-IPV-Hib vaccine is authorized for use in children 6 weeks to 23 months of age and may be given to children aged 24 months to less than 7 years, if necessary. DTaP-IPV or Tdap-IPV vaccine should be used as the booster dose for children at 4 to 6 years of age. Children 7 years of age and older should receive the adolescent/adult formulation of diphtheria-tetanus-pertussis-containing vaccine with or without polio (Tdap or Tdap-IPV) as it contains less diphtheria toxoid than preparations given to younger children and is less likely to cause reactions in older children. Tdap vaccine should be administered to adolescents at 14 to 16 years of age as the first 10-year booster dose; Tdap-IPV vaccine should be used if IPV vaccine is also indicated.

ADULTS (18 years of age and older)

Adults who have not previously received a primary series (at least 3 doses) of diphtheria toxoid-containing vaccine should receive one dose of Tdap-IPV vaccine followed by two doses of Td-IPV vaccine. There is new evidence that a booster dose of Td vaccine may not be required every 10 years. Pending review, a booster dose of Td vaccine is recommended every 10 years.

Refer to Schedule and Booster doses and re-immunization. Refer to Tetanus Toxoid, Pertussis Vaccine, Poliomyelitis Vaccine, Haemophilus influenzae type b Vaccine and Hepatitis B Vaccine in Part 4 for additional information.

PERSONS WITH INADEQUATE IMMUNIZATION RECORDS

Children and adults lacking adequate documentation of immunization should be considered unimmunized and started on an immunization schedule appropriate for their age and risk factors. When available, serologic testing for diphtheria and tetanus antitoxin concentrations may guide the need for continued immunization. Refer to Immunization of Children and Adults with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

Susceptible pregnant women may receive Td vaccine if indicated. There is no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with Td vaccine. The use of Tdap vaccine during pregnancy is currently under review. Refer to Pertussis Vaccine in Part 4 for additional information. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

INFANTS BORN PREMATURELY

Premature infants in stable clinical condition should be immunized with a diphtheria toxoid-containing vaccine at the same chronological age and according to the same schedule as full-term infants. Infants born prematurely (especially those weighing less than 1,500 grams at birth) are at higher risk of apnea and bradycardia following vaccination. Hospitalized premature infants should have continuous cardiac and respiratory monitoring for 48 hours after their first immunization. Refer to Immunization of Infants Born Prematurely in Part 3 for additional general information.

PATIENTS/RESIDENTS IN HEALTH CARE INSTITUTIONS

Residents of long-term care facilities should receive all routine immunizations appropriate for their age and risk factors, including diphtheria toxoid-containing vaccine. Refer to Immunization of Patients in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

Diphtheria-tetanus-pertussis-polio-Hib-containing vaccines may be administered to immunocompromised persons. When considering immunization of an immunocompromised person, consultation with the individual's attending physician may be of assistance in addition to the guidance provided below. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

Congenital (primary) immunodeficiency

Individuals with congenital immunodeficiencies involving any part of the immune system, including persons with partial T-lymphocyte defects (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia), may receive diphtheria-tetanus-pertussis-polio-Hib -containing vaccine if indicated.

Acquired (secondary) immunodeficiency

Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)

Post-transplantation

- All children (less than 7 years of age) should receive three doses of DTaP-IPV-Hib vaccine. Vaccination can be initiated at 6 to 12 months post-transplant and three doses are recommended separated by an interval of at least 4 weeks. Acceptable schedules include 6, 8, and 18 months or 12, 14 and 24 months after transplantation.

- Persons 7 to 17 years of age should receive three doses of Tdap-IPV vaccine. Persons 18 years of age and older should receive one dose of Tdap-IPV vaccine followed by two doses of Td-IPV vaccine after transplantation. Three doses of Hib vaccine are also recommended. Vaccination can be initiated at 6 to 12 months post-transplant and three doses are recommended separated by an interval of at least 4 weeks. Acceptable schedules include 6, 8, and 18 months or 12, 14 and 24 months after transplantation.

Solid organ transplantation

- Children (less than 7 years of age) should receive diphtheria-tetanus-pertussis-polio-Hib-containing vaccine before or after transplantation to complete the routine immunization schedule. If immunization needs to continue after transplant, it should be resumed at 3 to 6 months post-transplant when immunosuppression has been reduced to maintenance levels.
- Persons 7 years of age and older should receive required tetanus-diphtheria-pertussis-polio containing vaccines at least 2 weeks before or 3 to 6 months after transplantation to complete the routine immunization schedule

Immunosuppressive therapy

Vaccination status for diphtheria, tetanus, pertussis, polio, and Hib should be reviewed for immunocompetent persons who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency. Although diphtheria-tetanus-pertussis-polio-Hib-containing vaccine can safely be given at any time before, during or after immunosuppression, all attempts should be made to time vaccination so that optimal immunogenicity is achieved.

If indicated, diphtheria-tetanus-pertussis-polio-Hib-containing vaccines as appropriate for age should be administered at least 14 days before the initiation of immunosuppressive therapy (e.g., high-dose systemic corticosteroids [2 mg/kg per day or 20 mg/day or more of prednisone or its equivalent] for 14 days or more; chemotherapy; radiation therapy; azathioprine; cyclosporine; cyclophosphamide; infliximab). If this cannot be done, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of diphtheria-tetanus-pertussis-polio-Hib-containing vaccines to ensure immunogenicity. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and administration of diphtheria-tetanus-pertussis-polio-Hib-containing vaccines. The interval between discontinuation of immunosuppressive drugs and diphtheria-tetanus-pertussis-polio-Hib-containing preparations may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.

