PART 4
TABLE OF CONTENTS

Bacille Calmette-Guérin (BCG) Vaccine
Cholera Vaccine
Diphtheria Toxoid
Haemophilus Vaccine
Hepatitis A Vaccine
Hepatitis B Vaccine
Herpes Zoster (shingles) Vaccine
Human Papillomavirus Vaccine
Influenza Vaccine
Japanese Encephalitis Vaccine
Measles Vaccine
Meningococcal Vaccine
Mumps Vaccine
Pertussis Vaccine
Pneumococcal Vaccine
Poliomyelitis Vaccine
Rabies Vaccine
Rotavirus Vaccine
Rubella Vaccine
Smallpox Vaccine
Tetanus Toxoid
Typhoid Vaccine
Varicella Vaccine
Yellow Fever Vaccine
PART 4

BACILLE CALMETTE-GUÉRIN (BCG) VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | ● Tuberculosis (TB) is transmitted by the airborne route and usually requires prolonged exposure for infection to occur.
|      | ● In Canada, TB occurs more commonly among Aboriginal people and foreign-born populations.
|      | ● Risk factors for the acquisition of TB include proximity to a person with infectious TB, particularly in crowded living conditions.
|      | ● Risk factors for progression to active TB include co-morbidities (such as HIV/AIDS, other immunodeficiencies, diabetes, silicosis), malnutrition, and smoking.
|      | ● Bacille Calmette-Guérin (BCG) vaccine efficacy is estimated to be about 51% in preventing any TB disease and up to 78% in protecting newborns from miliary (disseminated) or meningeal TB.
|      | ● Intradermal administration of BCG vaccine usually results in erythema and a papule or ulceration, followed by a scar at the immunization site.

| Who  | ● 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.
|      | ● In high risk communities, infants less than 2 months of age do not need to be tuberculin skin tested before administering BCG vaccine. For infants 2 to 6 months of age, an individual assessment of the risks and benefits of tuberculin skin testing prior to BCG vaccination is indicated. For infants over 6 months of age, administer BCG vaccine if the one-step tuberculin skin test (TST) is negative.
|      | ● Immunocompromised persons and pregnant women should not receive BCG vaccine.

| How  | ● BCG vaccine is administered as a single intradermal dose.
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


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, overcrowding 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% to 10%. 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.
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. 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**

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 chemophylaxis 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 +2º C to +8º C. Do not freeze. Store the reconstituted product in a refrigerator at +2º C to +8º 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
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 to immunization, 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.

SELECTED REFERENCES


# PART 4

## CHOLERA AND ENTEROTOXIGENIC ESCHERICHIA COLI (ETEC) TRAVELLERS’ DIARRHEA VACCINE

- **Epidemiology**
- **Preparations Authorized for Use in Canada**
- **Efficacy, Effectiveness and Immunogenicity**
- **Recommendations for Use**
- **Vaccine Administration**
- **Serologic Testing**
- **Storage Requirements**
- **Simultaneous Administration with Other Vaccines**
- **Vaccine Safety and Adverse Events**
  - Common and local adverse events
  - Contraindications and precautions
- **Selected References**

## KEY INFORMATION (refer to text for details)

### What

- Cholera –
  - Is caused by *Vibrio cholerae* serogroups O1 and O139
  - Is associated with poor sanitation; generally acquired from contaminated water or food
  - If untreated, severe fluid loss can lead to rapid dehydration and hypovolemic shock, which may be life-threatening
- Enterotoxigenic *Escherichia coli* (ETEC) –
  - Accounts for 25% to 50% of travellers’ diarrhea
  - Is transmitted by contaminated food and, less often, contaminated water
  - 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 cholerae* 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 –
  - 6 years of age and older: give 2 doses orally, 1 to 6 weeks apart
  - 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

Incidences/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).

(https://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.
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.
Table 1: Immunization Schedule for cholera and travellers’ diarrhea and cholera vaccine, by indication and age

<table>
<thead>
<tr>
<th>Primary immunization</th>
<th>Cholera</th>
<th>ETEC Travellers’ Diarrhea</th>
<th>General instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 5 years of age</td>
<td>3 doses orally, 1-6 weeks apart</td>
<td>2 doses orally, 1-6 weeks apart</td>
<td>If more than 6 weeks elapses between doses, re-peat primary series</td>
</tr>
<tr>
<td>6 years of age and older</td>
<td>2 doses orally, 1-6 weeks apart</td>
<td>2 doses orally, 1-6 weeks apart</td>
<td>Give final dose at least 1 week before departure</td>
</tr>
</tbody>
</table>

Boosted

| 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.
SELECTED REFERENCES


PART 4

DIPHTHERIA TOXOID

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine and Antitoxin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th>Diphtheria is rare in Canada. It occurs worldwide and is endemic in many developing countries.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Diphtheria toxoid-containing vaccines are only available as a combination vaccine.</td>
</tr>
<tr>
<td></td>
<td>Diphtheria toxoid-containing vaccines may be used for diphtheria post-exposure immunization in non-immune persons.</td>
</tr>
<tr>
<td></td>
<td>Diphtheria antitoxin for treatment of diphtheria is available on an emergency basis through local public health officials.</td>
</tr>
<tr>
<td></td>
<td>After a complete primary series (at least 3 doses) more than 97% of vaccinees develop antibody concentrations that are protective against diphtheria.</td>
</tr>
<tr>
<td></td>
<td>Redness, swelling and pain at the injection site are the most common adverse reactions to diphtheria toxoid-containing vaccines.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Diphtheria toxoid-containing vaccine is recommended for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- routine immunization of infants and children</td>
</tr>
<tr>
<td></td>
<td>- immunization of children who missed diphtheria immunization on the routine schedule</td>
</tr>
<tr>
<td></td>
<td>- immunization of previously unvaccinated or incompletely vaccinated adults</td>
</tr>
<tr>
<td></td>
<td>- routine booster immunization of adolescents and adults</td>
</tr>
</tbody>
</table>

| 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://wwwn.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://wwwn.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)

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 vaccine).
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-fr.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 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.

SELECTED REFERENCES

Centers for Disease Control and Prevention. ACIP Provisional Recommendations for Health Care Personnel on use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) and use of Postexposure Antimicrobial Prophylaxis.


Centers for Disease Control and Prevention. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine in Adults Aged 65 Years and Older — Advisory Committee on Immunization Practices (ACIP), 2012.


Gautret P, Wilder-Smith A. Vaccination against tetanus, diphtheria, pertussis
and poliomyelitis in adult travellers. Travel Med Infect Dis 2010;8:155-60.


Sanofi Pasteur Ltd. Product Monograph - ADACEL®, August 2009.

Sanofi Pasteur Ltd. Product Monograph - ADACEL®-POLIO, October 2010.


PART 4

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

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 cases¹ and incidence rates, Canada, 1979-2010²
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

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

\(^1\) Follow the routine, age-appropriate vaccination schedule for children less than 5 years old except for post-HSCT.

\(^2\) 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.

Concentrated (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.
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 influenzae* type b vaccines\(^*1\), by age at first dose\(^*2\)

<table>
<thead>
<tr>
<th>Age at 1(^{st}) dose of Hib(^*1) vaccine</th>
<th>Hib(^*1) vaccine schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 6 months</td>
<td>3 doses, 2 months apart(^*3)</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>1 booster dose(^*4)</td>
</tr>
<tr>
<td>7 to 11 months</td>
<td>2 doses, 2 months apart</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>1 booster dose(^*4)</td>
</tr>
<tr>
<td>12 to 14 months</td>
<td>1 dose</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>1 booster dose(^*4)</td>
</tr>
<tr>
<td>15 to 59 months(^*2)</td>
<td>1 dose</td>
</tr>
</tbody>
</table>

\(^*1\) 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.

SELECTED REFERENCES


Scheifele D. Recent trends in pediatric Haemophilus influenzae type b infections in Canada. Immunization Monitoring Program, ACTive (IMPACT) of the Canadian Paediatric Society and the Laboratory Centre for Disease Control. CMAJ 1996;154(7):1041-47.


PART 4
HEPATITIS A VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Immune Globulin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | In Canada, risk factors for hepatitis A (HA) infection include:  
|      | Travel to HA endemic countries  
|      | Household or close contact with an acute HA case  
|      | Men who have sex with men (MSM)  
|      | Illicit drug use  
|      | Populations or communities that have high endemic rates of HA or are at risk of HA outbreaks  
|      | Household or close contact with children adopted from HA endemic countries  
|      | HA infection usually causes clinical hepatitis in adults and older children but often causes a febrile illness without jaundice or is asymptomatic in younger children.  
|      | HA vaccine is at least 85% to 90% effective pre-exposure.  
|      | Reactions to HA vaccine are generally mild and transient and include soreness and redness at the injection site. |
| Who | Pre-exposure HA immunization is recommended for high risk groups.  
|     | Post-exposure prophylaxis should be offered to:  
|     | Household and sexual contacts of people infected with HA  
|     | Contacts in group child care centres and kindergartens  
|     | Co-workers and clients of infected food handlers |
| How | Primary immunization is achieved with one dose of HA vaccine with a booster dose given 6 to 36 months later depending on the product.  
|     | With few exceptions, immunize persons with indications for both HA and hepatitis B (HB) vaccine with combined HAHB vaccine. |
| Why | HA is one of the most common vaccine-preventable diseases in travellers.  
|     | HA occurs worldwide and is most common in regions with poor food and water sanitation.  
|     | Recovery from HA infection often takes 4 to 6 weeks but may take months and about 25% of adult cases require hospitalization. |
Since the publication of the 2006 Canadian Immunization Guide:

- New data have been obtained on the epidemiology of hepatitis A (HA) in Canada.
- New recommendations have been made for HA vaccination of household or close contacts of children adopted from HA endemic countries.

**Epidemiology**

**Disease Description**

**Infectious agent**
Hepatitis A (HA) virus is single serotype, ribonucleic acid (RNA) virus of the *Picornaviridae* family.

**Reservoir**
Humans, rarely chimpanzees and other primates

**Transmission**
HA is transmitted via the fecal-oral route, which can occur from direct person-to-person contact, from contamination of the environment or objects, or through contaminated food or water. Transmission through infected blood or blood products has also been reported. Symptoms appear after an incubation period of 15 to 50 days (average 28 days). Cases are typically infectious two weeks before the onset of symptoms and remain infectious until a week after the onset of jaundice. The virus may remain infectious in the environment for several weeks. Viral shedding can be greatly prolonged in immunocompromised individuals.

**Risk factors**
Persons at increased risk of HA infection include:

- Travellers to HA endemic countries. Studies estimate that 44% to 55% of reported HA cases are linked to travel. Low-budget travellers, volunteer humanitarian workers, and Canadian-born children of new Canadians returning to their country of origin to visit friends and relatives, may be at increased risk.
- Household or close contacts of an acute HA case.
- Residents of certain institutions, such as correctional facilities and those for developmentally challenged individuals.
- Men who have sex with men (MSM).
- Illicit drug users. Increased risk is associated with low hygiene standards, contaminated drugs, and sharing of materials for oral or nasal use of drugs.
- Household or close contacts of children adopted from HA endemic countries.
- Residents in some Aboriginal communities. Higher risk may be attributed to inadequate water supplies and high housing density.
- Hemophiliacs who use plasma-derived blood products

Many reported cases of hepatitis A have no identifiable risk factors.

**Spectrum of clinical illness**
Older children and adults infected with HA typically have abrupt onset of anorexia, nausea, fatigue, fever and jaundice. In children less than 6 years of age, illness may be asymptomatic or mild; jaundice is uncommon. The severity of HA can range from a mild illness lasting 1 to 2 weeks to a severely disabling disease lasting several months. Approximately 25% of adult cases are hospitalized. The overall case fatality rate is 0.1% to 0.3%, but can reach 1.8% in adults over 50 years of age. Individuals with chronic liver disease have an increased risk of progressing to fulminant hepatic failure.
resulting in death. Chronic hepatitis and carrier states are not associated with HA; however, relapsing hepatitis lasting up to a year occurs in 15% of cases. Lifelong immunity to HA follows infection.

**DISEASE DISTRIBUTION**

**Incidence/prevalence**

*Global*

HA occurs worldwide. Regions with higher levels of endemicity and risk of HA transmission include: South Asia, Sub-Saharan Africa, Central Asia, Latin America, North Africa/Middle East, and Oceania. A map of countries and areas of risk for HA is available from the World Health Organization (WHO). ([http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepA_IHRiskMap.png](http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepA_IHRiskMap.png))

*National*

Since the introduction of HA vaccine in Canada in 1996, the incidence of HA has declined. The number of cases of HA reported annually has varied from 2,978 (1991) to 298 (2008), (10.6 and 0.9 per 100,000 population, respectively). Age specific-incidence is highest among those 5 to 9 years old with a rate of 2.1 per 100,000, followed by those aged 1 to 4 years (1.5 per 100,000 population). In recent years, there has been no significant difference in incidence rates for males and females (refer to Figure 1). Given the under-diagnosis and under-reporting of HA and the occurrence of subclinical infections, the actual number of HA cases is estimated to be seven times higher than reported.

**Figure 1: Hepatitis A – reported incidence by sex, Canada 1990-2008**

In a 2003 nationwide seroprevalence study, 2.0% of unvaccinated Canadian-born children between 8 and 13 years of age had anti-HA antibodies. A similar study found 20% seropositivity in Canadian-born, non-vaccinated adults. The study also found seroprevalence increased with age, from 2.6% of 18-29 year olds to 45.9% of 60-69 year olds.
Recent outbreaks
Community HA outbreaks linked to infected food handlers have been reported in Canada. Although no outbreaks linked to imported food from endemic regions have been reported in Canada, large multi-state outbreaks have occurred in the United States. During the 1990s there were several HA outbreaks among MSM across Canada. There have been no outbreaks reported in these communities in recent years, likely the result of targeted vaccination programs. Outbreaks with no identifiable source were reported among First Nations communities in the 1990s. There were no additional First Nations outbreaks reported for several years until a prolonged multi-community outbreak in British Columbia from 2010 to 2012.

PREPARATIONS AVAILABLE FOR USE IN CANADA

HEPATITIS A-CONTAINING VACCINES

- **AVAXIM®** and **AVAXIM®—Pediatric** (inactivated hepatitis A vaccine), (HA).
- **HAVRIX® 1440** and **HAVRIX® 720 Junior** (inactivated hepatitis A vaccine), GlaxoSmithKline Inc. (HA)
- **TWINRIX®** and **TWINRIX® Junior** (combined hepatitis A and hepatitis B (HB) vaccine), (HAHB).
- **VAQTA®** (inactivated hepatitis A vaccine), (HA).
- **VIVAXIM®** (combined purified Vi polysaccharide typhoid and inactivated hepatitis A vaccine), (HA-Typh-I).

HUMAN IMMUNE GLOBULIN

- **GamaSTAN® S/D**: immune globulin (human), Grifols Therapeutics Inc. (Ig)

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 Contents in 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

EFFICACY AND EFFECTIVENESS

Pre-exposure
HA vaccines have demonstrated at least 85% to 90% efficacy in preventing clinical illness.

Post-exposure
Epidemiologic studies of HA outbreaks have shown that the use of vaccine in the susceptible population interrupts the outbreak. The protective efficacy of vaccine in one study when vaccine was used within one week of exposure was 79%.

IMMUNOGENICITY

In serologic studies of HA vaccines, 95% to 100% of vaccinees developed protective concentrations of antibody against HA after a single dose of HA vaccine, and nearly 100% seroconverted after receiving two doses.

There is no reduction, and possibly even an increase, in seroprotection rates achieved by HAHB vaccine compared with monovalent HA and HB vaccines. Equivalent seroconversion rates are achieved by HA-Typh-I vaccine compared with typhoid and monovalent HA vaccines.
RECOMMENDATIONS FOR USE

PRE-EXPOSURE IMMUNIZATION

HA-containing vaccine

HA vaccine is recommended for pre-exposure immunization of persons one year of age and older at increased risk of infection or severe HA (refer to Table 1). All persons who wish to decrease their risk of acquiring HA should be encouraged to be vaccinated. The off-label use of HA vaccine in 6 to 11 month olds (e.g., for travel to endemic areas) is under National Advisory Committee on Immunization (NACI) review. In some First Nations communities HA vaccine is given to infants starting at 6 months of age. With few exceptions, combined hepatitis A and hepatitis B vaccine (HAHB) is the preferred vaccine for people with indications for immunization against both hepatitis A and hepatitis B. Refer to Hepatitis B Vaccine in Part 4 for additional information.