If immunosuppressive therapy cannot be stopped or reduced, diphtheria-tetanus-pertussis-polio-Hib-containing vaccine should be given when the person is least immunosuppressed, unless it is urgently needed (such as based on exposure risk to circulating diseases or for a tetanus booster post-exposure).

Refer to Haemophilus influenza type b Vaccine in Part 4 for additional information. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Neurologic disorders

People with neurological disorders with onset preceding immunization should receive all routinely recommended immunizations. Refer to Tetanus Toxoid and Pertussis Vaccine in Part 4 for information regarding other components in diphtheria toxoid-containing combination vaccines. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional general information.

TRAVELLERS

Unimmunized or incompletely immunized travellers should receive diphtheria-tetanus-pertussis-polio-Hib-containing vaccine as appropriate for age. For infants embarking on travel, the first dose of DTaP-IPV-Hib or DTaP-HB-IPV-Hib vaccine can be given at 6 weeks of age (refer to Schedule). Previously immunized adult travellers should receive a booster dose of a tetanus-diphtheria toxoid-containing preparation every 10 years. For adults who have not previously received a dose of acellular pertussis vaccine in adulthood, it is recommended that the Td vaccine booster dose be replaced by Tdap vaccine. Some travellers may also need a polio booster. Refer to Poliomyelitis Vaccine in Part 4 for additional information. Refer to Immunization of Travellers in Part 3 for additional general information.

PERSONS NEW TO CANADA

Health care providers who see people newly arrived in Canada should review the immunization status and update immunization for these individuals. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS

All health care workers should be immune to diphtheria and receive a booster dose of Td vaccine every 10 years as recommended for all adults. All health care and child care workers, regardless of age, should receive a single dose of Tdap vaccine for pertussis protection if not previously received in adulthood, even if not due for a tetanus and diphtheria booster. Refer to Immunization of Workers in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION

Diphtheria toxoid-containing vaccine

Close contacts (e.g., household, classroom) of a diphtheria case should receive a dose of a diphtheria toxoid-containing vaccine as appropriate for age unless the contact is known to have been fully immunized and the last dose of diphtheria toxoid-containing vaccine was given within 10 years. The diphtheria toxoid-containing vaccine series should be completed for previously unimmunized or incompletely immunized contacts.

Diphtheria antitoxin (equine)

Prophylaxis of diphtheria

Diphtheria antitoxin is not recommended for prophylaxis of immunized or unimmunized close contacts of diphtheria cases, given the substantial risk of allergic reaction to equine serum and lack of evidence of additional benefit of antitoxin for contacts who have received antimicrobial prophylaxis.

Treatment of diphtheria

Diphtheria antitoxin for treatment of diphtheria disease is available on an emergency basis through local public health officials. Antitoxin should be administered when there is clinical suspicion of diphtheria, before bacteriologic confirmation. The method of testing for sensitivity to equine serum, as well as the dose and route of administration, are indicated in the manufacturer's product leaflet. If sensitivity tests are positive, desensitization must be undertaken according to the manufacturer's recommendations. Intramuscular administration usually suffices, but intravenous administration may be necessary in some cases.

Persons who have recovered from diphtheria should receive diphtheria toxoid-containing vaccine as recommended for people who have not had the disease. Because symptoms of diphtheria are largely mediated through toxins produced by the diphtheria bacterium and not the bacterium itself, recovery from diphtheria disease does not necessarily confer immunity.

Refer to Vaccine and Antitoxin Safety and Adverse Events for safety information.

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-fra.php)

Refer to Passive Immunizing Agents Part 5 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose of diphtheria toxoid-containing vaccine is 0.5 mL.

Route of administration

Diphtheria toxoid-containing vaccines must be administered intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Infants and children (2 months to 6 years of age)

Routine diphtheria immunization of infants: DTaP-IPV-Hib vaccine should be given at 2, 4, 6 and 12 to 23 months of age (generally given at 18 months of age).

If infant immunization for hepatitis B is undertaken, DTaP-HB-IPV-Hib vaccine may be used as an alternative to separately administered hepatitis B and DTaP-IPV-Hib vaccines. DTaP-HB-IPV-Hib vaccine is authorized for use in children 6 weeks to 23 months of age and may be given to children aged 24 months to less than 7 years, if necessary. DTaP-HB-IPV-Hib vaccine may be given at 2, 4, 6 and 12 to 23 months of age but the fourth dose is unlikely to provide significant additional hepatitis B protection and will increase cost. Alternative schedules may be used as follow:

- DTaP-HB-IPV-Hib vaccine (2, 4 and 6 months of age) with DTaP-IPV-Hib vaccine at 12 to 23 months of age
- DTaP-HB-IPV-Hib vaccine (2, 4 and 12 to 23 months of age) with DTaP-IPV-Hib vaccine at 6 months of age.

If rapid protection is required for an infant, the first dose of DTaP-IPV-Hib or DTaP-HB-IPV-Hib vaccine can be given at 6 weeks of age. The first three doses may be administered at intervals of 4 weeks and, optimally, the fourth dose given 12 months after the third dose. The fourth dose may be given at a minimum interval of 6 months after the third dose in certain situations (e.g., travel) but must be administered at or after 12 months of age for sustained immunity.

Children less than 7 years of age not immunized in infancy: should receive three doses of DTaP-IPV (with or without Hib) vaccine with an interval of 8 weeks between doses, followed by a dose of DTaP-IPV vaccine 6 to 12 months after the third dose. A booster dose of either DTaP-IPV or Tdap-IPV vaccine should be administered at 4 to 6 years of age (school entry). The booster dose at 4 to 6 years of age is not required if the fourth dose of tetanus-toxoid containing vaccine was administered after the fourth birthday.

If rapid protection is required for a child less than 7 years of age not immunized in infancy, the first three doses of vaccine may be administered at intervals of 4 weeks and, optimally, the fourth dose given 12 months after the third dose. The fourth dose may be given at a minimum interval of 6 months after the third dose in certain situations (e.g., travel).

Children who received a primary series of a diphtheria toxoid-containing vaccine and a booster dose 6-12 months later as outlined above should receive a booster dose of either DTaP-IPV or Tdap-IPV vaccine at 4 to 6 years of age (school entry); and, 10 years later, a booster dose of Tdap vaccine at 14 to 16 years of age. The booster dose at 4 to 6 years of age is not required if the fourth dose of diphtheria toxoid-containing vaccine was administered after the fourth birthday.

Children and adolescents (7 years to 17 years of age)

Children 7 years of age and older not previously immunized should receive three doses of Tdap-IPV vaccine with an interval of 8 weeks between the first two doses followed by a third dose administered 6 to 12 months after the second dose. A booster dose of Tdap vaccine should be administered 10 years after the last dose.

Adults (18 years of age and older)

Adults who have not previously received a primary series (at least 3 doses) of diphtheria toxoid-containing vaccine should receive one dose of Tdap-IPV vaccine and two doses of Td-IPV vaccine. The dose of Tdap-IPV vaccine should be given first, followed 8 weeks later by a dose of Td-IPV vaccine. The second dose of Td-IPV vaccine should be given 6 to 12 months after the previous dose of Td-IPV vaccine.

BOOSTER DOSES AND RE-IMMUNIZATION

There is new evidence that booster doses of Td vaccine may not be required every 10 years. Pending review, booster doses of Td vaccine are recommended every 10 years. Adults who have not received an adult dose of pertussis-containing vaccine should receive one dose of Tdap vaccine which can be administered regardless of the interval since the last dose of tetanus and diphtheria toxoid-containing vaccine. Refer to Schedule.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving diphtheria toxoid-containing vaccine.

STORAGE REQUIREMENTS

Store diphtheria toxoid-containing preparations in a refrigerator at +2°C to +8°C and do not freeze. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Diphtheria toxoid-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE AND ANTITOXIN SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety in Part 2 for additional general information. Refer to Tetanus Toxoid, Pertussis Vaccine, Poliomyelitis Vaccine, Haemophilus influenzae type b Vaccine and Hepatitis B Vaccine in Part 4 for additional information regarding other components in diphtheria toxoid-containing combination vaccines.

COMMON AND LOCAL ADVERSE EVENTS

Diphtheria-toxoid containing vaccines

Redness, swelling and pain at the injection site are the most common adverse reactions to childhood diphtheria toxoid-containing combination vaccines. A nodule may be palpable at the injection site and persist for several weeks. Abscess at the injection site has been reported.

In clinical trials, injection site adverse reactions, including tenderness, erythema, and/or swelling were reported in 10% to 40% of children after each of the first 3 doses of diphtheria-toxoid containing vaccine. Mild systemic reactions such as fever, irritability and/or fussiness were commonly reported (8% to 29%), as well as drowsiness (40% to 52%).

In two clinical studies, swelling (greater than 5 cm) and erythema were reported in 15% to 20% of vaccinees after the fourth or fifth doses of DTaP vaccines. Extensive limb swelling (greater than 10 cm in diameter) possibly involving the entire proximal limb may occur in 2% to 6% of children. While these injection site reactions produce significant swelling, pain is generally limited. There is some evidence that children with extensive limb swelling following the fourth dose of a DTaP vaccine are at increased risk of such an event following the fifth dose. The presence of a large injection site reaction to a previous dose is not a contraindication to continuing the recommended schedule.

Among adults given a booster dose of Tdap vaccine, very common reactions include pain, redness and swelling at the injection site, headache, and fatigue. Fever and chills are common reactions. Adverse reactions following Td vaccine are similar. Overall, adverse reactions are less common in adults than adolescents. The interval between the childhood DTaP vaccine series or a dose of Td vaccine, and a dose of Tdap vaccine does not affect the rate of injection site or systemic adverse events.

DAtx

Diphtheria antitoxin may trigger allergic reactions of varying severity. The most commonly reported reactions are: skin pruritus/pain/swelling/redness; urticaria; dry cough/hoarseness; nausea/vomiting; or asthma-like crisis. The frequency varies and the reactions occur within the first 24 hours after administration of DAtx. Persons previously treated with serum of equine origin may have a higher risk of reaction.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Diphtheria-toxoid containing vaccines

Serious adverse events are rare following immunization with diphtheria toxoid-containing vaccines and, in most cases, data are insufficient to determine a causal association. Severe systemic reactions such as generalized urticaria, anaphylaxis, or neurologic complications have been reported rarely.

Severe (arthus-type) injection site reactions are occasionally reported following receipt of diphtheria toxoid or tetanus toxoid-containing vaccines. There may be extensive painful swelling around the injection site, often involving the arm from shoulder to elbow and generally beginning 2 to 8 hours after injection. Such reactions are most often reported in adults, particularly those who have received frequent doses of diphtheria and/or tetanus toxoid. Persons experiencing severe injection site reactions usually have very high serum antitoxin concentrations and should not receive further routine booster doses of Td vaccine for at least 10 years.