Table 1: Recommended recipients of hepatitis A vaccine for pre-exposure prevention
(for post-exposure prevention refer to Post-exposure immunization)

<table>
<thead>
<tr>
<th>Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travellers to or immigrants from HA endemic areas. Refer to Travellers.</td>
</tr>
<tr>
<td>Household or close contacts of children adopted from HA endemic countries</td>
</tr>
<tr>
<td>Populations or communities at risk of HA outbreaks or in which HA is highly endemic (e.g., some aboriginal communities).</td>
</tr>
<tr>
<td>Persons with lifestyle risks for infection, including those who use illicit drugs (injectable and non-injectable) and men who have sex with men (MSM).</td>
</tr>
<tr>
<td>Persons who have chronic liver disease from any cause, including persons infected with hepatitis C. While these persons may not be at increased risk of hepatitis A infection, they may be at risk of more severe disease if infection occurs.</td>
</tr>
<tr>
<td>People with haemophilia A or B receiving plasma-derived replacement clotting factors.</td>
</tr>
<tr>
<td>Military personnel and humanitarian relief workers likely to be posted to areas with high rates of HA.</td>
</tr>
<tr>
<td>Zoo-keepers, veterinarians and researchers who handle non-human primates.</td>
</tr>
<tr>
<td>Workers involved in research on HA virus or production of HA vaccine who may be exposed to HA virus.</td>
</tr>
<tr>
<td>Any person who wishes to decrease his or her risk of HA.</td>
</tr>
</tbody>
</table>

Human immune globulin

HA vaccine is the preferred agent for pre-exposure prophylaxis. Human immune globulin (Ig) will provide protection against HA when administered intramuscularly before exposure or during the incubation period and may be indicated for pre-exposure prophylaxis in the following circumstances:

- Infants under one year of age.
- Immunocompromised persons (who may not respond fully to the vaccine). Administering Ig immediately before travel will ensure that protective concentrations of antibody are adequate for short-term (up to 6 months depending on the dose) travel and could be considered in this group of travellers, along with administration of HA vaccine.
- People for whom HA vaccine is contraindicated.

The effectiveness of Ig depends upon the timing of administration and the dose given. The recommended dose of Ig varies according to the duration of required protection. In general, for protection lasting less than 3 months the dose is 0.02 mL/kg. If protection is required for 3 months or longer, 0.06 mL/kg should be administered and repeated every 4 to 6 months.
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. HA or HAHB vaccine may be given, if indicated, regardless of possible previous receipt of the vaccine or pre-existing immunity because adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Children and Adults with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

The safety of HA-containing vaccines given during pregnancy has not been studied in clinical trials. However, because the vaccines are prepared from inactivated viruses, any risk to the developing fetus is theoretical only. HA vaccine should be considered for pregnant women in high risk situations when benefits outweigh risks. Refer to Hepatitis B Vaccine and Typhoid Vaccine in Part 4 for additional information. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

HA vaccine may be administered to immunocompromised persons. Vaccine efficacy may be reduced in the immunosuppressed; however, the vaccine will provide some protection and should be considered for pre-exposure and post-exposure use when indicated. Along with HA vaccine, Ig should be considered for pre-exposure and post-exposure management of immunocompromised persons since they may not adequately respond to HA vaccine. Serology testing to determine immune status may be considered in immunocompromised people when considering immunization prior to potential exposure (e.g., travel to high risk areas). However, post-HA vaccine serology testing has poor sensitivity. If the serology test result is positive, the person can be assumed to be immune; however, if the test result is negative, the person cannot be assumed to be non-immune.

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 may receive HA vaccine if other risks are present (refer to Table 1).

Acquired (secondary) immunodeficiency

Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)

If indicated, HA vaccine may be given, ideally at least 6 months post-transplant. Non-immune household contacts of HSCT recipients should receive HA vaccine if other risks are present (refer to Table 1).

Solid organ transplantation

HA vaccine is recommended for all transplant candidates with chronic liver diseases and can be given to all solid organ transplant candidates and recipients if other risks are present (refer to Table 1). If possible, the HA vaccine series should be completed prior to transplant. If HA vaccine wasn’t given or if the series was only partially completed prior to transplant, the vaccine series should be started or completed at 6 months post-transplant. Non-immune household contacts of solid organ transplant recipients should receive HA vaccine if other risks are present (refer to Table 1).
Immunosuppressive therapy

If indicated, HA vaccine can safely be given at any time before, during or after immunosuppressive therapy. In particular, for post-exposure or outbreak management, HA vaccine should be given at any time before, during or after immunosuppressive therapy. However, to ensure optimal immunogenicity when being used for non-urgent indications, the following timelines should be followed whenever possible.

HA vaccine 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] lasting for 14 days or more; chemotherapy [e.g., azathioprine, cyclosporine, cyclophosphamide, infliximab]; or radiation therapy). 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 HA vaccine to ensure immunogenicity. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and administration of HA vaccine. The interval between discontinuation of immunosuppressive drugs and HA vaccine may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.

If immunosuppressive therapy cannot be stopped, HA vaccine should be given when the person is least immunosuppressed if possible.

HIV-infected

HA vaccine is recommended for HIV-infected individuals with risk factors (e.g., MSM or illicit drug use.)

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

PERSONS WITH CHRONIC DISEASES

Chronic renal disease/dialysis

One study assessing the immune response to standard doses of HA vaccine in hemodialysis patients showed a good HA antibody response in all study subjects and no serious adverse effects were observed.

Chronic liver disease

Hepatitis A immunization is recommended for non-immune persons with chronic liver disease, including those infected with hepatitis C and chronic hepatitis B carriers, because they are at risk of more severe disease if infection occurs. Vaccination should be completed early in the course of the disease, as the immune response to vaccine is suboptimal in advanced liver disease.

Non-malignant hematologic disorders

Haemophilia

Hepatitis A immunization is recommended for people with haemophilia A or B receiving plasma-derived replacement clotting factors. The solvent-detergent method used to prepare all current plasma-derived factor VIII products and some factor IX concentrates does not reliably inactivate HA virus because the virus does not have an envelope. Historically there has been evidence of transmission from clotting factors; however with testing protocols in place currently this risk is very low.

Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information.
TRAVELLERS
Hepatitis A is one of the most common vaccine preventable diseases in travellers. Protection against HA is recommended for all travellers to developing countries, especially to rural areas or places with inadequate sanitary facilities. View a map of countries and areas of risk for HA through WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepA_ITHRiskMap.png)

Given the long incubation period for HA and the demonstrated efficacy of post-exposure use of HA vaccine, administration of HA vaccine up to the day of departure is considered appropriate and efficacious. Ig is only used for travel prophylaxis in people for whom HA vaccine is contraindicated or may not be effective. Refer to Pre-exposure immunization.

As hepatitis B (HB) vaccination is also indicated for most travellers, concurrent immunization with HA and HB vaccines, is recommended. For those who are susceptible to both HA and HB virus, a combined HAHB vaccine can be used. For travellers who present 21 to 27 days before departure, a rapid dosing schedule with HAHB vaccine may be given to adults at 0, 7, and 21 days with a booster dose required at 12 months to achieve long term immunity. For travellers presenting less than 21 days before departure, monovalent HA (which has double the antigen content of HA compared to HAHB vaccine) and HB vaccines should be administered at different injection sites using separate needles and syringes, with the completion of both vaccine series required after travel. Refer to the CATMAT Statement on hepatitis vaccines for travellers (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-2/index-eng.php) for additional information. 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 their immunization status and update immunization as needed. In many countries outside of Canada, HA vaccine is in limited use. To view information on vaccination schedules in other countries through the WHO. (http://www.who.int/vaccines/GlobalSummary/Immunization/ScheduleSelect.cfm)

Vaccination against HA should be considered for all persons from a country where HA is endemic. Individuals born in developing countries are more likely to be immune to HA, therefore, testing for immunity before administering HA vaccine to persons from HA endemic countries should be considered. If persons from HA endemic countries are not immune, they should be offered HA immunization because they are at increased risk for HA exposure through visits back to their country of origin, or when receiving friends and family from their country of origin.

In addition, persons new to Canada should be tested for hepatitis C antibody and susceptible persons chronically infected with hepatitis C should be vaccinated against HA and HB. Persons new to Canada should also be tested for hepatitis B and vaccinated against HA if found to be a hepatitis B carrier. Household or close contacts of children adopted from HA endemic countries should be immunized with HA-containing vaccine. Adults going to pick up adopted children from HA endemic countries should be vaccinated before travel. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
Pre-exposure HA vaccination is recommended for:

- Military personnel and humanitarian relief workers likely to be posted abroad to areas with high rates of HA
- Zoo-keepers, veterinarians and researchers who handle non-human primates
- Workers involved in research on HA virus or production of HA vaccine who may be exposed to HA virus

Refer to Immunization of Workers in Part 3 for additional general information.
POST-EXPOSURE IMMUNIZATION
Post-exposure prophylaxis should be offered to household and close contacts of proven or suspected cases of HA. It should be given when HA occurs in group child care centres and kindergartens and should be offered to co-workers and clients of infected food handlers. Post-exposure prophylaxis is not necessary for other contacts, such as school, workplace or health care workers caring for HA cases unless an outbreak is suspected.

Hepatitis A vaccine
HA vaccine is effective as post-exposure prophylaxis to prevent infection in contacts and is recommended in preference to Ig for people over one year of age. One dose of HA vaccine should be given to susceptible contacts as soon as possible and preferably within 14 days of last exposure. However, HA vaccine should still be considered if more than 14 days have elapsed since last exposure, as there are no data on the outer limit of efficacy.

Immune globulin
Ig is the recommended post-exposure immunoprophylactic agent for infants less than one year of age, for those for whom vaccine is contraindicated, and if HA vaccine is unavailable. Immunocompromised people should receive Ig in addition to HA vaccine because they may not respond fully to the vaccine. For post-exposure prophylaxis, the dose of Ig is usually 0.02 mL/kg, given as soon as possible after an exposure. Efficacy of Ig is unknown after 14 days of exposure. Refer to Passive Immunizing Agents Part 5 for additional general information.

VACCINE ADMINISTRATION
DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose and schedule
HA vaccine
One dose of monovalent HA vaccine is given for primary immunization with a booster dose given 6 to 36 months later depending on the product. The booster dose can be given anytime thereafter if not given during this recommended interval. Refer to Table 3.

HAHB vaccine
There are several authorized schedules for HAHB vaccines (refer to Table 3). In addition, clinical trials have shown that other schedules and dosages provide good seroprotection rates. A dose of adult formulation HAHB vaccine (TWINRIX®) contains a standard adult dose of HB vaccine and one-half an adult dose of HA vaccine. For individuals 19 years of age and over, the regular schedule of HAHB vaccine is months 0, 1 and 6. There is also a rapid schedule of days 0, 7 and 21, followed by a fourth dose at month 12. For individuals from 1 to 18 years of age, the authorized schedule for pediatric/adolescent formulation HAHB (TWINRIX® Junior) vaccine is months 0, 1 and 6. Another authorized schedule is for children 1 to 15 years of age consisting of two doses of adult HAHB vaccine given at months 0 and 6-12. Clinical trials have shown that other schedules and dosages provide good seroprotection rates and geometric mean titres (GMT). For example, a two-dose schedule with pediatric/adolescent HAHB vaccine given at months 0 and 6 in Canadian school children (8 to 10 years of age) has been tested with good results.

Monovalent HA vaccine may be used to complete a HA series begun with HAHB vaccine and vice versa, however, monovalent HB will also be required for complete hepatitis B protection. Once a HAHB vaccine series is begun, it is preferable to finish the series with HAHB vaccine. Refer to Table 2 for options on completing HA vaccination series. Refer to Table 3 for schedules according to age for each product.
### Table 2: Options for completing hepatitis A vaccination series in adults, children and adolescents

<table>
<thead>
<tr>
<th>Adult presents with history of:</th>
<th>Options to complete HA series</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose adult HAHB vaccine</td>
<td>2 doses adult HAHB vaccine OR 2 doses adult HA vaccine&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 doses adult HAHB vaccine</td>
<td>1 dose adult HAHB vaccine OR 1 dose adult HA vaccine&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 dose adult HA vaccine</td>
<td>1 dose adult HA vaccine OR 2 doses adult HAHB vaccine&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child or adolescent&lt;sup&gt;3&lt;/sup&gt; presents with history of:</th>
<th>Options to complete HA series</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose pediatric/adolescent HAHB vaccine</td>
<td>2 doses pediatric/adolescent HAHB vaccine&lt;sup&gt;4&lt;/sup&gt; OR 2 doses pediatric/adolescent HA vaccine&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 dose adult HAHB vaccine</td>
<td>1 dose adult HA vaccine unless 16 years or older&lt;sup&gt;5&lt;/sup&gt; OR 1 dose pediatric/adolescent HA vaccine&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 doses pediatric/adolescent HAHB vaccine</td>
<td>1 dose pediatric/adolescent HAHB vaccine&lt;sup&gt;4&lt;/sup&gt; OR 1 dose pediatric/adolescent HA vaccine&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 doses adult HAHB vaccine</td>
<td>No additional doses needed unless 16 years of age or older&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 dose pediatric/adolescent HA vaccine</td>
<td>1 dose pediatric/adolescent HA vaccine</td>
</tr>
</tbody>
</table>

<sup>1</sup> Refer to Hepatitis B Vaccine in Part 4 for details of hepatitis B vaccine schedules. In adults and children of most ages (except 11 to 15 years), three doses of hepatitis B vaccine are required for hepatitis B protection.

<sup>2</sup> Once the HAHB vaccine series is started, it is preferable to finish it with HAHB vaccine. HA vaccine may be given if HAHB vaccine is not available and only HA coverage is needed.

<sup>3</sup> Refer to Table 3 for schedule and age cut-offs for each product.

<sup>4</sup> In children 8 to 10 years of age, a two-dose schedule with pediatric/adolescent HAHB vaccine given at months 0 and 6 has been tested with good results.

<sup>5</sup> In children 1 to 15 years of age, two doses of adult HAHB vaccine is an authorized schedule. In children 16 to 18 years of age, clinician discretion is advised as there is no evidence or authorized schedule for this situation; an adult schedule of 3 doses should be considered.

**HA-Typh-I vaccine**

One dose of HA-Typh-I vaccine is given for primary immunization in those 16 years of age and older. To provide long term protection against HA infection, a booster dose of monovalent HA vaccine should be given 6 to 36 months later. Alternatively HA-Typh-I can be given as a booster vaccine after 36 months. HA-Typh-I vaccine may be used as a booster vaccine in persons who have received HA vaccine 36 months earlier and who require protection against typhoid. Refer to Typhoid Vaccine Part 4 for additional information.
Table 3: Dosages and schedules for Hepatitis A-containing vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Antigen(s)*</th>
<th>Dose</th>
<th>Schedule (Months: 1st dose = month 0)</th>
<th>Age**</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVAXIM®</td>
<td>160 antigen units HA</td>
<td>0.5 mL</td>
<td>0, 6-36</td>
<td>12 years and older</td>
</tr>
<tr>
<td>AVAXIM® Pediatric</td>
<td>80 antigen units HA</td>
<td>0.5 mL</td>
<td>0, 6-12</td>
<td>1 to 15 years</td>
</tr>
<tr>
<td>HAVRIX® 1440</td>
<td>1440 ELISA units HA</td>
<td>1.0 mL</td>
<td>0, 6-12</td>
<td>19 years and older</td>
</tr>
<tr>
<td>HAVRIX® 720 Junior</td>
<td>720 ELISA units HA</td>
<td>0.5 mL</td>
<td>0, 6-12</td>
<td>1 to 18 years</td>
</tr>
<tr>
<td>VAQTA®</td>
<td>50 units HA</td>
<td>1.0 mL</td>
<td>0, 6</td>
<td>18 years and older</td>
</tr>
<tr>
<td>VAQTA® Pediatric</td>
<td>25 units HA</td>
<td>0.5 mL</td>
<td>0, 6-18</td>
<td>1 to 17 years</td>
</tr>
<tr>
<td>TWINRIX®</td>
<td>720 ELISA units HA, 20 µg HB</td>
<td>1.0 mL</td>
<td>0, 1, 6 or 0, day 7, day 21, month 12</td>
<td>19 years and older</td>
</tr>
<tr>
<td>TWINRIX® Junior</td>
<td>360 ELISA units HA, 10 µg HB</td>
<td>0.5 mL</td>
<td>0, 1, 6</td>
<td>1 to 18 years ***</td>
</tr>
<tr>
<td>ViVAXIM®</td>
<td>160 antigen units HA, <em>Salmonella typhi</em></td>
<td>1.0 mL</td>
<td>0, booster dose of HA vaccine at month 6-36 or HA-Typh-l vaccine at month 36</td>
<td>16 years and older</td>
</tr>
</tbody>
</table>

* There is no international standard for HA antigen measurement. Each manufacturer uses its own units of measurement.
** Ages for which the vaccine is authorized for use
*** A two-dose schedule with pediatric/adolescent HAHB vaccine given at months 0 and 6 in Canadian school children (8 to 10 years of age) has been tested with good results.

HA = hepatitis A
HB = hepatitis B

For vaccine-specific recommendations, 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 Hepatitis B Vaccine in Part 4 for additional information.

**Route of administration**

HA-containing vaccine should be administered intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Protective concentrations of antibody will likely persist for at least 20 years, possibly for life, following immunization with two doses of HA vaccine. Immune memory has been demonstrated indicating that protection may persist even when antibodies are no longer measurable.
SEROLOGICAL TESTING

PRE-IMMUNIZATION
Pre-immunization serologic testing should be considered in populations with potentially higher levels of pre-existing immunity such as older Canadians, people from HA endemic areas, and people with a history of hepatitis or jaundice that may have been caused by HA.

POST-IMMUNIZATION
Serologic testing is not routinely recommended after receiving HA-containing vaccine.

STORAGE REQUIREMENTS
Store HA-containing vaccine at +2°C to +8°C and do not freeze. Administer HA-Typh-I vaccine immediately after mixing. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information. Refer to Passive Immunizing Agents Part 5 for information regarding Ig storage.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES
HA and HAHB vaccines may be administered concomitantly with other vaccines or with Ig at different injection sites using separate needles and syringes. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE AND IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS
Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

HA vaccine
HA vaccine is well tolerated. Reactions are generally mild and transient, and are usually limited to soreness and redness at the injection site. Other less frequent reactions include headache, irritability, malaise, fever, fatigue and gastrointestinal symptoms. Injection site reactions occur less frequently in children than in adults (21% versus 56%, respectively) as do mild, systemic events (2%-9% versus 16%). No significant difference in reactions is evident between initial and subsequent doses of vaccine or in the presence of pre-existing immunity.

HAHB vaccine
There is no increase in adverse events when HAHB vaccine is compared with HA vaccine given alone or concomitantly with HB vaccine at a different injection site. When adult dose HAHB vaccine is given to children in the two dose schedule, there is no increase in adverse events compared with those occurring after administration of the pediatric dose.

Ig
Injection site pain and tenderness, urticaria and angioedema may occur.

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. Anaphylaxis following vaccination with HA-containing vaccine may occur but is very rare.
OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

While serious events and chronic illnesses have been alleged or reported following receipt of the HB vaccine component of HAHB vaccines, no evidence of a causal association has been demonstrated in a number of studies. These chronic illnesses or serious events include chronic fatigue syndrome, multiple sclerosis, Guillain-Barré syndrome, rheumatoid arthritis, autoimmune disease and sudden infant death syndrome.

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) (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

HA-containing vaccines and Ig are contraindicated in persons with a history of anaphylaxis after previous administration of the product and in persons with proven immediate or anaphylactic hypersensitivity to any component of the product or its container.

Refer to 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 HA-containing vaccines, potential allergens include:

- AVAXIM® and AVAXIM® Paediatric: neomycin
- HAVRIX® 1440 and HAVRIX® 720 Junior: neomycin, latex in plunger stopper of pre-filled syringe
- TWINRIX® and TWINRIX® Junior: neomycin, latex in plunger stopper of pre-filled syringe, yeast protein
- VAQTA® and VAQTA® Pediatric/Adolescent: neomycin, latex in vial stopper
- ViVAXIM®: neomycin

Yeast protein is used in the development of HB and HAHB vaccines. TWINRIX® and TWINRIX® Junior contain a small amount of yeast protein. 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.

The safety of HA or HAHB vaccine given during pregnancy has not been studied in clinical trials. However, because the vaccines are prepared from inactivated viruses, any risk to the developing fetus is theoretical.

Administration of HA-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

Monovalent HA vaccines may be used interchangeably. Any HA vaccine indicated for the age of the vaccinée will provide an effective booster dose after a first dose of vaccine from a different manufacturer. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.
SELECTED REFERENCES


# PART 4

## HEPATITIS B VACCINE

- **Epidemiology**
- **Preparations Authorized for Use in Canada**
- **Efficacy, Effectiveness and Immunogenicity**
- **Recommendations for Use**
- **Vaccine Administration**
- **Serologic Testing**
- **Storage Requirements**
- **Simultaneous Administration with Other Vaccines**
- **Vaccine Immune Globulin Safety and Adverse Events**
- **Other Considerations**
- **Selected References**

### KEY INFORMATION (refer to text for details)

**What**
- In Canada, most acute cases of hepatitis B (HB) occur in unimmunized people 25 years of age and older who acquire infection through unprotected sexual activity, sharing injection drug equipment, household contact with a HB carrier or procedures with percutaneous exposure. A high proportion of HB carriers in Canada are immigrants from HB endemic areas.
- Initial infection with HB may be asymptomatic in up to 50% of adults and 90% of children.
- Infants, young children and immunocompromised persons are at highest risk of becoming chronic HB carriers.
- HB vaccine is 95% to 100% effective pre-exposure.
- Reactions to HB vaccine are generally mild and transient and include: irritability, headache, fatigue, as well as pain and redness at the injection site.

**Who**
- Routine HB immunization is recommended for all children.
- Pre-exposure HB immunization is recommended for high risk groups.
- Post-exposure prophylaxis should be offered to:
  - infants born to HB-infected mothers
  - persons potentially exposed to blood or bodily fluids containing HB virus
  - household and sexual contacts of an acute HB case or chronic carrier

**How**
- There are many different HB-containing vaccine schedules and dosages.
- For monovalent HB vaccine, the preferred schedule (particularly for infants) is months 0, 1 and 6. The date of the first dose for infants is at birth which is considered as month 0.
- With few exceptions, immunize persons with indications for both hepatitis A (HA) and HB vaccine with combined HAHB vaccine.

**Why**
- A person with acute HB can become a chronic carrier and remain infectious. Chronic infection may lead to serious liver disease.
- Infants born to infected mothers are at highest risk of becoming chronic HB carriers.
Since the publication of 2006 Canadian Immunization Guide:

- New data have been obtained on the epidemiology of hepatitis B (HB) in Canada
- The recommended recipients of HB vaccine have been modified
- A new HB-containing hexavalent vaccine for children has become available
- A new HB immune globulin preparation has become available
- Multi-dose preparations of HB vaccine are no longer available
- All HB vaccines are thimerosal-free

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**
Hepatitis B (HB) virus is a deoxyribonucleic acid (DNA) virus of the *Hepadnaviridae* family. Several genotypes have been described. The following two antigens are important in evaluating people with HB infection and are markers of HB carriage: hepatitis B surface antigen (HBsAg), which is present in either acute or chronic infection with HB virus and hepatitis B antigen (HBeAg), which typically is associated with higher viral loads, increased infectivity and more actively replicating virus. Increasingly, viral loads are followed for indicators of infectivity and response to treatment.

**Reservoir**
Humans

**Transmission**
HB is transmitted through percutaneous or mucosal contact with infectious biological fluids. Transmission of HB occurs through close contact with infectious bodily fluids, including through sharing of injection drug equipment (such as needles), sexual contact, and from mothers who are acute cases or carriers to their newborns. The risk of transfusion-related HB is extremely low because all blood and blood products are tested. Saliva is considered infectious in bite wounds with broken skin involving the inoculation of saliva, or when it is visibly tainted with blood. Almost one-third of people with HB infection have no identified risk factors.

The incubation period is 45 to 160 days (average 120 days). HBsAg can be detected in serum 30 to 60 days after exposure and persists until the infection resolves. Persons in the acute stage of HB are considered infectious. In most cases, antibody to HbsAg (anti-HBs) appears after HBsAg has disappeared and the infection has resolved. In severe acute HB infections, anti-HBs may be present simultaneously with HBsAg. The presence of anti-HBs confers long-term immunity. In addition, antibody to HB core antigen (anti-HBc) will appear in persons who have been exposed to the virus. This includes those who are currently infected and those who were infected in the past but have cleared the virus. Persons with anti-HBs and anti-HBc are not infectious. However, some individuals with acute HB infection will become chronic carriers. Chronic carriers will generally express HBsAg and may have HBeAg and measurable HB DNA in blood. These individuals are infectious.

**Risk factors**
The highest risk of transmission and of subsequent chronic carriage is in infants exposed during child birth to their mothers who are carriers of HB. Other groups at higher risk of HB include injection drug users, households with HB carriers and people at risk of sexually transmitted diseases. In Canada, most cases of acute HB occur in unimmunized people 25 years of age and older who acquire infection through unprotected sexual activity, sharing injection drug equipment, household contact with an HB
carrier, or treatments or procedures with percutaneous exposure. People on dialysis are considered at high risk. A high proportion of HB carriers in Canada are immigrants from HB endemic areas.

**Spectrum of clinical illness**
Initial infection with HB may be asymptomatic in up to 50% of adults and 90% of children. When symptoms occur, they include insidious onset of anorexia, abdominal pain, nausea, vomiting and jaundice. Acute illness may last up to 3 months and has a case fatality rate of 1% to 2%, which increases with age. Although 90% of adults infected with HB recover completely, fulminant hepatitis occurs in 1% to 2% and chronic infection in approximately 10%, eventually leading to a chronic carrier state that may result in cirrhosis and hepatocellular carcinoma. The risk of becoming a chronic carrier varies inversely with the age at which infection occurs (infants - 90% to 95%; children less than 5 years of age - 25% to 50%; adults - 3% to 10%). The risk of becoming a chronic carrier is also greater in immunocompromised patients. The risk of fulminant hepatitis and death is increased in pregnant women, with consequences to the fetus including premature delivery, asphyxia and death.

**DISEASE DISTRIBUTION**

**Incidence/prevalence**

**Global**
It is estimated that there are more than 300 million HB carriers worldwide, of whom approximately 500,000 to 1.2 million die annually from HB related liver disease. Despite the availability of HB vaccines, the rates of HB related hospitalizations, cancers and deaths have more than doubled during the past decade. HB remains highly or moderately endemic in the Far East, the Middle East, Africa, South America, Eastern Europe and Central Asia, with carrier rates of 2% to 20% in the general population. View a WHO map of countries and areas of risk for HB. (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepB_ITHRiskMap.png)

**National**
Canada is considered an area of low HB endemicity. It is estimated that less than 5% of residents have markers of past infection, and less than 1% are carriers. The epidemiology of HB infection has been modified by the introduction of routine childhood HB immunization programs and the increased use of vaccine in targeted groups. The incidence of HB has decreased in all age groups in recent years, coinciding with the increasing use of vaccine and has virtually disappeared in the cohorts that have benefited from routine immunization programs (refer to Figure 1).
PREPARATIONS AVAILABLE FOR USE IN CANADA

HEPATITIS B-CONTAINING VACCINES

- **ENGEX**®-B (hepatitis B vaccine, recombinant), GlaxoSmithKline Inc. (HB).
- **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).
- **RECOMBIVAX HB** (hepatitis B vaccine, recombinant), Merck Canada Inc. (HB).
- **TWINRIX**® and **TWINRIX**® Junior (combined hepatitis A and hepatitis B vaccine), GlaxoSmithKline Inc. (HAHB)

HEPATITIS B IMMUNE GLOBULIN (HBIg)

- **HepaGam B**™ (hepatitis B immune globulin (human), Cangene Corp.
- **HyperHEP B**™ S/D (hepatitis B immune globulin (human), Grifols Therapeutics Inc.

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 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

EFFICACY AND EFFECTIVENESS

Pre-exposure

HB vaccine is 95% to 100% effective in preventing HB in people who receive a complete vaccine series.
Post-exposure
HB vaccination and one dose of hepatitis B immune globulin (HBlg) administered within 24 hours after
birth are 85% to 95% effective in preventing HB infection in exposed neonates. Studies have
demonstrated the efficacy of HBlg and/or HB vaccine in percutaneous or mucosal exposure to HB-
positive blood or sexual exposure to HB-positive persons. A single dose of HBlg is 75% effective if
administered within 2 weeks of last sexual exposure.

IMMUNOGENICITY
People with an anti-HBs titre of at least 10 IU/L after immunization are considered protected for life with
the exception of those who are immunocompromised (refer to Immunocompromised persons). Anti-HBs
titres may eventually disappear, more quickly if the initial titre was low. High titres of anti-HBs result in
longer persistence of antibodies and may be predictive of a longer duration of protection. However,
immune memory persists despite the disappearance of anti-HBs. In endemic regions, the duration of
protection induced by vaccination has been shown to be at least 15 years in most vaccinees.

The major determinant of seroprotection rates achieved is the age at vaccination, but outcome also varies
with the schedule used, the dosage, and the health of the vaccinee. While children less than 2 years of
age have a 95% response rate, the best response is observed in children between the ages of 5 and 15
years with 99% seroprotection rates. Generally, the response rate for adults decreases with age. The
antibody response is lower in patients with diabetes mellitus (70% to 80%), renal failure (60% to 70%),
and chronic liver disease (60% to 70%). Immunization of obese people, smokers and those with
alcoholism may also produce lower antibody titres. Immunocompromised patients, such as those infected
with HIV, will have a diminished response in proportion to the level of immune deficiency. Most people
undergoing dialysis do not respond well to HB vaccine and do not develop an immune memory.

Studies have demonstrated the immunogenicity of DTaP-HB-IPV-Hib for all six antigens in the vaccine.
There is no reduction, and possibly even an increase, in seroprotection rates achieved by HAHB vaccine
compared with monovalent HA and HB vaccines.

RECOMMENDATIONS FOR USE

PRE-EXPOSURE IMMUNIZATION

Infants and children
HB-containing vaccine should be given for routine immunization of infants or children and for
immunization of children and adolescents who have missed HB immunization on the routine schedule.
The age at which HB-containing vaccine is offered varies from jurisdiction to jurisdiction. In
jurisdictions where children do not receive HB vaccine in infancy, children at increased risk should be
given HB-containing vaccine as soon as the risk is identified (refer to Table 1).

If infant immunization for hepatitis B is undertaken, DTaP-HB-IPV-Hib vaccine may be used as an
alternative to separately administered HB and DTaP-IPV-Hib vaccines. DTaP-HB-IPV-Hib vaccine is
authorized for children 6 weeks to 23 months of age and may be given to children aged 24 months to
less than 7 years, if necessary.