DAtx

Severe reactions are uncommon. Fatal anaphylactic shock has been reported in 1:50,000 persons receiving DAtx. Serum sickness (fever, urticaria, arthralgia, adenomegaly and, more rarely, neurological or renal compromise) may occur between 5 and 24 days after the administration DAtx in approximately 8%.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Cases of Guillain-Barre Syndrome (GBS) or polyneuritis have been reported following receipt of diphtheria toxoid-containing vaccine. While the evidence favours a causal relationship between tetanus toxoid and GBS, there is little evidence to support an independent association between receipt of diphtheria toxoid and GBS.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report, through local public health officials, any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization or a change in the frequency of a known AEFI. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada in Vaccine Safety Part 2 for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

Diphtheria toxoid-containing vaccines are contraindicated in persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer to Table 1 and Table 2 in Contents of Immunizing Agents Available for Use in Canada in Part 1 for lists of all vaccines and passive immunizing agents available for use in Canada and their contents. For the diphtheria toxoid-containing vaccines, potential allergens include:

- ADACEL®-POLIO: neomycin, polymyxin B, streptomycin
- BOOSTRIX®: latex in plunger stopper of pre-filled syringe
- BOOSTRIX®-POLIO: latex in plunger stopper of pre-filled syringe, neomycin, polymyxin B
- INFANRIX hexa™: latex in plunger stopper of pre-filled syringe, neomycin, polymyxin B, yeast
- PEDIACEL®: neomycin, polymyxin B, streptomycin
- QUADRACEL®: neomycin, polymyxin B
- Td POLIO ADSORBED: neomycin, polymyxin B

There are no currently known potential allergens in ADACEL® or Td ADSORBED vaccines.

Hypersensitivity to yeast is very rare and a personal history of yeast allergy is not generally reliable. In situations of suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.

Administration of diphtheria toxoid-containing vaccine should be postponed in persons with moderate or severe acute illness. Persons with minor acute illness (with or without fever) may be vaccinated.

It is prudent to not administer further doses of tetanus-toxoid containing vaccine to persons who develop GBS within 6 weeks of receiving such vaccine. Those who develop GBS outside the 6 week interval may receive subsequent doses of tetanus toxoid-containing vaccine. If there is a history of both *Campylobacter* infection (which has been associated with GBS) and receipt of a tetanus and diphtheria toxoid-containing vaccine within the 6 weeks before the onset of GBS, consultation with an infectious disease specialist is advised.

People who experience a severe injection site reaction following a dose of tetanus toxoid-containing vaccine should not be given another dose for at least 10 years.

Refer to General Contraindications and Precautions in Part 2 and Passive Immunization Part 5 (currently in development) for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

The primary series of three doses of diphtheria toxoid-containing vaccine should be completed with an appropriate vaccine from the same manufacturer whenever possible. However, if the original vaccine is unknown or unavailable, an alternative combination vaccine from a different manufacturer may be used to complete the primary series. On the basis of expert opinion, an appropriate product from any manufacturer can be used for all booster doses. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

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PART 4

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

KEY INFORMATION (refer to text for details)

What	• *Haemophilus influenzae* type b (Hib) occurs worldwide and is most prevalent in children aged 2 months to 2 years. • Hib can cause bacterial meningitis and other serious invasive infections in young children. • Receipt of a dose of Hib vaccine at or after 12 months of age is critical for sustained protection. Clinical efficacy of Hib vaccination has been estimated at 95% to 100%. • When the primary series is given and one dose is given at or after 12 months of age, more than 95% of infants develop protective antibody concentrations. • Injection site reactions, including pain, redness and swelling, occur in 5% to 30% of children immunized with Hib-containing vaccine.
Who	• Hib-containing vaccine is recommended for routine immunization of infants and children 2 to 59 months of age (up to the fifth birthday). • Hib vaccine is recommended for individuals (5 years of age and older) with: congenital (primary) immunodeficiency; malignant hematologic disorders; HIV; anatomic or functional asplenia (including sickle cell disease); all transplant recipients; and cochlear implant recipients.
How	• **Routine Hib immunization of infants:** administer DTaP-IPV-Hib* vaccine at 2, 4, 6 and 12 to 23 months of age (generally given at 18 months of age). If infant immunization for hepatitis B is undertaken, DTaP-HB-IPV-Hib* vaccine may be used. • **Children beginning immunization after 2 months of age or with incomplete vaccination schedules:** assess the number of doses required to complete the series. The number of doses of Hib vaccine required varies by age at first dose. Hib-containing vaccine is not routinely recommended in healthy children after 59 months of age (fifth birthday). • **Children 5 years of age and older or adults with chronic conditions** with increased risk of invasive Hib disease: administer a single dose of Hib vaccine. • Hib-containing vaccines may be administered concomitantly with routine childhood vaccines at different injection sites using separate needles and syringes.

Why	• Hib causes meningitis and bacteremia. It also commonly causes otitis media and pneumonia. The case-fatality rate of Hib meningitis is about 5%. • Severe neurologic sequelae occur in 10% to 15% of survivors and deafness in 15% to 20%.

* Refer to *Haemophilus influenzae type b-containing vaccines* for complete vaccine description.

Since the publication of the *2006 Canadian Immunization Guide*:

- A new combination vaccine containing diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine (DTaP-HB-IPV-Hib) has become available for primary immunization of infants and young children.
- The combination vaccine containing diphtheria and tetanus toxoids, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine (DTaP-IPV-Hib) has become available in a pre-mixed format.

For additional information, refer to the National Advisory Committee on Immunization (NACI) *Statement on the recommended use of pentavalent and hexavalent vaccines*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-01/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Haemophilus influenzae is a gram-negative coccobacillus that is either encapsulated (typeable) or non-encapsulated (non-typeable). Encapsulated strains are divided into serotypes "a" through "f" (depending on the antigenic characteristics of their polysaccharide capsule) and are more likely to cause invasive disease while non-encapsulated strains generally cause milder infections. *Haemophilus influenzae* serotype b (Hib) is the most pathogenic and caused 95% of invasive disease prior to the introduction of vaccine programs.

Reservoir

Humans

Transmission

Hib is transmitted through the nasopharynx by contact with respiratory droplets or nasal or throat discharges of infected persons. The incubation period is unknown but is probably about 2 to 4 days. Infected persons can transmit disease as long as Hib bacteria are present, which may be for a prolonged period. Hib is non-communicable within 24 to 48 hours of starting effective antibiotics.

Risk factors

Historically, the risk of Hib meningitis was increased among children with splenic dysfunction (e.g., sickle cell disease, asplenia) or antibody deficiency, children attending group child care centres, Inuit children, and persons who had received a cochlear implant.

Spectrum of clinical illness

Before the introduction of Hib vaccines in 1988, Hib was the most common cause of bacterial meningitis and a leading cause of other serious invasive infections in young children. About 55% to 65% of affected children developed meningitis, the remainder suffering from epiglottitis, bacteremia, cellulitis, pneumonia or septic arthritis. Hib also commonly causes otitis media. The case-fatality rate of Hib meningitis was about 5%. Severe neurologic sequelae occurred in 10% to 15% of survivors and deafness in 15% to 20%.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

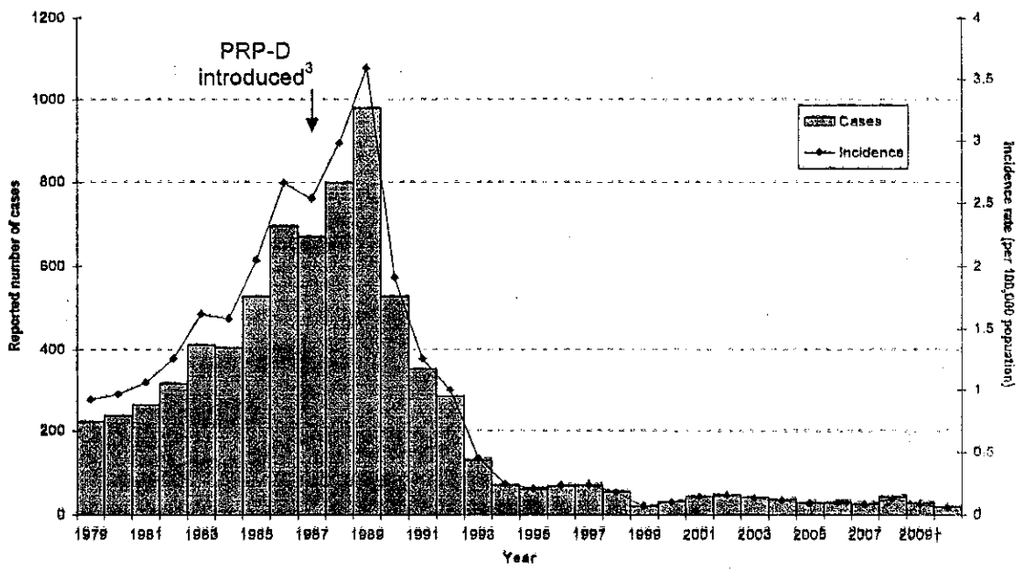
Hib infection occurs worldwide with a peak incidence in children less than 6 months of age in developing countries and between 6 and 12 months in industrialized countries. The World Health Organization (WHO) has estimated that Hib causes at least three million serious infections and 386,000 deaths per year, mainly due to meningitis and pneumonia.

National

As seen in *Figure 1*, since the introduction of Hib vaccines in Canada in 1988, the overall incidence of reported Hib disease has decreased by 94% from an average of 1.51 cases per 100,000 population during the period 1981 to 1985 (385 cases per year) to an average of 0.09 cases per 100,000 for the 2006 to 2010 period (31 cases per year). Between 2006 and 2010, average Hib incidence remained greatest among infants less than one year of age (2.08 cases per 100,000) and children aged one to four years (0.22 cases per 100,000). Between 2007 and 2009, only 17 Hib cases were reported in children less than 17 years of age by the Immunization Monitoring Program, ACTive (IMPACT) enhanced surveillance program, none of whom died of their infection. Most reported paediatric cases occurred in unimmunized children, children too young to have received their primary series, or those with either an immunodeficiency or other chronic illness.

Invasive disease due to non-type b *H. influenzae* became nationally notifiable in 2007. In 2010, Hib made up only 10% of nationally reported *H. influenzae* cases. The incidence of invasive non-type b *H. influenzae* disease was 0.51 cases per 100,000 population (177 cases), with the highest incidence among infants less than one year old (3.15) followed by children one to four years old (1.60) and adults 60 years of age and older (1.22). Similarly, between 2000 and 2010, 132 invasive *H. influenzae* cases in northern Canada were reported to the International Circumpolar Surveillance system (ICS). Of these, only 19 (14%) were *H. influenzae* type b.

Figure 1: *Haemophilus influenzae* type b disease – reported number of cases[1] and incidence rates, Canada, 1979-2010[2]



[1] Case data obtained from the Canadian Notifiable Disease Surveillance System. Population data obtained from Statistics Canada July 1st annual estimates. Data for 2009 and 2010 are preliminary.
[2] Only Hib meningitis was reportable from 1979 to 1985. After this, all invasive disease caused by Hib became reportable.
[3] PRP-D: Hib conjugate vaccine containing purified polyribosylribitol phosphate capsular polysaccharide of Hib covalently bound to diphtheria protein. The vaccine was licensed in 1986 and in 1988 introduced into the majority of provincial vaccination programs.