Adults
Persons who are at increased risk of exposure to HB should receive HB-containing vaccine (refer to
Table 1). All persons who do not have immunity from past infection or previous vaccination and all
persons who wish to decrease their risk of acquiring HB should be encouraged to be vaccinated. With
few exceptions, combined hepatitis A and hepatitis B vaccine (HAHB) is the preferred vaccine for
people with indications for immunization against both hepatitis A and hepatitis B. Refer to Hepatitis A
Vaccine in Part 4 for additional information.
Table 1: Recommended recipients of hepatitis B vaccine for pre-exposure prevention
(refer to Post-exposure immunization for post-exposure prevention)

<table>
<thead>
<tr>
<th>Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults and children who have immigrated to Canada from areas where there is a high prevalence of HB</td>
</tr>
<tr>
<td>Children born in Canada whose families have immigrated from areas where there is a high prevalence of HB and who may be exposed to HB carriers through their extended families or when visiting their family's country of origin.</td>
</tr>
<tr>
<td>Children and workers in child care settings in which there is a child or worker who has acute HB or is an HB carrier</td>
</tr>
<tr>
<td>Household and sexual contacts of acute HB cases and HB carriers</td>
</tr>
<tr>
<td>Household or close contacts of children adopted from HB-endemic countries if the adopted child is HBsAg positive</td>
</tr>
<tr>
<td>Populations or communities in which HB is highly endemic</td>
</tr>
<tr>
<td>Residents and staff of institutions for the developmentally challenged</td>
</tr>
<tr>
<td>Staff and inmates of correctional facilities</td>
</tr>
<tr>
<td>Persons with lifestyle risks for infection, including:</td>
</tr>
<tr>
<td>• persons who have unprotected sex with new partners</td>
</tr>
<tr>
<td>• persons who have had more than one sexual partner in the previous 6 months</td>
</tr>
<tr>
<td>• persons with a history of sexually transmitted infections</td>
</tr>
<tr>
<td>• persons seeking evaluation or treatment for a sexually transmitted infection</td>
</tr>
<tr>
<td>• persons who engage in high risk sexual practices</td>
</tr>
<tr>
<td>• persons who use injection drugs</td>
</tr>
<tr>
<td>• men who have sex with men (MSM)</td>
</tr>
<tr>
<td>Persons with chronic liver disease from any cause, including persons infected with hepatitis C. While these persons may not be at an increased risk of hepatitis B infection, they may be at risk of more severe disease if infection occurs.</td>
</tr>
<tr>
<td>Hemophiliacs and other people receiving repeated infusions of blood or blood products.</td>
</tr>
<tr>
<td>Persons with chronic renal disease or who are undergoing chronic dialysis (hemodialysis or peritoneal dialysis)</td>
</tr>
<tr>
<td>Persons with congenital immunodeficiencies</td>
</tr>
<tr>
<td>Persons who have undergone hematopoietic stem cell transplantation (HSCT) or are awaiting solid organ transplant</td>
</tr>
<tr>
<td>HIV-infected persons</td>
</tr>
<tr>
<td>Travellers to HB endemic areas</td>
</tr>
<tr>
<td>Health care workers, emergency service workers, and others with potential occupational exposure to blood, blood products and bodily fluids that may contain HB virus</td>
</tr>
<tr>
<td>Any person who wishes to decrease his or her risk of HB</td>
</tr>
</tbody>
</table>
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 (unless known to be immune based on laboratory testing). Refer to Immunization of Children and Adults with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

All pregnant women should be routinely tested for HBsAg. A pregnant woman who has no markers of HB infection but who is at high risk of HB should be offered HB vaccine at the first opportunity during the pregnancy and should be tested for antibody response (refer to Serologic Testing). HB vaccine can be used safely in pregnancy and during breastfeeding and should be administered when indicated, because acute HB in a pregnant woman may result in severe disease for the mother and chronic infection of the infant. The safety of HAHB vaccine given during pregnancy has not been studied in clinical trials. However, because the vaccine is prepared from inactivated viruses, the risk to the developing fetus is theoretical only. Refer to Hepatitis A Vaccine in Part 4 for additional information. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

INFANTS BORN PREMATURELY

The response to HB vaccine may be diminished in pre-term infants with a birth weight of less than 2,000 grams. Routine HB immunization of infants of mothers known to be negative for HBsAg should be delayed until the infant reaches 2,000 grams or until discharge from hospital (whichever comes first).

Premature infants who are born to women who are HBsAg positive should receive the first dose of monovalent HB vaccine and HBlg within 12 hours of birth. Premature infants weighing less than 2,000 grams at birth require four doses of HB vaccine (at birth, 1, 2 and 6 months of age). Premature infants weighing 2,000 grams or more at birth require three doses of HB vaccine (at birth, 1 and 6 months). All infants of HBsAg positive mothers should have an assessment of the anti-HBs titre 4 weeks after their series of HB vaccine has been completed to assess the success of immunoprophylaxis. Refer to Table 2 and Post-exposure immunization.

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.
Table 2: Hepatitis B immunization recommendations for preterm infants*¹ weighing less than 2,000 grams, by maternal hepatitis B surface antigen (HBsAg) status

<table>
<thead>
<tr>
<th>Maternal HBSAg status</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Positive              | • Administer HBIg and monovalent HB vaccine within 12 hours of birth.  
• Administer 3 additional monovalent HB vaccine doses at ages 1, 2, and 6 months*²; HB-containing combination vaccine may be given for the 2 and 6 month doses  
• Test for HBsAg and antibody to HBsAg 4 weeks after completion of the 4 dose HB vaccine series |
| Negative              | • Give HB vaccine according to provincial/territorial schedule except if first dose is routinely given at birth.  
• If first dose is routinely given at birth, delay first dose of HB vaccine until infant weighs more than 2,000 grams or hospital discharge (whichever comes first). |
| Unknown               | • Test mother for HBsAg.  
• If maternal HB status will not be available within 12 hours of delivery, consider administering monovalent HB vaccine and HBIg within 12 hours of birth based on risk factors and erring on the side of providing vaccine and HBIg when uncertain.  
• If mother is HBsAg positive, follow recommendations for positive HBsAg result  
• If mother is HBsAg negative, follow recommendations for negative HBsAg result. |

*¹ Pre-term infants are defined as those born before 37 weeks of gestational age.  
*² The final dose in the vaccine series should not be administered before age 24 weeks (168 days).

NOTE: This table is adapted from the Centers for Disease Control and Prevention (CDC) table: Hepatitis B Immunization Management of Preterm Infants Weighing <2,000 g, by Maternal Hepatitis B Surface Antigen (HBsAg) Status published in Morbidity and Mortality Weekly Report (MMWR) December 7, 2007;56(48):1267. Available at: http://www.cdc.gov/hepatitis/hbv/pdfs/correctedtable4.pdf

IMMUNOCOMPROMISED PERSONS

HB vaccine 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.

Immunocompromised people (e.g., hematopoietic stem cell transplant recipients, solid organ transplant recipients, HIV-infected persons) often respond sub-optimally to HB vaccine and may require higher doses of antigen to respond initially (refer to Higher vaccine dosing) as well as booster doses. Post-immunization serologic testing within 1 to 6 months of completion of the vaccine series is recommended in these immunocompromised individuals to monitor the success of immunoprophylaxis. In addition, people undergoing chemotherapy, those on other immunosuppressive therapy, and those with congenital immunodeficiency may have a lower immune response so require serologic testing 1 to 6 months after completing the series. Vaccinees who do not develop an anti-HBs titre of at least 10 IU/L after the first series of immunizations should receive a second series and serology should be rechecked within 1 to 6 months after completion of the second series. If a protective antibody concentration is still not present, the individual should be counselled on alternative risk reduction measures. Should protective antibody concentrations be achieved and then wane, subsequent HB exposure in these individuals can result in acute disease or carrier state. Therefore, periodic monitoring of anti-HBs titres should be considered, taking into account the severity of the immunocompromised state and whether the risk of HB is still
present. Should antibody testing show subsequent suboptimal protection, a booster dose and retesting one month later should be undertaken.

**Higher vaccine dosing**

For some immune compromising or chronic conditions, a higher dose of monovalent HB vaccine is recommended (refer to Table 3 for schedule). This higher dose is defined as follows:

- for children 0 to less than 16 years of age, double the routine dose of monovalent HB vaccine for their age
- for adolescents 16 to less than 20 years of age:
  - 40 microgram dose of ENGERIX®-B vaccine OR
  - double the routine dose of RECOMBIVAX HB® vaccine for their age
- for adults 20 years of age and older:
  - 40 microgram dose of monovalent HB vaccine

**Congenital (primary) immunodeficiency**

Individuals with congenital immunodeficiencies involving any part of the immune system should receive HB vaccine. Immunization with a higher dosage as defined in Higher vaccine dosing is recommended.

**Acquired (secondary) immunodeficiency**

*Hematopoietic stem cell transplantation (HSCT)*

HB vaccine is recommended for all persons after transplantation. Three doses are required, starting at 6 to 12 months post-transplantation following the standard intervals. Immunization with a higher dosage as defined in Higher vaccine dosing is recommended.

*Solid organ transplantation*

Children and adults who are transplant candidates should receive HB vaccine following routine vaccination schedules. Immunity should be documented using the anti-HBs titre. For susceptible transplant recipients, vaccination should not be initiated or re-initiated until at least 3 to 6 months after transplantation in order to attain optimal immunogenicity. Immunization with a higher dosage as defined in Higher vaccine dosing is recommended.

*Immunosuppressive therapy*

Vaccination status for hepatitis B should be reviewed for immunocompetent persons who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency. Although HB 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. An exception is made for post-exposure prophylaxis, in which case the HB vaccine should be given as soon as possible after the exposure.

If indicated, HB vaccine 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 HB vaccine in an effort to ensure immunogenicity. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and administration of HB vaccine. The interval between discontinuation of immunosuppressive drugs and HB vaccine may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.
If immunosuppressive therapy cannot be stopped, HB vaccine should be given when the person is least immunosuppressed.

**HIV-infected**

HB vaccine is recommended for all non-immune HIV-infected individuals. Immunization should be completed as early in the course of disease as possible. Immunization with a higher dose of vaccine as defined in **Higher vaccine dosing** is recommended.

**Household contacts**

Non-immune household or close contacts of immunocompromised people should be given HB vaccine.

Refer to Dose and schedule, Booster doses and re-immunization and Serologic Testing. Refer to Immunization of Immunocompromised Persons in Part 3 for additional information.

**PERSONS WITH CHRONIC DISEASES**

**Chronic renal disease/dialysis**

Individuals on dialysis are at increased risk for HB infection and these individuals, as well as those with chronic renal disease, may respond sub-optimally to HB vaccinations. As well, anti-HBs concentrations decline rapidly. For dialyzed adults and children and those with chronic renal disease, immunization with higher dosing as defined in **Higher vaccine dosing** is recommended. The anti-HBs titre should be evaluated yearly and booster doses using a higher dose should be given as necessary.

**Neurologic disorders**

People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including HB-containing vaccine.

**Chronic liver disease**

HB immunization is recommended for non-immune persons with chronic liver disease, including those infected with hepatitis C, because they are at risk of more severe disease if infection occurs. Vaccination should be completed early in the course of the disease, as the immune response to vaccine is suboptimal in advanced liver disease. Anti-HBs titre testing may be used to document vaccine response.

For people with advanced liver disease, including disease caused by hepatitis C, seroconversion should be assessed after vaccination and consideration given to offering higher doses as defined in **Higher vaccine dosing** to those who do not respond (i.e., who do not achieve an anti-HBs titre of at least 10 IU/L) to the first series of vaccine.

**Non-malignant hematologic disorders**

Persons with bleeding disorders and other people receiving repeated infusions of blood or blood products are considered to be at higher risk of contracting hepatitis B and should be offered HB vaccine.

**Endocrine and metabolic diseases**

HB immunization for previously unvaccinated adults with type 1 or type 2 diabetes is currently under review by NACI.

Refer to Dose and schedule, Booster doses and re-immunization and Serologic Testing. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information.
TRAVELLERS
The risk of HB for non-immune travellers to developing countries has been estimated to be 0.2 to 0.6/1,000 per month and may be much higher for those engaging in high risk activities and those working in health care settings. HB vaccination should be recommended to travellers who will be residing in areas with high levels of endemic HB or working in health care facilities, and those likely to have contact with blood or to have sexual contact with residents of such areas. Complete HB immunization is recommended for children who will live in an HB endemic area. A map of countries and areas of risk for HB can be viewed through the WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepB_ITHRiskMap.png)

It is not necessary to request anti-HBs titres in previously immunized travellers, unless the person is a health care worker who has never had their anti-HBs titres verified. Refer to Workers.

Concomitant immunization with HA and HB vaccines is recommended as HA vaccination is also indicated for travellers to developing countries. For those who are susceptible to both HA and HB virus, a combined HAHB vaccine can be used. For travellers presenting less than 21 days before departure, monovalent HA and HB vaccines should be administered separately, with the completion of both vaccine series after travel. Refer to Hepatitis A 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 persons newly arrived in Canada should review the immunization status and update immunization for these individuals. In many countries outside of Canada, HB vaccine is in limited use. Information on vaccination schedules in other countries can be viewed through WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_HepB_ITHRiskMap.png)

All persons from a country that is endemic for HB should be assessed and vaccinated against HB if not immune. Individuals born in developing countries are more likely to be carriers of HB, necessitating vaccination of their sexual and household contacts. HB vaccine is recommended for all household contacts whose families have immigrated to Canada from areas where there is a high prevalence of HB and who may be exposed to HB carriers through their extended families or when visiting their country of origin.

Persons new to Canada should be tested for:

- HBsAg, anti-HBs, and anti-HBc. If any member of a family is found to be positive for HBsAg, the entire family should be tested for HB markers and vaccinated as appropriate.
- Hepatitis C antibody. Persons chronically infected with hepatitis C should be vaccinated against HB if susceptible.

Children adopted from countries in which there is a high prevalence of HB infection should be screened for HBsAg and, if positive, household or close contacts in the adopting family should be immunized before adoption or as soon as possible thereafter. Adults going to pick-up children from these countries should be vaccinated before departure. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
Immunization with HB vaccine and post-immunization serologic testing within 1 to 6 months of completion of the vaccine series are recommended for people who are at increased risk of infection through occupational exposure to blood, blood products and bodily fluids that may contain HB virus. This group includes all health care workers and others (e.g., staff of correctional facilities or institutions for the developmentally challenged) who may be exposed to blood or blood products, or are at risk of injury by instruments contaminated by blood, or are at risk of bites or penetrating injuries. Students in these occupations should complete their vaccine series before occupational exposure. Emergency service
workers, such as police and firefighters, may also be at higher risk of exposure, although there are no data to quantify their risk. Workers who have no contact with blood or blood products are at no greater risk than the general population.

If a worker has documentation of receiving a complete HB vaccine series but does not have documentation of anti-HBs serology following immunization, or, if a worker reports HB immunization but has no or incomplete documentation of HB immunization, serologic testing for anti-HBs should be done and then:

- If an anti-HBs titre of at least 10 IU/L is confirmed, testing need not be repeated nor should further immunization be undertaken, with the exception of immunocompromised persons who should be tested periodically for waning immunity and persons with chronic renal disease or on dialysis who should be tested yearly.

- If testing for anti-HBs is done 1 to 6 months after vaccination and the anti-HBs titre is less that 10 IU/L, this indicates a primary vaccine failure and the worker should be given a second vaccine series. The worker should be retested 1 to 6 months after completion of the second series.

- If the worker is tested more than 6 months after the initial series and the anti-HBs titre is less than 10 IU/L this may indicate a primary vaccine failure or waning antibody. Evidence shows that in immunocompetent people immunity is long lasting although antibody may be non-detectable. The worker should receive one booster dose and be retested one month later to document an anamnestic response; if the anti-HBs titre is still less than 10 IU/L then a second vaccine series is indicated followed by anti-HBs serology 1 to 6 months after completing the second series.

- Workers who have documented evidence of failure to respond to two series of HB vaccine (i.e., anti-HBs titre of less than 10 IU/L) are unlikely to benefit from further immunization and will need passive immunization after potential exposure to HB.

If an HB exposure occurs, and a worker has had a documented anti-HBs titre of at least 10 IU/L, no further testing is needed, unless the worker is immunocompromised or has chronic renal disease or dialysis. These workers should be tested for anti-HBs after a potential HB exposure and given additional vaccine and HBIg if their anti-HBs titre is less than 10 IU/L. Refer to Figure 2 and Figure 3.

Refer to Serologic Testing and Booster doses and re-immunization. Refer to Immunization of Workers in Part 3 for additional general information.

**POST-EXPOSURE IMMUNIZATION**

Post-exposure prophylaxis should be offered to susceptible individuals in the following circumstances:

- Infant born to a mother with acute or chronic HB infection
- Percutaneous or mucosal exposure to blood or body fluids potentially containing HB virus

Sexual or household contacts of an acute case or chronic carrier of HB

**Infants born to a mother with acute or chronic hepatitis B infection**

All pregnant women should be routinely tested for HBsAg. If maternal testing has not been conducted during pregnancy, it should be done at the time of delivery and urgent testing requested. If maternal HB status is not available within 12 hours of delivery, consideration should be given to administering HB vaccine with or without HBIg to the infant while the results are pending, *taking into account the mother’s risk factors* and erring on the side of providing vaccine and considering HBIg if there is any suspicion that the mother could be an acute case or a carrier.
All infants born to infected mothers should be given a dose of HB vaccine within 12 hours of birth. The second and third doses should be given 1 and 6 months after the first. For these infants the 6 month dose can be given as DTaP-HB-IPV-Hib vaccine. Premature infants weighing less than 2,000 grams at birth who are born to infected mothers should receive four doses of HB vaccine at 0, 1, 2 and 6 months of age. DTaP-HB-IPV-Hib vaccine can be used for the 2 and 6 month doses (refer to Infants born prematurely).

Vaccine is the most important intervention, providing 90% of the protection from HB; HBIg may provide some additional protection. An intramuscular (IM) dose of 0.5 mL HBIg should also be given as soon as possible and preferably within 12 hours after birth to infants born to mothers with acute or chronic hepatitis B. Vaccine and HBIg may be given at the same time but at different injection sites, using separate needles and syringes. The efficacy of HBIg decreases significantly after 48 hours, but may be given up to 7 days after birth. The benefit of HBIg given more than 7 days after exposure is unknown. The timing and use of HBIg is currently under review by NACI.