PREPARATIONS AVAILABLE FOR USE IN CANADA

HAEMOPHILUS INFLUENZAE TYPE B-CONTAINING VACCINES

- **Act-HIB®** (*Haemophilus influenzae* type b conjugate vaccine (tetanus protein conjugate)), Sanofi Pasteur SA (manufacturer), sanofi pasteur Ltd. (distributor). (Hib)
- **INFANRIX hexa™** (adsorbed vaccine containing diphtheria and tetanus toxoids, acellular pertussis, hepatitis B (recombinant), inactivated poliomyelitis and conjugated *Haemophilus influenzae* type b vaccine (tetanus toxoid conjugate)), GlaxoSmithKline Inc. (DTaP-HB-IPV-Hib)
- **PEDIACEL®** (adsorbed vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *Haemophilus influenzae* type b conjugate vaccine (tetanus protein conjugate)), sanofi pasteur Ltd. (DTaP-IPV-Hib)

The tetanus protein carriers used in Hib conjugate vaccines should not be considered immunizing agents against tetanus disease.

For complete prescribing information, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the *Drug Product Database*, (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Table 1 in Contents of Immunizing Agents Available in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

Clinical efficacy of Hib vaccination has been estimated at 95% to 100%. A significant component of protection of children arises because of herd immunity and so relies upon good vaccination coverage. The efficacy for persons with congenital or acquired immunodeficiency conditions is unknown. Hib vaccine failure occurs rarely and may be associated with immunodeficiency. Therefore, children who develop invasive Hib disease after completing a primary series should be evaluated for evidence of an immunodeficiency condition.

IMMUNOGENICITY

When the primary series is given and one dose is given at or after 12 months of age, more than 95% of infants develop protective antibody concentrations. Higher vaccine response rates (95% to 100%) were observed in studies with a 2, 4 and 6 month schedule as compared with compressed schedules of either 2, 3 and 4 months or 3, 4 and 5 months. The duration of immunity following completion of age-appropriate immunization is unknown but data suggest that protection is long lasting.

RECOMMENDATIONS FOR USE

INFANTS AND CHILDREN (2 months to 12 years of age)

Hib-containing vaccine is recommended for routine infant immunization beginning at 2 months of age. DTaP-IPV-Hib vaccine is authorized for use in children less than 7 years of age. DTaP-HB-IPV-Hib

vaccine is authorized for use in children 6 weeks to 23 months of age and may be given to children aged 24 months to less than 7 years, if necessary.

CHILDREN AND ADULTS (5 years of age and older)

Hib-containing vaccine is not routinely indicated in children 5 years of age and older.
Hib vaccination is recommended for individuals (5 years of age and older) with: congenital (primary) immunodeficiency; malignant hematologic disorders; HIV; anatomic or functional asplenia (including sickle cell disease); all transplant recipients; and cochlear implant recipients (refer to *Table 1*).
Consultation with an infectious disease expert is advised. Refer to *Immunocompromised Persons* and *Persons with chronic diseases* for additional information.

Table 1: Recommendations for Hib vaccination for persons 5 years of age and older[*1] with conditions with increased risk of invasive Hib disease

Condition	5 years of age and older, including ADULTS
Asplenia or hyposplenism (including sickle cell disease)	1 dose recommended regardless of Hib immunization history[*2]
Cochlear implant	1 dose recommended regardless of Hib immunization history[*2]
Congenital (primary) immunodeficiency	1 dose recommended regardless of Hib immunization history[*2]
HIV	1 dose recommended regardless of Hib immunization history[*2]
HSCT	*Post-HSCT:* 3 doses
Malignant hematologic disorders	1 dose recommended regardless of Hib immunization history[*2]
Solid organ transplant	*Pre-transplant:* 1 dose recommended regardless of Hib immunization history[*2] *Post-transplant:* • *If vaccinated pre-transplant:* Hib vaccine not needed • *If not vaccinated pre-transplant:* 1 dose recommended

[*1] Follow the routine, age-appropriate vaccination schedule for children less than 5 years old except for post-HSCT. HSCT recipients should receive 3 doses of Hib-containing vaccine regardless of prior Hib immunization.
[*2] At least one year after any previous dose

Hib infection does not always confer immunity. Persons who have recovered from Hib should be immunized as appropriate for age and risk factors.

Refer to *Schedule*. Refer to *Diphtheria Toxoid*, *Tetanus Toxoid*, *Pertussis Vaccine*, *Poliomyelitis Vaccine*, and *Hepatitis B Vaccine* in Part 4 for additional information.

PERSONS WITH INADEQUATE IMMUNIZATION RECORDS

Children and adults lacking adequate documentation of immunization should be considered unimmunized and started on an immunization schedule appropriate for their age and risk factors. Hib vaccine can be given, if indicated, without concern about prior receipt of the vaccine because adverse events associated with repeated immunization with the vaccine have not been demonstrated. Refer to Immunization of Children and Adults with Inadequate Immunization Records in Part 3 for additional general information.

INFANTS BORN PREMATURELY

Premature infants in stable clinical condition should be immunized with a Hib-containing vaccine at the same chronological age and according to the same schedule as full-term infants. Infants born prematurely (especially those weighing less than 1,500 grams at birth) are at higher risk of apnea and bradycardia following vaccination. Hospitalized premature infants should have continuous cardiac and respiratory monitoring for 48 hours after their first immunization. Refer to Immunization of Infants Born Prematurely in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

Diphtheria-tetanus-pertussis-polio-Hib-containing vaccines may be administered to immunocompromised persons. Immunocompromised children under 5 years of age should receive Hib-containing vaccine according to routine vaccination schedules. Some immunocompromised individuals 5 years of age and older should receive Hib-containing vaccine regardless of prior history of Hib vaccination, and at least 1 year after any previous dose, because of increased susceptibility to invasive Hib disease. Refer to *Table 1*.