Infants born to infected mothers should be tested for HBsAg and anti-HBs 4 weeks after completion of the vaccine series to assess success of immunoprophylaxis. If HBsAg is present, the child will likely become a chronic carrier. If the infant is negative for both HBsAg and anti-HBs (i.e., a vaccine non-responder), additional doses of vaccine (up to a second full course) should be given with repeated serologic testing for antibody response. Refer to Serologic Testing.

Percutaneous (needlestick, bite) or mucosal exposure
The management of potential percutaneous or mucosal exposure to HB should be based on the immunization and antibody status of the injured person and the infectious status, if known, of the source (refer to Figure 2 and Figure 3). Testing of the source should be conducted according to Health Canada/Public Health Agency of Canada guidelines An integrated protocol to manage health care workers exposed to bloodborne pathogens. (http://www.collectionscanada.gc.ca/webarchives/20071124191322/http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/97vol23/index.html) If the assessment results of the exposed person and the source are not available within 48 hours, management of the exposed person should assume possible exposure. If indicated, HBIg should be administered to susceptible individuals within 48 hours after exposure. The efficacy of HBIg decreases significantly after 48 hours, but may be given up to 7 days after exposure. The benefit of HBIg given more than 7 days after exposure is unknown. The dose of HBIg for older children and adults is 0.06 mL/kg given intramuscularly (IM). All those susceptible and exposed should be counselled on the use of risk reduction measures until the vaccine series has been completed and protective concentrations of anti-HBs demonstrated.

Sexual and household contacts of hepatitis B
All non-immune and non-infected sexual and household contacts of acute cases and chronic carriers of HB should be immunized with HB vaccine and tested for antibody response 1 to 6 months after completion of the vaccine series. HBIg is not indicated for household contacts of an acute HB case with the exception of newborns when the mother is acutely or chronically infected. For sexual contacts, a single IM dose of HBIg (0.06 mL/kg) should be given within 48 hours after exposure. The efficacy of HBIg decreases significantly after 48 hours, but may be given up to 14 days after exposure from the last sexual contact, due to a lower level of exposure. Refer to Figure 2. People with identifiable exposure to the infected person’s blood (e.g., sharing toothbrushes or razors) should be managed as a percutaneous or mucosal exposure (refer to Percutaneous or mucosal exposure).

Refer to Passive Immunizing Agents Part 5 for additional general information.
Figure 2*: Management of individuals with percutaneous or mucosal exposure to an infected or high risk source

1 A known source is high risk if the person comes from a region highly endemic for HB; has sexual relations with multiple partners; has a partner infected with HB or at high risk of being so; is in close family contact with an infected person; uses injection drugs; or received blood or blood products prior to 1970. Wherever possible, the source should be tested. In the case of an unknown source, background circumstances may provide some indication of the degree of risk.

2 Interventions are not required if the exposed person is known to be immune following HB infection.

3 Responder with a documented anti-HBs titre of at least 10 IU/L on prior testing.

4 Determine anti-HBs titre as soon as possible. HBIG should be administered to susceptible individuals within 48 hours after exposure. The benefit of HBIG given more than 7 days after exposure is unknown.

5 Omit administration of HBIG if the source is tested within 48 hours and the result is negative. Follow the non-infected source algorithm (refer to Figure 3).

6 Give the second dose of HBIG 1 month after the first dose.

7 Complete the vaccine series regardless of the anti-HBs titre. The anti-HBs titre may reassure the exposed individual about the immediate risk of becoming infected.

8 Omit administration of HBIG if it is possible to obtain anti-HBs serology within 48 hours and a titre of at least 10 IU/L is confirmed.

9 Determine anti-HBs titre 1 to 6 months after completion of the vaccine series.

10 Determination of anti-HBs titre should be delayed for 6 months to allow HBIG antibodies to wane.

11 Except if person is immunocompromised, has chronic renal failure or is on dialysis in which case repeat serologic testing may be needed.

* This figure has been adapted from Protocole d’immunisation du Québec, 5e édition, 2009, and published with the permission of the Ministère de la santé et des services sociaux du Québec.
Figure 3*: Management of individuals with percutaneous or mucosal exposure to an uninfected or low risk source

1 Interventions are not required if the exposed person is known to be immune following hepatitis B infection.
2 Determine anti-HBs titre 1 to 6 months after completion of the vaccine series.
3 Except if person is immunocompromised, has chronic renal failure or is on dialysis in which case repeat serologic testing may be needed.

* This figure has been adapted from Protocole d’immunisation du Québec, 5e edition, 2009 and published with the permission of the Ministère de la santé et des services sociaux.
VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose and schedule

**HB vaccine**

There are several authorized schedules for HB vaccines. The preferred schedule (particularly for children under 12 months of age) is 0, month 1 and month 6, with at least 4 weeks between the first and second dose, 2 months between the second and third dose and 4 months between the first and the third dose. For infants immunized at birth, this is considered month 0. People with chronic renal failure or on dialysis, and others with immunocompromising conditions as outlined in Immunocompromised persons may not respond well to HB vaccine and may require a higher dose. Refer to Table 3.

**DTaP-HB-IPV-Hib vaccine**

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 –

- 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.

Refer to Table 3. Refer to Diphtheria Toxoid, Tetanus Toxoid, Pertussis Vaccine and Poliomyelitis Vaccine in Part 4 for additional information.

**HAHB vaccine**

There are several authorized schedules for HAHB vaccines (refer to Table 3). In addition, studies have shown that other schedules and dosages provide good seroprotection rates. Refer to Hepatitis A Vaccine in Part 4 for additional information.
Table 3: Dosages and schedules for hepatitis B-containing vaccines

<table>
<thead>
<tr>
<th>Recipients</th>
<th>Monovalent hepatitis B</th>
<th>DTaP-HB-IPV-Hib</th>
<th>HAHB</th>
<th>TWINRIX®</th>
<th>TWINRIX® Junior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg HBsAg</td>
<td>mL</td>
<td>Schedule (Months: 1st dose = month 0)</td>
<td>µg HBsAg</td>
<td>mL</td>
</tr>
<tr>
<td>Infants and children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants of HB-negative mothers</td>
<td>2.5</td>
<td>0.2</td>
<td>0, 1, 6**</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Infants of HB-positive mothers†</td>
<td>5</td>
<td>0.5</td>
<td>0, 1, 6**</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>12 months to 23 months of age</td>
<td>2.5</td>
<td>0.2</td>
<td>0, 1, 6**</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>May be given to children aged 24 months to 7 years, if necessary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months to less than 11 years of age</td>
<td>2.5</td>
<td>0.2</td>
<td>0, 1, 6**</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>11 to 15 years of age (inclusive)</td>
<td>10</td>
<td>1.0</td>
<td>0, 4-6</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>16 to 18 years of age (inclusive)</td>
<td>5</td>
<td>0.5</td>
<td>0, 1, 6**</td>
<td>10</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Months: 1st dose = month 0)
<table>
<thead>
<tr>
<th>Recipients</th>
<th>Vaccine</th>
<th>Monovalent hepatitis B</th>
<th>DTaP-HB-IPV-Hib</th>
<th>HAHB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RECOMBIVAX HB®</td>
<td>ENGERIX®-B</td>
<td>INFANRIX hexa™</td>
<td>TWINRIX®</td>
</tr>
<tr>
<td></td>
<td>µg HBsAg</td>
<td>mL</td>
<td>Schedule (Months: 1st dose = month 0)</td>
<td>µg HBsAg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis, chronic renal failure and some immunocompromised children, under 16 years of age</td>
<td></td>
<td></td>
<td>double the µg dose for healthy child of same age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double</td>
<td>3 or 4 dose schedule</td>
<td>3 or 4 dose schedule</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Dialysis, chronic renal failure and some immunocompromised children, 16 to 19 years of age</td>
<td></td>
<td></td>
<td>double the µg dose for healthy child of same age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double</td>
<td>3 or 4 dose schedule</td>
<td>40 2.0 0, 1, 2, 6</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 years of age</td>
<td>5</td>
<td>0.5</td>
<td>0, 1, 6**</td>
<td>10x</td>
</tr>
<tr>
<td>20 years of age and older</td>
<td>10</td>
<td>1.0</td>
<td>0, 1, 6**</td>
<td>20</td>
</tr>
</tbody>
</table>
## Canadian Immunization Guide • Hepatitis B Vaccine

<table>
<thead>
<tr>
<th>Recipients</th>
<th>Vaccine</th>
<th>Monovalent hepatitis B</th>
<th>DTaP-HB-IPV-Hib</th>
<th>HAHB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RECOMBIVAX HB®</td>
<td>ENGERIX®-B</td>
<td>INFANRIX hexa™</td>
</tr>
<tr>
<td></td>
<td>µg HBsAg</td>
<td>mL Schedule (Months: 1st dose = month 0)</td>
<td>µg HBsAg</td>
<td>mL Schedule (Months: 1st dose = month 0)</td>
</tr>
<tr>
<td>Dialysis, chronic renal failure and some immunocompromised^, 20 years of age and older</td>
<td>40 (adult dialysis formulation) or 10 (standard formulation)</td>
<td>1.0 or 4.0</td>
<td>0, 1, 6</td>
<td>40</td>
</tr>
</tbody>
</table>

† For post-exposure immunization of infants of HB-infected mothers, refer to Post-exposure immunization.

** Premature infants (<37 weeks) <2,000 grams of HB-infected mothers, require four doses of HB vaccine. Refer to Infants born prematurely.

^ Although a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is months 0, 1 and 6.

¥ The manufacturer recommends the standard adult dosage (20 µg/1.0 mL) using a two dose schedule if it is unlikely that there will be compliance with the three or four dose schedule.

^ Immunocompromised defined as: congenital immunodeficiency, hematopoietic stem cell transplant, solid organ transplant, HIV-infected

µg = micrograms
Dose and schedule
HB-containing vaccine should be administered IM. Refer to Vaccine Administration Practices in Part 1 for additional information.

BOOSTER DOSES AND RE-IMMUNIZATION
Routine boosters are not recommended for immunocompetent persons. Absence of a protective antibody titre in a healthy person who has previously demonstrated an adequate anti-HBs titre does not mean lack of protection because immune memory persists. Evidence shows immunity is long lasting although antibody may be non-detectable. People immunized as an infant, child or adolescent who may be exposed to HB virus (e.g., health care workers, those with other occupational risks, men who have sex with men, injection drug users, contacts of carriers etc.) should have serology testing for anti-HBs to ensure response to vaccination (refer to Serologic Testing – post-immunization).

Immunocompromised persons, persons with chronic renal disease or on dialysis and persons undergoing chemotherapy who have responded initially to HB vaccine, may require booster doses periodically if anti-HBs titres fall below 10 IU/L (refer to Immunocompromised persons and Persons with chronic diseases). If a higher dose was indicated for the initial series, then a higher dose should also be used for the booster dose.

Additional doses of vaccine (up to three doses) will produce a protective antibody response in 50% to 70% of healthy adults and children who fail to respond after the first series of vaccine. Individuals who fail to respond to three additional doses of vaccine are unlikely to benefit from further immunization. Refer to Serologic Testing.

SEROLOGICAL TESTING

PRE-IMMUNIZATION

Prenatal
If HBsAg testing has not been done during pregnancy, it should be done at the time of delivery. An unimmunized pregnant woman who has no markers of acute or chronic HB infection but who is at high risk of acquiring HB should be offered a complete HB vaccination series at the first opportunity and tested for antibody response. Repeat testing before delivery should be considered in uninfected and unimmunized women with continuing high risk behaviour.

High risk groups
Routine pre-immunization serologic testing for HB is recommended for people at high risk of infection to identify those already infected or immune for whom vaccine will provide no benefit.

Children adopted from countries or family situations in which there is a high prevalence of HB should be screened for HBsAg and, if positive, household or close contacts in the adopting family should be immunized before adoption or as soon as possible thereafter.

POST-IMMUNIZATION

Serologic testing of infants and children is not recommended after receiving HB-containing vaccine in routine infant and childhood programs.

Post-immunization serologic testing within 1 to 6 months of completion of the vaccine series is recommended for the following groups because it is important to ensure that they are protected against HB:

- Immunocompromised persons. Periodic monitoring of the anti-HBs titre should also be considered, taking into account the severity of the immunocompromised state and whether the risk of HB is still present. Refer to Booster doses and re-immunization and Immunocompromised persons.
● Persons with chronic renal disease or on dialysis. Anti-HBs titres should also be evaluated yearly. Refer to Booster doses and re-immunization and Immunocompromised persons.
● High risk pregnant women who are immunized before or during pregnancy. Refer to Pregnancy and breastfeeding.
● Infants born to infected mothers should be tested for HBsAg and anti-HBs one month after completion of the vaccine series. Refer to Post-exposure immunization.
● Persons with potential percutaneous or mucosal exposure, such as men who have sex with men and injection drug users. Refer to Post-exposure immunization.
● Sexual partners and household contacts of acute cases and chronic carriers of HB. Refer to Post-exposure immunization.
● Workers who have been immunized because of risk of occupational exposure. Refer to Workers.

Refer to Booster doses and re-immunization.

**STORAGE REQUIREMENTS**

Store HB-containing vaccine 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. Refer to Passive Immunizing Agents Part 5 for information regarding HBIg storage.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**

Hepatitis B-containing vaccines may be administered concomitantly with other 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 IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS**

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

**COMMON AND LOCAL ADVERSE EVENTS**

**HB vaccine**

HB vaccine is well tolerated. Reactions are usually mild and transient, and include irritability, headache, fatigue and injection site reactions (e.g., pain and redness) in 10% or more of recipients.

**HAHB vaccine**

There is no increase in adverse events when HAHB vaccine is compared with HA vaccine given alone or concomitantly with HB vaccine at a different injection site. When adult dose HAHB vaccine is given to children in the two dose schedule, there is no increase in adverse events compared with those occurring after administration of the pediatric dose.

**DTaP-HB-IPV-Hib vaccine**

Reactions are usually mild and transient, and include fever, irritability, restlessness and injection site reactions (e.g., redness, swelling and pain).

**HBIg**

Headache, diarrhea, fever, urticaria, angioedema and injection site reactions (e.g., pain and tenderness) may occur.

**LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS**

Serious adverse events are rare following HB immunization and, in most cases, data are insufficient to determine a causal association. Anaphylaxis following vaccination with HB-containing vaccine may occur but is very rare.
OTHER REPORTED ADVERSE EVENTS AND CONDITIONS
While serious events and chronic illnesses have been alleged or reported following HB vaccination, no evidence of a causal association has been demonstrated in a number of studies. These chronic illnesses or serious events include chronic fatigue syndrome, multiple sclerosis, Guillain-Barré syndrome, rheumatoid arthritis and sudden infant death syndrome.

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) (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
HB-containing vaccines and HBlg are contraindicated in persons with a history of anaphylaxis after previous administration of the product and in persons with proven immediate or anaphylactic hypersensitivity to any component of the product or its container. Refer to 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 HB-containing vaccines, potential allergens include:

- ENGERIX®-B: yeast
- INFANRIX™-hexa: latex in plunger stopper of pre-filled syringe, neomycin, polymyxin B, yeast
- RECOMBIVAX HB®: latex in vial stopper, yeast
- TWINRIX® and TWINRIX® Junior: latex in plunger stopper of pre-filled syringe, neomycin, yeast

Yeast protein is used in the development of HB and HAHB 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.

The safety of HAHB vaccine given during pregnancy has not been studied in clinical trials. However, because the vaccine is prepared from inactivated viruses, the theoretical risk to the developing fetus is expected to be low.

Routine administration of HB-containing vaccine should be postponed in persons with moderate or severe acute illness, but this is subject to a risk/benefit assessment if immunization is recommended for post-exposure management. Consultation may be advised. 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
Monovalent HB vaccines may be used interchangeably, using the dosage and schedules recommended by the manufacturer for the age group. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.
SELECTED REFERENCES


PART 4
HERPES ZOSTER (SHINGLES) VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Selected References

KEY INFORMATION (refer to text for details)

| What | • Primary varicella zoster virus infection causes varicella (chickenpox) and reactivated infection results in herpes zoster (shingles).
|      | • Herpes zoster (HZ) occurs most frequently among older adults and immunocompromised persons.
|      | • Post-herpetic neuralgia is the most frequent complication of HZ.
|      | • HZ vaccine reduces the incidence of HZ and post-herpetic neuralgia.
|      | • Reactions are usually mild; injection site pain, swelling or redness occur in 48% of vaccine recipients. |

| Who  | • Recommended for persons without contraindications 60 years of age and older, and may be used in adults 50 years of age and older.
|      | • May be administered to individuals 50 years of age and older with a prior history of HZ disease with at least one year recommended following the last episode of HZ.
|      | • In general, should not be given to individuals with primary or acquired immune deficiency but may be administered to individuals on low dose immunosuppression; consultation with a medical expert is advised in some instances. |

| How  | HZ vaccine is a live vaccine that contains the same components as the univalent varicella vaccine, VARIVAX® III (Merck Canada Inc.), but with an approximately 14-fold or higher virus concentration. |

| Why  | • HZ is painful and can have severe complications.
|      | • The incidence and severity of HZ and its complications increase with age.
|      | • The lifetime risk of HZ is estimated to be as high as 30%.
|      | • HZ vaccine is safe and effective |

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Herpes zoster (shingles) is a manifestation of reactivation of the varicella zoster virus (VZV), a DNA virus of the Herpesvirus family, which, as a primary infection, causes varicella (chickenpox).