When considering immunization of an immunocompromised person, consultation with the individual's attending physician may be of assistance in addition to the guidance provided below. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

Congenital (primary) immunodeficiency

Children with congenital immunodeficiencies involving any part of the immune system, including persons with partial T-lymphocyte defects (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia) should receive Hib-containing vaccine according to routine vaccination schedules unless otherwise advised by an immunologist. Individuals (5 years of age and older) should receive one dose of Hib-containing vaccine regardless of prior history of Hib vaccination, and at least 1 year after any previous dose.

Acquired (secondary) immunodeficiency

Malignant hematologic disorders (e.g., leukemia, lymphomas or other malignant neoplasms affecting the bone marrow or lymphatic systems)

Children with malignant hematologic disorders should receive Hib-containing vaccine according to routine vaccination schedules. Individuals (5 years of age and older) should receive one dose of Hib vaccine regardless of prior history of Hib vaccination, and at least 1 year after any previous dose.

Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)

Post-transplantation

All individuals should receive a 3 dose series of Hib vaccine. Vaccination can be initiated at 6 to 12 months post-transplant and 3 doses are recommended separated by an interval of at least 4 weeks. Acceptable schedules include 6, 8 and 18 months or 12, 14 and 24 months after transplantation.

Solid organ transplantation

Hib immunization status should be reviewed for all solid organ transplant candidates. Vaccination should follow age-appropriate recommendations for children. For individuals 5 years of age and older who are transplant candidates, one dose of Hib vaccine should be administered regardless of prior history of Hib immunization, and at least 1 year after any previous dose. If not given prior to transplant, the vaccine can be given 3 to 6 months post-transplant.

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HIV-infected

HIV-infected children (less than 5 years of age) should receive an age appropriate primary series of Hib vaccine. HIV-infected individuals (5 years of age and older) should receive one dose of Hib vaccine regardless of prior history of Hib immunization, and at least 1 year after any previous dose. When possible, Hib vaccine should be given early in the course of HIV infection; however, there is no contraindication to the use of Hib-containing vaccines at any time.

Refer to *Diphtheria Toxoid* for additional information. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Hyposplenism or asplenia

Hyposplenic (such as sickle cell disease and hemoglobinopathies) or asplenic children less than 5 years of age should receive an age appropriate primary series of Hib-containing vaccine. Hyposplenic or asplenic persons (5 years of age and older) should receive one dose of Hib vaccine regardless of prior history of Hib immunization, and at least 1 year after any previous dose. When elective splenectomy is planned, all recommended vaccines should be given at least 2 weeks before surgery. In the case of an emergency splenectomy, vaccines should be given 2 weeks after surgery or before discharge (if the person might not return for vaccination after discharge).

Neurologic disorders

Refer to *Tetanus Toxoid* and *Pertussis Vaccine* in Part 4 for information regarding other components in Hib-containing combination vaccines.

Cochlear implants

People who have received a cochlear implant are at increased risk for meningitis and otitis media. Prior to surgery they should receive all-age appropriate vaccinations, including Hib-containing vaccine. Individuals (5 years of age and older) should receive one dose of Hib vaccine regardless of prior history of Hib vaccination, and at least 1 year after any previous dose.

Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional general information.

TRAVELLERS

Unimmunized or incompletely immunized travellers should receive diphtheria-tetanus-pertussis-polio-Hib-containing vaccine as appropriate for age. Refer to *Diphtheria Toxoid* and *Poliomyelitis Vaccine* in Part 4 for information regarding other components in Hib-containing combination vaccines. Refer to Immunization of Travellers in Part 3 for additional general information.

PERSONS NEW TO CANADA

Health care providers who see persons newly arrived in Canada should review the immunization status and update immunization for these individuals. Many countries do not have routine Hib immunization programs for infants. Review of Hib vaccination status is particularly important for persons identified as having sickle cell disease or genetic hemoglobinopathies, which may predispose to hyposplenia, as these persons are at risk of serious Hib infections (refer to *Hyposplenism or asplenia*). Information on vaccination schedules in other countries can be viewed through the WHO. (http://www.who.int/vaccines/GlobalSummary/Immunization/ScheduleSelect.cfm)

Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION

Chemoprophylaxis is not required for household contacts of cases of invasive Hib infection when the contacts have completed a vaccine series (refer to *Table 2*). When contacts less than 48 months of age are incompletely immunized, consultation with local public health officials is advised.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose of Hib-containing vaccine is 0.5 mL.

Route of administration

Hib-containing vaccines must be administered intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Infants and children (2 months to 4 years of age)

Routine Hib immunization of infants: DTaP-IPV-Hib vaccine should be given at 2, 4, 6 and 12 to 23 months of age (generally given at 18 months of age).

If infant immunization for hepatitis B is undertaken, DTaP-HB-IPV-Hib vaccine may be used as an alternative to separately administered hepatitis B and DTaP-IPV-Hib vaccines. DTaP-HB-IPV-Hib vaccine is authorized for use in children 6 weeks to 23 months of age and may be given to children aged 24 months to less than 7 years, if necessary, although Hib vaccine is generally not indicated in those 5 years of age and older. DTaP-HB-IPV-Hib vaccine may be given at 2, 4, 6 and 12 to 23 months of age but the fourth dose is unlikely to provide significant additional hepatitis B protection and will increase cost. Alternative schedules may be used as follow:

- DTaP-HB-IPV-Hib vaccine (2, 4 and 6 months of age) with DTaP-IPV-Hib vaccine at 12 to 23 months of age
- DTaP-HB-IPV-Hib vaccine (2, 4 and 12 to 23 months of age) with DTaP-IPV-Hib vaccine at 6 months of age.