Reservoir
Humans

Transmission
VZV can be spread from a person with HZ to an individual that has never had varicella by direct contact with skin lesions. Less commonly, VZV can be spread by the airborne route if the person has disseminated HZ. Less frequently, transmission can occur from fomites, such as articles freshly soiled by discharges from vesicles or, in the case of disseminated HZ, mucous membrane secretions. The person who acquires VZV through these routes will develop varicella (chickenpox). The incubation period is from 10 to 21 days, usually in the range of 14 to 16 days. HZ is less likely to result in transmission of VZV than varicella. Persons with HZ are infectious until all lesions are crusted over.

Risk factors
Any person who has had varicella is at risk of developing HZ; however, HZ occurs most frequently among older adults and immunocompromised persons. Age is the most important risk factor for development of HZ and two-thirds of the cases occur in individuals over 50 years of age. This age-related risk may be explained by both waning immunity over time following the initial varicella infection, and the loss of components of VZV-specific cell mediated immunity as a result of natural aging processes. The severity of illness associated with HZ and its complications also increases markedly with age. Up to 10% of person over 65 years of age will be admitted to hospital with an episode of HZ. Recent studies have shown that the widespread use of varicella vaccine has not impacted the incidence of HZ.

Spectrum of clinical illness
VZV causes two distinct clinical syndromes: primary infection (varicella, also called chickenpox) and reactivation of latent infection (HZ, also called shingles). Following varicella, VZV establishes latency in the sensory nerve ganglia, and may reactivate later as HZ.

HZ infection is characterized by pain and a unilateral vesicular eruption, usually in a single dermatome. Complications of acute HZ are potentially severe and may include sight-threatening eye infections, central nervous system infection, nerve palsies including the Ramsay-Hunt Syndrome, neuromuscular disease including Guillain-Barré Syndrome, and secondary bacterial infections. The most frequent complication of acute HZ is post-herpetic neuralgia (PHN) which is characterized by prolonged and often debilitating neurogenic pain that persists for more than 90 days from the onset of rash. This complication occurs in approximately 20% of adults with HZ and in one-third or more of octogenarians and often has a major adverse impact on quality of life, especially in elderly persons. Treatment options for PHN are of limited effectiveness. The risk of mortality from VZV-associated disease is low.
DISEASE DISTRIBUTION

Incidence/prevalence

Global
Globally, the incidence of HZ ranges from 1.2 to 3.4 cases per 1,000 healthy persons per year, increasing to 3.9 to 11.8 cases per 1,000 individuals per year among those over 65 years of age. HZ-associated hospitalization rates vary across countries and are estimated to range from 5 to 10 per 100,000 people for an average length of stay of 10 to 13 days.

National
In recent studies, the lifetime risk of HZ has been estimated to be as high as 30% in the general population. In Canada, it is estimated that each year, there are 130,000 new cases of HZ, 17,000 cases of PHN and 20 deaths, which result in 252,000 physician consultations and 2,000 hospitalizations.

The relationship between the introduction of routine childhood varicella immunization programs and the incidence of HZ in adults is unclear. It had been hypothesized that implementation of childhood varicella immunization programs might decrease natural immune boosting of older persons from circulating wild-type VZV and thereby increase the risk of VZV reactivation. However, different jurisdictions have reported increases and decreases in the incidence of HZ over time, and it is likely that multiple other factors contribute to variations in the incidence of HZ, including modifications to reporting or diagnostic coding of cases or changes in risk factors.

PREPARATION AVAILABLE FOR USE IN CANADA

HERPES ZOSTER VACCINE

- ZOSTAVAX® (varicella zoster vaccine live, attenuated [Oka/Merck]), Merck Canada Inc. (Zos)

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

EFFICACY, EFFECTIVENESS AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS
The incidence of HZ and PHN, as well as the duration and severity of HZ were significantly reduced in HZ vaccine recipients in a large clinical trial of people 60 years of age and older. Overall vaccine efficacy was 51.3% for HZ incidence and 66.5% for PHN. Subsequent studies in people aged 50 to 59 years showed HZ vaccine to be safe, immunogenic and effective in this population as well. Vaccine protection against HZ remains statistically significant up to 5 years and results also suggest some efficacy up to year 7.

IMMUNOGENICITY
The immune correlates of protection from HZ among individuals previously infected with varicella are not well established, and none have been accepted as markers of protection. A clinical trial has demonstrated that HZ vaccine elicited higher VZV-specific immune responses at 6 weeks post-vaccination than placebo. Vaccine-related immune responses declined significantly over the subsequent year, then remained relatively stable for the following two years.
RECOMMENDATIONS FOR USE

ADULTS

Adults (60 years of age and older)
One dose of HZ vaccine is recommended for persons without contraindications 60 years of age and older for the prevention of HZ and PHN. HZ vaccine is not intended for the prevention of varicella or for the treatment of HZ or PHN.

Adults (50 to 59 years of age)
HZ vaccine may be used in adults aged 50 to 59 years of age without contraindications. The incidence and severity of HZ begins to increase with age after 50 years. While all adults aged 50 and older receive some benefit, the duration of protection is unknown beyond 5 years, and it is uncertain whether vaccination in this age group will provide ongoing protection at older ages when the incidence of HZ is higher.

Adults with a history of herpes zoster disease
HZ disease may recur in individuals who have previously had one or more episodes of HZ disease. Vaccinated individuals may have lower recurrence rates as shown in one study. Other studies have shown that administration of HZ vaccine to individuals with a prior history of HZ disease is safe. Based on these findings and favourable immunogenicity studies, HZ vaccine may be administered to individuals 50 years of age and older with a prior history of HZ disease. Based on expert opinion, there should be an interval of at least one year between an episode of HZ and receipt of HZ vaccine. Persons with active HZ should not be immunized with HZ vaccine.

Adults with a history of herpes zoster ophthalmicus
There are few reports of recurrent HZ ophthalmicus (HZO) in patients who have a history of HZO and subsequently receive HZ vaccine. NACI has reviewed these reports but causality has been difficult to determine, since HZO may recur at any time. Therefore, if considering immunization of individuals with a history of HZO, it is important to discuss these cases with an ophthalmologist and to ensure that patients with a history of HZO no longer have active disease. Patients with a history of HZO should be informed by their healthcare provider that cases of recurrent HZO following vaccine have occurred, although causality has not been established, and that the risk of recurrent HZO relative to the potential benefit of preventing future recurrences is unknown. Refer to Less common and serious or severe adverse events.

Adults with or without a history of varicella or documented prior varicella infection
HZ vaccine should be administered to individuals indicated for vaccine regardless of whether or not the person has a history of varicella infection. Given that nearly all Canadians eligible for HZ immunization will have had prior varicella exposure, even if a diagnosis of varicella cannot be recalled, routine testing of adults aged 50 years and older for VZV antibody prior to immunization is not recommended. There is no known safety risk associated with vaccination of healthy individuals who are susceptible to VZV. In the rare circumstance that an adult aged 50 years and older is known to be serologically susceptible to VZV, based on previous testing for another reason, the individual should be vaccinated with two doses of univalent varicella vaccine rather than HZ vaccine.

PREGNANCY AND BREASTFEEDING
HZ vaccine is not normally indicated for women of childbearing potential but, as a live vaccine, it is contraindicated during pregnancy. It is recommended that women avoid pregnancy for at least 4 weeks after receipt of HZ vaccine. It is not known whether HZ vaccine virus is secreted in human milk. Given the age indication for HZ vaccine, pregnant or breastfeeding women are unlikely among the target population. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.
PERSONS/RESIDENTS IN HEALTH CARE INSTITUTIONS
Residents of long-term care facilities should receive all routine immunizations appropriate for their age and risk factors, including HZ vaccine. Refer to Immunization of Patients in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS
In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strain. There is some evidence, however, that HZ disease may occur more frequently in immunocompromised persons compared with immunocompetent persons. One study found a statistically significant increase in the incidence of HZ recurrence in immunocompromised persons of 12% compared to 5.7% in immunocompetent persons at 8 years after the initial HZ episode. Literature suggests that HZ vaccine may be safely administered to individuals on low-dose immunosuppression. Given the higher burden of illness in immunocompromised persons, the safety and efficacy of HZ vaccine in this population is an important area of ongoing research. Refer to Immunosuppressive therapy.

When considering immunization of an immunocompromised person, approval from the individual’s attending physician should be obtained before vaccination. For complex cases, referral to a physician with expertise in immunization or immunodeficiency is advised.

Congenital (primary) immunodeficiency
All live vaccines, including HZ vaccine, are contraindicated in people with defects in T cell function (e.g., T cell, natural killer cell, and combined cellular and antibody defects). Persons with isolated immunoglobulin deficiency, phagocytic defects (e.g., chronic granulomatous disease), complement deficiency, and neutrophil disorders (e.g., neutropenia, Chediak-Higashi syndrome) may be vaccinated with HZ vaccine.

Acquired (secondary) immunodeficiency

Malignant hematologic disorders
HZ vaccine is contraindicated in individuals with severe immunodeficiency due to conditions such as: blood dyscrasias, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems. HZ vaccine is contraindicated in people with immunodeficiency due to acute or chronic leukemia. However, persons with leukemia in remission and who have not received immunosuppressive chemotherapy or radiation for at least 3 months and who do not have defects in T cell function can receive HZ vaccine; consultation with an immunologist may be required.

Malignant solid tumours
HZ vaccine is contraindicated in people undergoing immunosuppressive treatment for any malignant solid tumours.

Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)
- Pre-transplantation: People awaiting HSCT should not receive HZ vaccine. Vaccination of donors immediately before stem cell harvest is not recommended as there is no evidence that immunity can be transferred from the donor to the recipient and there are no safety data.
- Post-transplantation: HSCT recipients should not receive HZ vaccine. Immunization of HSCT recipients with univalent varicella vaccine (not HZ vaccine) may be considered at two years after transplantation. Refer to Varicella (Chickenpox) Vaccine in Part 4 for additional information.
- data are not available regarding administration of more than one dose of varicella-containing vaccine after HSCT.

Solid organ transplantation
HZ vaccine should not be given after solid organ transplantation.
Immunosuppressive therapy

Vaccination status for HZ should be reviewed for immunocompetent persons aged 50 years and older who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency.

If indicated, HZ vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy (e.g. 20 mg/day or more of prednisone or its equivalent for an adult for 14 days or more; chemotherapy; extensive radiation therapy; cyclosporine; cyclophosphamide). If vaccine cannot be given in this time frame before immunosuppressive therapy, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of live vaccines. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of live vaccines. The interval between discontinuation of immunosuppressive drugs and HZ vaccine administration may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.

Unlike other live vaccines, HZ vaccine is not used for eliciting a primary immune response and most persons receiving this vaccine have prior immunity to varicella. Therefore, it is reasonable to consider HZ vaccine in people receiving low dose immunosuppressive therapy as follows:

- ≤ methotrexate 0.4 mg/kg/week;
- ≤ azathioprine 3.0 mg/kg/day;
- ≤ 6-mercaptopurine 1.5 mg/kg/day;

Retrospective data also demonstrate the safety of HZ vaccine in people receiving anti-TNF biologics (TNF-alpha antagonists and TNF-receptor blockers) for inflammatory conditions. The risk associated with HZ vaccine may increase if people who are also receiving other immunosuppressive agents such corticosteroid therapy. It is reasonable to consider HZ vaccine in patients receiving anti-TNF biologics on a case by case basis after review with an expert in immunodeficiency.

Corticosteroid therapy is not a contraindication to administering a live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 20 mg of prednisone or equivalent per day for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically (e.g., joint injection).

HIV-infected

A specialist in HIV infection/immunologist should be consulted for advice on HZ immunization in HIV-infected people. HZ vaccine is contraindicated in persons with advanced HIV/AIDS.

Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information

PERSONS WITH CHRONIC DISEASES

Autoimmune diseases

Although definitive data are lacking, individuals with autoimmune disease not being treated with immunosuppressive drugs are not considered significantly immunocompromised and should receive HZ immunization following consultation with a physician. Rheumatic disease modifying agents such as hydroxychloroquine, sulfasalazine, or auranofin are not considered immunosuppressive. The nature of the person’s underlying disease should be considered. HZ vaccine may be considered in persons on low doses of immunosuppressive agents. Refer to Immunosuppressive therapy for additional information.
Refer to *Immunization of Persons with Chronic Diseases* in Part 3 for additional general information.

WORKERS

Workers are not at increased risk of developing HZ because HZ is due to reactivation of a latent VZV infection. However, it is important to promote varicella (chickenpox) immunization with those who are at occupational risk of exposure or transmission to high risk individuals. Refer to *Varicella (Chickenpox) Vaccine* in Part 4 for more specific information and to *Immunization of Workers* in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION

HZ vaccine is not indicated for post-exposure management of individuals susceptible to varicella. Refer to *Post-exposure immunization* in *Varicella (Chickenpox) Vaccine* in Part 4 for appropriate management of individuals who are susceptible to varicella following close contact with a person with HZ. Close contact to a person with HZ includes:

- Touching the rash, exposed lesion or vesicle fluid
- Contact with an individual who has disseminated HZ.
- Contact with articles freshly soiled by discharges from vesicles.
- Contact with articles freshly soiled by mucous membrane secretions of an infected person with disseminated HZ.
- Exposure to an immunosuppressed person with localized HZ anywhere on the body, as their viral shedding may be greater.

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

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

**Dose**

Each dose is 0.65 mL (the entire contents of the reconstituted vial).

**Route of administration**

HZ vaccine should be administered subcutaneously. Refer to *Vaccine Administration Practices* in Part 1 for additional information.

**Schedule**

Persons, 60 years of age and older without contraindications, should receive one dose of HZ vaccine. Adults 50 to 59 years of age without contraindications may receive one dose of HZ vaccine.

BOOSTER DOSES AND RE-IMMUNIZATION

There is no current recommendation for booster doses of HZ vaccine. The efficacy of protection has not been assessed beyond 7 years and it is not known whether booster doses of vaccine are beneficial. This is an area of ongoing research.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving HZ vaccine. There is no known safety risk associated with HZ vaccination of healthy individuals who are VZV susceptible. In the rare circumstance that an adult aged 50 years and older is known to be susceptible to VZV, based on previous serological testing for another reason, the individual should be vaccinated with two doses of univalent varicella vaccine rather than HZ vaccine.
STORAGE REQUIREMENTS

HZ vaccine should be stored frozen at -15°C or colder. Diluent should be stored at room temperature (+20°C to +25°C) or in the refrigerator (+2°C to +8°C) and should not be frozen. Before reconstitution, the vaccine should be protected from light. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

In general, HZ vaccine may be administered concomitantly with other live vaccines given by the parenteral, oral, or intranasal routes. For concomitant parenteral injections, different injection sites and separate needles and syringes should be used. HZ vaccine may be given at any time before or after live oral or intranasal vaccines. If two live parenteral vaccines are not administered concomitantly, there should be a period of at least 4 weeks before the second live parenteral vaccine is given. Concomitant administration of pneumococcal 23-valent polysaccharide vaccine (Pneu-P-23) and HZ vaccine has not resulted in decreased efficacy and so the two vaccines can be given concomitantly.

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

HZ vaccine has been evaluated for safety in the large placebo-controlled Shingles Prevention Study (SPS) that included a subgroup followed closely for adverse events. Reactions were usually mild and included injection site pain, swelling or redness in up to 48.3% of recipients, compared to 16.6% in placebo recipients. Most reactions resolved within 4 days. The rate was higher in recipients aged 60 to 69 years than those over 70 years of age. Less serious systemic adverse events, such as headache, were more common in vaccine recipients (6.3% versus 4.9%).

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

In the SPS study, a varicella-like rash occurred at the injection site in 0.11% of vaccinees (0.04% in placebo recipients) and lasted between 5 and 6 days, but varicella-like rashes elsewhere were similar in the two groups and lasted longer in both. In an earlier study, vaccine strain virus had been rarely identified in specimens of lesions from subjects who reported varicella-like rashes, but none were found in the SPS.

In the SPS, there were no clinically significant differences in serious adverse events between the vaccine and placebo groups. Overall and HZ–related rates of hospitalization were similar between the vaccine and placebo groups. There was no overall difference in observed deaths in the HZ vaccinated group as compared to the placebo group.

The safety and tolerability of a second dose of HZ vaccine administered 42 days following the initial dose was evaluated in a clinical trial of 98 adults. The frequency of adverse events after the second dose was generally similar to that seen with the first dose.

Recurrence or exacerbation of herpes zoster ophthalmicus (HZO) has been reported in several cases worldwide following HZ vaccination in people with a history of HZO. Following a causality assessment of seven cases of HZO which were temporally associated with the administration of HZ vaccine, NACI concluded that there was insufficient evidence to recommend for or against the administration of HZ vaccine in individuals with a history of HZO. More evidence is required for further assessment of risk.
related to HZO recurrence. See *Contraindications and Precautions* if considering vaccinating a person with previous HZO.

Refer to *Guidance on reporting Adverse Events Following Immunization*.

**GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)**

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Any serious or unexpected serious adverse events 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.
- Suspected transmission of vaccine-strain virus to a close household or occupational contact. This phenomenon has been documented following varicella vaccine but it is rare, and transmission has not been documented with HZ vaccine.
- Recurrent HZ following immunization of individuals with a history of HZ prior to immunization, noting the area of recurrence.
- Recurrent HZO following HZ vaccination of a person who has had a previous episode of HZO should be reported as an adverse event of special interest. If available, a vitreous fluid specimen should be sent to a laboratory with a request to determine whether the virus is the vaccine strain or wild type virus.

Refer to Table 1 *Vaccine Safety* in Part 2 and the *User Guide to the Completion and Submission of the AEFI Reports* for additional information about AEFI reporting. ([http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php](http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php))

**CONTRAINDICATIONS AND PRECAUTIONS**

HZ 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. Refer to *Contents of Immunizing Agents available for use in Canada* in Part 1 for lists of vaccines and passive immunizing agents available for use in Canada and their contents. For ZOSTAVAX®, known allergens include neomycin and porcine gelatin.

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.

With some exceptions (refer to *Immunocompromised persons*), HZ vaccine should not be given to individuals with primary or acquired immune deficiency due to conditions such as: acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS; or cellular immune deficiencies. Furthermore, the safety and efficacy of HZ vaccine has not been established in adults who are known to be infected with HIV without evidence of immunosuppression.

HZ vaccine should not be administered to individuals who have recently used or are currently using immune suppressive medications outlined in *Table 1*. The vaccine is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids in people who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency) or low dose immunosuppressives as defined above. Individuals on anti-TNF biologics for inflammatory conditions should be considered on a case by case basis.
Table 1: Immunosuppressive medication

<table>
<thead>
<tr>
<th>Immunosuppressive medication</th>
<th>Example brand name (company)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mercaptopurine*</td>
<td>PURINETHOL®(Novopharm Ltd.)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>MabCampath®(Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>Thymoglobulin®(Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)</td>
</tr>
<tr>
<td>Azathioprine*</td>
<td>IMURAN (Triton Pharma Inc.)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>SIMULECT™ (Novartis Pharmaceuticals Canada Inc.)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>PROCYTOX (Baxter Corp.) CYTOXAN</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>NEORAL™ (Novartis Pharmaceuticals Canada Inc.)</td>
</tr>
<tr>
<td>High-dose systemic corticosteroids (20 mg/day or more of prednisone or its equivalent for an adult) for 14 days or more*</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>ARAVA®(Sanofi-Aventis Canada Inc.)</td>
</tr>
<tr>
<td>Methotrexate*</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td></td>
</tr>
<tr>
<td>Most cancer chemotherapies (except tamoxifen, hydroxyurea, and gonadotropin release inhibitors which are not considered immunocompromising) - If 3 months post-chemotherapy and the cancer is in remission, the person is not considered immunocompromised</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>CellCept®(Hoffman-LaRoche Ltd.)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Rapamune®(Pfizer Canada Inc.)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Prograf®(Astellas Pharma Canada Inc.)</td>
</tr>
<tr>
<td>Non-TNF biologic immunosuppressives used in inflammatory disease</td>
<td>Orecnia™ (Bristol-Myers Squibb Canada) RITUXAN®(Hoffman-LaRoche Ltd.)</td>
</tr>
</tbody>
</table>

Adapted from: Guidelines to Determining Immunosuppressing Conditions or Medications for which MMR is contraindicated. Nova Scotia Department of Health and Wellness. Product monographs for drugs authorized by Health Canada can be found at Health Canada’s Drug Product Database.

* For lower doses of these medications (such as used for rheumatologic conditions), refer to the Immunosuppressive therapy section above.

Vaccination should be deferred in individuals with active untreated tuberculosis.

HZ vaccine is contraindicated during pregnancy and it is recommended that women avoid pregnancy for at least 4 weeks after the receipt of the vaccine.

As with all live vaccines, there is a theoretical risk of transmission of HZ vaccine virus from vaccinated to susceptible individuals. While post-marketing experience with varicella vaccines has documented transmission of vaccine virus between vaccinees who develop a varicella-like rash and susceptible
contacts, no case of transmission of HZ vaccine virus from a vaccinated individual who develops a rash to another person has been documented to date.

If considering immunization of individuals with a history of HZO, it is important to discuss these cases with an ophthalmologist and ensure that patients with a history of HZO no longer have active disease. Patients with a history of HZO should be informed by their healthcare provider that cases of recurrent HZO following vaccine have occurred, although causality has not been established, and the risk of recurrent HZO relative to the potential benefit of preventing future recurrences is unknown.

Administration of HZ vaccine should be postponed in persons suffering from severe acute illness. Immunization should not be delayed because of minor acute illness, with or without fever.

Refer to **Contraindications, Precautions and Concerns** in Part 2 for additional general information.

**DRUG INTERACTIONS**

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of VZV-containing vaccine such as HZ vaccine. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of VZV vaccine and should not restart antiviral therapy until 14 days after.

Although no safety or efficacy data are available for the administration of HZ vaccine to individuals who have recently received immune globulins or other blood products, the vaccine is known to be immunogenic in adults with pre-existing antibody to VZV. In theory, administration of Ig should not interfere with the vaccine response; therefore, some experts do not consider recent administration of Ig or blood products as a reason to delay the administration of herpes zoster vaccine. Refer to **Blood products, human immune globulin and timing of immunization** in Part 1 for additional information concerning the administration of live vaccines and blood products of human origin.

**SELECTED REFERENCES**


PART 4
HUMAN PAPILLOMAVIRUS VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | • Human papillomavirus (HPV) infections are the most common sexually transmitted infections. Most HPV infections occur without symptoms and resolve without treatment. |  
|      | • If not immunized, most sexually active Canadians will have an asymptomatic HPV infection at some time. |  
|      | • High-risk HPV types 16 and 18 and others can lead to cervical and anogenital cancers as well as certain cancers of the head and neck. |  
|      | • Low-risk HPV types 6 and 11 can cause genital warts. |  
|      | • CERVARIX™ (GlaxoSmithKline Inc., HPV2) and GARDASIL® (Merck Canada Inc., HPV4) vaccines help protect against cervical cancer. HPV4 vaccine also helps protect against genital warts. |  
|      | • The most commonly reported adverse events following HPV vaccination are injection site pain, swelling or redness. As with other vaccines, syncope can occur following HPV vaccination. |  

| Who | • HPV2 or HPV4 vaccine is recommended for prevention of cervical cancer in girls and women (9 to 26 years of age, including those who have had previous Papanicolaou [Pap] test abnormalities, cervical cancer or genital warts). |  
|     | • HPV4 vaccine is recommended for the prevention of vulvar, vaginal, anal cancers and their precursors and anogenital warts in girls and women (9 to 26 years of age). |  
|     | • HPV2 or HPV4 vaccine may be administered to women 27 years of age and older at ongoing risk of exposure. |  
|     | • The choice of vaccine for women depends upon the importance of protection against genital warts. |  
|     | • HPV4 vaccine is recommended for prevention of anogenital cancer and genital warts in boys and men (9 to 26 years of age), including men who have sex with men (MSM) as they are at higher risk of HPV infection and disease. |  
|     | • HPV4 vaccine may be administered to men 27 years of age and older, at ongoing risk of exposure. HPV2 vaccine is not recommended in boys and men. |
**How**

- Give HPV vaccine as three separate 0.5 mL doses - HPV2 vaccine at months 0, 1, and 6 or HPV4 vaccine at months 0, 2, and 6.
- Because fainting post-vaccination is more common in younger people, it is particularly important to observe each vaccinee for 15 minutes after vaccine administration to avoid serious injury in the event of syncope.
- Women should be advised to participate in regular cervical cancer screening regardless of HPV immunization.

**Why**

If not immunized, it is estimated that 75% of sexually active Canadians will have a HPV infection at some time. Even if already infected with one or more vaccine HPV type(s), the vaccine will provide protection against the other HPV type(s) contained in the vaccine.


---

**Epidemiology**

**Disease Description**

**Infectious agent**

Human papillomaviruses (HPV) are small, double-stranded DNA viruses that infect the epithelium. More than 100 HPV genotypes have been identified including approximately 40 genotypes that affect the human anogenital area. These HPV genotypes are categorized as low-risk/non-oncogenic (e.g., types 6 and 11) or high-risk/oncogenic (e.g., types 16 and 18) based on their association with cervical cancer.

**Reservoir**

Humans

**Transmission**

HPV infections are transmitted sexually by direct epithelial (skin or mucosa) contact and vertically to an infant exposed to the virus in the maternal genital tract.

**Risk factors**

**Women**

In women, risk factors for HPV infections include: number of sexual partners, previous sexually transmitted infection, history of sexual abuse, early age of first sexual intercourse, partner’s number of lifetime sex partners, tobacco and/or marijuana use, immune suppression, and HIV infection.

**Men**

The most consistent factor associated with increased risk of HPV infection among men is the lifetime number of sex partners, inconsistent condom use and men who have sex with men (MSM). MSM are about 20 times more likely than heterosexual men to develop anal cancer. Rates of anal cancer among HIV-positive MSM are higher than rates of cervical cancer among women even in countries with the highest cervical cancer rates. There is a significant protective effect associated with circumcision.
Spectrum of clinical illness

Most HPV infections are asymptomatic and self-limiting, clearing within 24 months. Infection with a given HPV type does not decrease the probability of being infected by other HPV types. Persistent infection with a high-risk HPV type is the major cause of cervical cancer and is implicated in cancers of the penis, anus, vulva, vagina, mouth and oropharynx. Infection with low-risk HPV types can cause non-cancerous lesions, such as genital warts. HPV infection can be transmitted to the fetus before and during birth. As a result, newborns can develop recurrent respiratory papillomatosis, which is associated with a high degree of morbidity; in some cases it can be fatal.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

- Women: HPV prevalence estimates for women worldwide range from 2% to 44%. The peak risk for HPV infection is within 5 to 10 years of the first sexual experience. Among women less than 25 years of age, high-risk HPV types predominate, whereas in women over 55 years of age, low-risk and uncharacterized HPV types are the most common.
- Men: A systematic review of studies identified HPV prevalence estimates of 1.3% to 72.9%, with 56% of studies reporting a prevalence of 20% or more in men. HPV type 16 is consistently among the most common HPV types reported. In men, no significant association between age and HPV prevalence, incidence or duration of infection has been found.
- HPV-associated cancers: Worldwide, the total burden of HPV-associated cancers in both genders is estimated at 5.2% of all cancers. Globally, cervical cancer is estimated to be the second most common malignancy affecting women. Almost all cervical cancers are associated with high-risk HPV types; types 16 and 18 are present in 70% of cervical cancers in North America. Among cancers affecting men, it is estimated that HPV infection is associated with 80% to 90% of anal cancers, 40% to 50% of penile cancers, 35% of oropharyngeal cancers and 25% of oral cavity cancers. Among HPV-associated cancers, approximately 92% of anal cancers, 63% of penile cancers and 89% of oral cavity and oropharyngeal cancers are attributable to HPV types 16 and 18.
- Genital warts: In the United Kingdom, genital wart prevalence is estimated at 130 per 100,000. Estimates from the United States are slightly higher, between 150 and 205 per 100,000. Genital warts are associated with HPV types 6 and 11 in more than 90% of cases, with 20% to 50% of cases co-infected with high-risk HPV types.

National

In North America, the lifetime cumulative incidence of HPV infection is estimated at more than 70% for all HPV types combined, which makes HPV the most common sexually transmitted infection. In the absence of vaccination, it is estimated that 75% of sexually active Canadians will have a sexually transmitted HPV infection at some point in their lives. The highest prevalence is found in persons 20 to 24 years of age.

- Women: A study of a Canadian population-based sample of women 13 to 86 years of age estimated overall HPV prevalence in women to be 16.8%. The prevalence of HPV types 6, 11, 16 and 18 was 4.0%, 0.2%, 10.7% and 3.5%, respectively. HPV positivity was most prevalent in women under 20 years of age with a significant trend of decreasing prevalence seen until 60 years of age.
- Men: There are few published Canadian studies of HPV prevalence or incidence among men. Estimates of HPV infection among men are primarily based on prevalence and incidence studies in selected populations, many of which may have a bias towards higher rates of infection because of multiple sexual partners. One Canadian study reported a prevalence of any HPV type of 69.8% in a sexually transmitted infection clinic population of heterosexual men ranging in age from 16 to 69 years (median age, 29 years).
HPV-associated cancers: In 2011, the cervical cancer incidence rate was estimated to be 7 cases per 100,000. Cervical cancer is the 13th most common cancer among Canadian women of all ages and the third most common among those aged 20 to 44 years. Annually, there are approximately 1300 cervical cancer cases and 350 deaths related to cervical cancer. In Canada, it is estimated that HPV infection is associated with 90% of anal cancers, 50% of penile cancers, 35% of oropharyngeal cancers and 25% of oral cavity cancers. Among HPV-associated cancers, approximately 92% of anal cancers, 63% of penile cancers and 89% of oral cavity and oropharyngeal cancers are attributable to high-risk HPV types 16 and 18.

Genital warts: Canadian studies have reported incidence rates of genital warts between 131 to 154 per 100,000 in men and 120 to 121 per 100,000 in women. Prevalence was estimated at 146.4 to 148.0 per 100,000. Prevalence and incidence were consistently higher among men compared to women and incidence peaked between 20 and 24 years of age for women and 25 to 29 years of age for men.

PREPARATIONS AVAILABLE FOR USE IN CANADA

- **CERVARIX™** (bivalent human papillomavirus (types 16, 18), recombinant, AS04 adjuvanted vaccine), GlaxoSmithKline Inc. (HPV2).
- **GARDASIL®** (quadrivalent human papillomavirus (types 6, 11, 16, 18), recombinant vaccine), Merck Canada Inc. (HPV4).

For complete prescribing information, consult the product leaflet or information contained within Health Canada’s authorized product monographs available through the Drug Product Database. 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

HPV vaccine is highly effective for the prevention of HPV vaccine type-related persistent infection and cervical cancer. In women 16 to 26 years of age, the efficacy of HPV4 vaccine against HPV types 16 and 18-related cervical disease is nearly 100%; efficacy against external genital lesions related to HPV types 6, 11, 16, or 18, including genital warts, is 95% to 99%. In men 16 to 26 years of age, HPV4 vaccine efficacy against vaccine type-related external genital lesions is 84% to 100%; efficacy against persistent vaccine-type related infection is 70% to 96%. Among HPV-naïve women 15-26 years of age, vaccination with HPV4 resulted in an overall reduction in abnormal PAP smears of 17.5%, colposcopy by 19.8%, cervical biopsy by 22% and cervical definitive therapy of 42.3%. In women 24-45 years of age, efficacy of HPV4 vaccine against a composite end point of HPV 6, 11, 16 and 18 persistent infection and cervical or external genital disease was 91% and against HPV types 16 and 18 only was 83%. In women aged 15 to 25 years, efficacy of HPV2 vaccine against HPV types 16 and 18-related cervical disease is 95% to 99%.

HPV vaccine has no proven therapeutic effect on existing HPV infection. Prior infection with one or more vaccine HPV types does not diminish vaccine efficacy against other vaccine HPV types. The duration of protection following HPV vaccination is not known. Clinical trial subjects have been followed for more than 7 years with no evidence of waning protection.