If rapid protection is required for an infant, the first dose of DTaP-IPV-Hib or DTaP-HB-IPV-Hib vaccine can be given at 6 weeks of age. The first three doses may be administered at intervals of 4 weeks and, optimally, the fourth dose given 12 months after the third dose. The fourth dose may be given at a minimum interval of 6 months after the third dose in certain situations (e.g., travel) but must be administered at or after 12 months of age for sustained immunity.

Children beginning immunization after 2 months of age or with interrupted or incomplete vaccination schedules should be assessed to determine the number of doses of Hib vaccine required to complete the series. The number of doses of Hib vaccine required varies by age at first dose. Because Hib vaccine is given as part of a combination vaccine, the schedule for the other components in the combination vaccine may differ for children starting the vaccine series after 6 months of age, and additional doses may be required to complete the series. Refer to *Table 2*.

Table 2: Detailed vaccination schedule for *Haemophilus influenza* type b vaccines*[1], by age at first dose*[2]

Age at 1st dose of Hib* vaccine	Hib*[1] vaccine schedule
2 to 6 months	3 doses, 2 months apart*[3] AND 1 booster dose*[4]
7 to 11 months	2 doses, 2 months apart AND 1 booster dose*[4]
12 to 14 months	1 dose AND 1 booster dose*[4]
15 to 59 months*[2]	1 dose

*[1] Hib vaccine is given as a combination vaccine. For children starting the vaccine series after 6 months of age, the schedule for the other components in the combination vaccine may differ and additional doses may be required to complete the series. Refer to *Diphtheria Toxoid*, *Tetanus Toxoid*, *Pertussis Vaccine*, *Poliomyelitis Vaccine* and *Hepatitis B Vaccine* in Part 4.

*[2] Some people 5 years of age and older with conditions with increased risk of invasive Hib disease may receive Hib vaccine. Refer to *Table 1*, *Immunocompromised persons*, and *Persons with chronic diseases* for details.

*[3] If rapid protection is required for an infant, the first dose of DTaP-IPV-Hib or DTaP-HB-IPV-Hib vaccine can be given at 6 weeks of age. The first three doses may be administered at intervals of 4 weeks and, optimally, the fourth dose given 12 months after the third dose. The fourth dose may be given at a minimum interval of 6 months after the third dose in certain situations (e.g., travel) but must be administered at or after 12 months of age for sustained immunity.

*[4] The booster dose should be given at least 2 months after the previous dose and is administered at or after 12 months of age to provide sustained immunity.

Refer to *Diphtheria Toxoid*, *Tetanus Toxoid*, *Pertussis Vaccine*, *Poliomyelitis Vaccine*, and *Hepatitis B Vaccine* in Part 4 for additional information.

Children and adults (5 years of age and older)

Some older children and adults with certain chronic conditions with increased risk of invasive Hib disease should be immunized with Hib vaccine (refer to *Table 1*). Refer to *Immunocompromised persons* and *Persons with chronic diseases* for details.

BOOSTER DOSES AND RE-IMMUNIZATION

Refer to *Immunocompromised persons* and *Persons with chronic diseases* for information.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving Hib vaccine. There is no role for serological testing in determining immunity to Hib.

STORAGE REQUIREMENTS

Store Hib-containing vaccines in a refrigerator at +2°C to +8°C and do not freeze. Reconstituted Hib vaccine should be used immediately. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Hib-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety in Part 2 for additional general information. Refer to *Diphtheria Toxoid*, *Tetanus Toxoid*, *Pertussis Vaccine*, *Poliomyelitis Vaccine* and *Hepatitis B Vaccine* in Part 4 for additional information regarding other components in Hib-containing combination vaccines.

COMMON AND LOCAL ADVERSE EVENTS

Injection site reactions, including pain, redness and swelling, occur in 5% to 30% of children immunized with Hib vaccine. These symptoms are mild and usually resolve within 24 hours. Fever has been reported in some infants given Hib vaccine either alone or in combination with other vaccines.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Serious adverse events are rare following immunization with Hib-containing vaccines and, in most cases, data are insufficient to determine a causal association. A meta-analysis, which included 257,000 infants, reported no serious adverse events following vaccination with Hib vaccine. Anaphylaxis following vaccination with Hib-containing vaccine may occur but is very rare.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report, through local public health officials, any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization or a change in the frequency of a known. Refer to Reporting Adverse Events Following Immunization (AEFI) (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php) in Canada in Vaccine Safety Part 2 for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS

Hib-containing vaccines are contraindicated in persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer to Table 1 in Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents. For Hib-containing vaccines, potential allergens include:

- INFANRIX hexa™: latex in plunger stopper of pre-filled syringe, neomycin, polymyxin B, yeast
- PEDIACEL®: neomycin, polymyxin B, streptomycin
- Act-HIB®: tetanus toxoid carrier protein

Act-HIB® vaccine should not be given to a person who has had a confirmed anaphylactic reaction to tetanus toxoid vaccine.

Hypersensitivity to yeast is very rare and a personal history of yeast allergy is not generally reliable. In situations of suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation

is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.

Administration of Hib-containing vaccine should be postponed in persons with moderate or severe acute illness. Persons with minor acute illness (with or without fever) may be vaccinated.

Refer to General Contraindications and Precautions in Part 2 for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

The primary series of Hib-containing vaccine should be completed with an appropriate vaccine from the same manufacturer whenever possible. However, if the original vaccine is unknown or unavailable, an alternative combination vaccine from a different manufacturer may be used to complete the primary series. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

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