Studies suggest that vaccination of women may prevent transmission of vaccine HPV types to men. While there are no studies that directly demonstrate that HPV vaccination of men will prevent transmission of vaccine HPV types from men to women with a reduction in incidence of cervical cancer, hypothetical models predict that addition of men to a routine HPV vaccination program will prevent additional cases of genital warts and cervical cancer among women to varying degrees.
IMMUNOGENICITY
HPV vaccine is highly immunogenic. More than 99% of recipients develop an antibody response to vaccine HPV types after completing the three dose series. The immune correlates of protection against HPV infection are unknown.

RECOMMENDATIONS FOR USE

GIRLS AND WOMEN

9 to 26 years of age
HPV2 or HPV4 vaccine is recommended for prevention of cervical cancer and precursors in girls and women 9 to 26 years of age, including those who have had previous Pap test abnormalities, cervical cancer or genital warts. HPV4 vaccine is recommended for the prevention of vulvar, vaginal, anal cancers and their precursors and anogenital warts in girls and women 9 to 26 years of age.

While efficacy of HPV vaccine in girls 9 to 13 years of age has not been demonstrated, immunogenicity evidence implies that efficacy will be high; HPV vaccination between 9 and 13 years of age (prior to onset of sexual activity and exposure to HPV) maximizes the benefit of the vaccine.

Although women with previous Pap test abnormalities, cervical cancer or genital warts may have had prior infection with one or more vaccine HPV types, they will benefit from receiving HPV vaccine for the HPV types to which they have not been exposed. Women should be advised that the vaccine does not have any therapeutic effect on pre-existing cervical disease.

Participation in cervical cancer screening programs should be recommended to women regardless of HPV immunization.

27 years of age and older
HPV2 or HPV4 vaccine may be administered to women 27 years of age and older at ongoing risk of exposure to HPV. While peak risk for HPV infection is within five to ten years of the first sexual experience, a second peak in HPV DNA prevalence is observed in women 45 years and older. Although the second peak is not as high as the peak rates in younger women, it represents an increased risk. While the reason for this second peak is not yet fully understood, receipt of HPV vaccine by previously unimmunized adult women could reduce the risk of HPV infection occurring later in life. Refer to Risk Factors for additional information. HPV4 vaccine immunogenicity, safety, and efficacy have been demonstrated in women between 24 and 45 years of age. Efficacy of HPV2 vaccine has not been demonstrated in this age group, but immunogenicity data suggest that efficacy will be high.

Choice of vaccine
The choice of HPV vaccine (HPV2 or HPV4) depends upon the importance of protection against genital warts. If genital wart protection is desired, vaccination with HPV4 vaccine is recommended. If the goal of vaccination is prevention of HPV type 16 and 18-related cancers and their precursors, either HPV2 or HPV4 vaccine may be used.

BOYS AND MEN

9 to 26 years of age
HPV4 vaccine is recommended in boys and men 9 to 26 years of age for the prevention of anogenital warts, penile and anal cancer, perineal intraepithelial neoplasias and associated cancers. While efficacy of HPV vaccine in boys 9 to 15 years of age has not been demonstrated, immunogenicity evidence implies that efficacy will be high. Receipt of HPV4 vaccine between 9 and 13 years of age
(prior to onset of sexual activity and exposure to HPV infection) is recommended to maximize the benefit of the vaccine.

**Men who have sex with men (MSM)**

Compared to the general population, MSM have a disproportionately high burden of HPV infection, particularly high-risk HPV types 16 and 18. Infection with high-risk HPV types is associated with anal cancer and its precursor, particularly among MSM who are HIV-positive. Early receipt of HPV4 vaccine will confer maximum benefit, because MSM may become infected with HPV more rapidly due to the high rate of infection in the MSM population. HPV4 vaccine is recommended for men less than 27 years of age who have sex with men. Although there are no data on the efficacy of HPV 4 vaccine in men 27 years and older who have sex with men, they should be strongly considered for HPV4 vaccine regardless of their age because of their increased risk of HPV related diseases.

**27 years of age and older**

There are no data on the safety, immunogenicity, or efficacy of HPV4 vaccine in men 27 years of age and older so no evidence-based recommendations can be made for the use of the vaccine in this age at this time. However, HPV4 vaccine may be considered for men 27 years of age and older who are at ongoing risk of exposure to HPV. Refer to Risk Factors for additional information.

**Choice of vaccine**

HPV2 vaccine is not recommended in boys or men at this time.

**IMMUNIZATION AFTER ONSET OF SEXUAL ACTIVITY**

HPV vaccination after the onset of sexual activity is beneficial because the vaccinee is very unlikely to be infected with all HPV types in the vaccine. Vaccinees who have already had sexual activity should be advised that they may already be infected with a vaccine HPV type and should be informed that the vaccine will not have any therapeutic effect on pre-existing vaccine HPV type infections. There are no data on the use of HPV vaccine in children less than 9 years of age. HPV vaccine may be considered in children less than 9 years of age who are at risk of exposure to HPV (e.g. those who are sexually active, have a history of sexual abuse or have been diagnosed with a sexually transmitted infection).

Refer to Schedule.

**PREGNANCY AND BREASTFEEDING**

HPV vaccines are not recommended for use in pregnancy because data on HPV vaccination in pregnancy are limited. HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus. Initiation of the HPV vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, completion of the series should be delayed until after pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

Vaccinees and health care providers are encouraged to report any exposure to HPV4 vaccine during pregnancy to the vaccine manufacturer (Merck Canada Inc.) at 1-800-567-2594. Exposure to HPV2 vaccine during pregnancy should be reported to the vaccine manufacturer (GlaxoSmithKline Inc.) at 1-800-387-7374.

There are limited data on the effects on breastfed infants from HPV vaccination of their mothers, however, there have been no reported adverse events thought to be vaccine-related. HPV vaccine may be administered to lactating women. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

**IMMUNOCOMPROMISED PERSONS**

HPV vaccine may be administered to immunocompromised persons according to routine vaccination schedules. However, the immune response and vaccine efficacy may be less than that in persons who
are immunocompetent. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised. For example, HPV vaccination may be considered prior to surgery in a 7 or 8 year old child who will be immunosuppressed following a renal transplant. Refer to *Immunization of Immunocompromised Persons* in Part 3 for additional general information.

**VACCINE ADMINISTRATION**

**DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE**

**Dose**
Each dose of HPV is 0.5 mL.

**Route of administration**
HPV vaccine should be administered intramuscularly. Refer to *Vaccine Administration Practices* in Part 1 for additional information.

**Post-immunization observation period**
Syncope can occur after any vaccination, most commonly among adolescents and young adults. HPV vaccine recipients should be observed for 15 minutes after vaccine administration to avoid serious injury in the event of syncope.

**Schedule**

*HPV2 vaccine*
Administer at months 0, 1 and 6 (first dose is month 0).

*HPV4 vaccine*
Administer at months 0, 2 and 6 (first dose is month 0). The minimum interval between the first and second dose is one month and the second and third doses should be separated by an interval of at least 12 weeks.

*Incomplete or interrupted vaccine schedule*
An HPV vaccine series should be initiated even if the series may not be completed according to schedule. If the vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible and the third dose given at the recommended interval from the second dose. If only the third dose is delayed, it should be administered as soon as possible.

*Two dose schedule*
Evidence regarding the use of a two dose schedule will be reviewed by the NACI in the future.

**BOOSTER DOSES AND RE-IMMUNIZATION**
Re-immunization with HPV vaccine is not recommended.

**SEROLOGICAL TESTING**
Serologic testing is not recommended before or after receiving HPV vaccine. Testing methods are not routinely available.

**STORAGE REQUIREMENTS**
Store HPV vaccine at +2°C to +8°C and do not freeze. Protect from light. Refer to *Storage and Handling of Immunizing Agents* in Part 1 for additional general information.
SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

HPV vaccine may be administered concomitantly with other age-appropriate 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 Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

Based on pre-licensure clinical trials involving more than 15,000 subjects given HPV4 vaccine and 12,000 given HPV2 vaccine, the most common adverse events in persons receiving HPV vaccine were vaccination site pain (82% to 92%), swelling (24% to 44%) or redness (24% to 48%). These adverse events were observed significantly more often following HPV vaccine than active vaccine or placebo controls (which included hepatitis A or hepatitis A/hepatitis B vaccine, aluminum phosphate or saline). In over 94% of subjects who received HPV vaccine, the reactions were mild to moderate in intensity, resolved over a few days, and did not prevent completion of the immunization schedule. Systemic adverse events, such as fatigue, myalgia, headache, fever, and nausea, generally occurred with comparable frequency in vaccine and placebo/control groups.

Since vaccine licensure, tens of millions of doses of both vaccines have been distributed worldwide. Data from post-licensure safety surveillance reporting systems have consistently mirrored the pre-licensure data with the most frequently reported adverse events following immunization (AEFI) being vaccination site reactions and muscle pain.

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. Clinical trials have found no increase in the number or type of serious adverse events in recipients of HPV vaccine compared with those who received placebo. Anaphylaxis following vaccination with HPV vaccine may occur but is very rare.

Syncope, sometimes accompanied by tonic-clonic movements, has been reported following vaccination with HPV vaccine. Similar events follow other vaccines given to adolescents and young adults and can also occur in other age groups. Such reactions are expected and usually occur within the first several minutes following immunization. However, secondary injury may occur from a fall. Of 1,896 reports of syncope to the US Vaccine Adverse Event Reporting System (VAERS), 293 (15%) resulted in a fall and, of these, 200 led to head injury. Most injuries are preventable by ensuring vaccinees are observed for 15 minutes after vaccination. Refer to Vaccine Administration for additional information.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Studies of the AS04 adjuvant used in HPV2 vaccine have demonstrated no evidence of an increase in risk of autoimmune disorders associated with receipt of AS04 adjuvanted vaccine.

The vaccine safety profile of HPV vaccines has been reviewed by both the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety and the US Institute of Medicine (IOM). (http://www.who.int/vaccine_safety/topics/hpv/Jun_2009/en/index.html)

To date the evidence supports an association between HPV vaccine and anaphylaxis and potential injury as a result of post-vaccination dizziness and syncope. Based on the IOM review, to date there has been no published evidence to support an association between HPV vaccine and any of the following conditions: Guillain-Barre Syndrome, transverse myelitis, acute disseminated encephalomyelitis, multiple
sclerosis, brachial neuritis, chronic inflammatory disseminated polyneuropathy, amyotrophic lateral sclerosis, neuromyelitis optica, pancreatitis, transient arthralgia or thromboembolic events.

Of 56 cases of venous thromboembolic events reported to the US VAERS, only 31 could be confirmed through clinical case review. Of these 31 cases, 90% had a known risk factor for venous thromboembolism including oral contraceptive use in 20 cases.

Deaths following HPV vaccine were observed in pre-licensure trials but occurred no more frequently than in the placebo groups. While post-market AEFI reports have included deaths, the rate is not in excess of what could be expected to occur by chance alone.

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 Vaccine Safety in Part 2 and additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

HPV 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. 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. HPV-4 (GARDASIL®) vaccine contains yeast protein. 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.

HPV vaccine is not recommended for use in pregnancy because data on HPV vaccination in pregnancy are limited. HPV vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the fetus. Refer to Pregnancy and Breastfeeding.

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

OTHER CONSIDERATIONS

CERVICAL CANCER SCREENING IN WOMEN WHO HAVE RECEIVED HPV VACCINES

All women should be screened for cervical cancer regardless of HPV immunization. While HPV vaccine has been shown to be highly effective against cervical cancer caused by HPV types 16 and 18, vaccinees remain susceptible to infection from other high-risk HPV types. In addition, sexually active women may have been infected with HPV type 16 and/or 18 prior to receiving HPV vaccine.

INTERCHANGEABILITY OF VACCINES

Whenever possible, one manufacturer's brand of HPV vaccine should be used to complete the vaccine series. If the brand of the previously received doses is not known, either brand of HPV vaccine may be used to complete series. Because both HPV vaccines provide protection against HPV types 16 and 18, protective antibody concentrations against these types will likely be achieved if HPV2 and HPV4 vaccines are interchanged. If less than three doses of HPV4 vaccine are administered, protection against HPV types 6 and 11 cannot be ensured. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.
SELECTED REFERENCES


PART 4

INFLUENZA VACCINE

- Key Information Table
- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications
  - Precautions
- Selected References

KEY INFORMATION (refer to text for details)

| What | Influenza is a respiratory infection primarily caused by influenza A and B viruses that occurs in Canada each year in the late fall and winter months. Most people will recover within a week or ten days, but some are at greater risk of more severe complications, such as pneumonia. There are currently eight seasonal trivalent influenza vaccines authorized for use in Canada. Influenza vaccine is safe and well-tolerated and may be given to persons starting from six months of age (noting product-specific age indications and contraindications). |
| Who | Immunization programs should focus on: |
|     | • those at high risk of influenza-related complications - adults and children with underlying health conditions, including morbid obesity; residents of nursing homes and other chronic care facilities; people 65 years of age and older; children 6 to 59 months of age; pregnant women; and Aboriginal peoples; |
|     | • those capable of spreading influenza to individuals at high risk of complications - health care providers in facilities and community settings; household contacts of high-risk persons including those 59 months of age and younger; those providing care to children 59 months of age and younger; and those providing services in closed settings to those at high risk (e.g., crew on a ship); and |
|     | • those who provide essential community services. |
|     | The National Advisory Committee on Immunization (NACI) also encourages influenza vaccine for all Canadians aged 6 months and older, because they can also benefit from influenza protection. |
How Each province or territory will advise which vaccines will be made available for the publicly-funded program in that jurisdiction.

Children who have been previously immunized with seasonal influenza vaccine and adults are to receive one dose of influenza vaccine each year. Children 6 months to less than 9 years of age receiving seasonal influenza vaccine for the first time should be given two doses, with a minimum interval of four weeks between doses. The route of administration and dosage varies by product. For intramuscular (IM) TIV, the dose is 0.5 ml for all age groups.

Why It is estimated that between 10-20% of the population becomes infected with influenza each year. Each year there is a new vaccine to protect against the influenza virus strains that are expected in the coming influenza season. Vaccination is the most effective way to prevent influenza and its complications.

The National Advisory Committee on Immunization (NACI) produces an annual Statement regarding seasonal influenza vaccination. Health care providers should consult the current annual Statement available at the NACI website for information and recommendations specific to the upcoming influenza season. (http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Influenza is a respiratory infection caused by influenza A and B viruses. Influenza A viruses are classified into subtypes on the basis of two surface proteins: hemagglutinin (HA) and neuraminidase (NA). Influenza B have evolved into two lineages, B/Yamagata/16/88-like and B/Victoria/2/87-like viruses. Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or B lineage.

Transmission
Influenza is primarily transmitted by droplets spread through coughing or sneezing and may also be transmitted through direct or indirect contact with contaminated respiratory secretions. The incubation period of seasonal influenza is usually two days but can range from one to four days. Adults may be able to spread influenza to others from one day before symptom onset to approximately five days after symptoms start. Children and people with weakened immune systems may be infectious for longer.

Risk factors
The people at greatest risk of influenza-related complications are adults and children with underlying health conditions, including morbid obesity; residents of nursing homes and other chronic care facilities; people 65 years of age and older; children 6 to 59 months of age; pregnant women; and Aboriginal peoples.

Seasonal/temporal pattern
In Canada, influenza generally occurs each year in the late fall and winter months.

Spectrum of clinical illness
Symptoms typically include the sudden onset of high fever, cough and muscle aches. Other common symptoms include headache, chills, loss of appetite fatigue and sore throat. Nausea, vomiting and diarrhea may also occur, especially in children. Most people will recover within a week or ten days, but some - including those 65 years of age and older and adults and children with chronic conditions - are at greater risk of more severe complications, such as pneumonia.
DISEASE DISTRIBUTION

Incidence/prevalence

Global

Worldwide, annual epidemics result in an approximately one billion cases of influenza, about three to five million cases of severe illness, and about 250,000 to 500,000 deaths. For current international influenza activity information refer to WHO’s FluNet website. (http://www.who.int/influenza/gisrs_laboratory/flunet/en/)

National

Influenza activity in Canada usually is low in the spring and summer, begins to rise over the fall and peaks in the winter months (depending on the year, the peak may occur as early as late fall or as late as early spring). The FluWatch program collects data and information from various sources to provide a national picture of influenza activity. For current influenza activity information refer to PHAC’s FluWatch website. (http://www.phac-aspc.gc.ca/fluwatch/index-eng.php)

PREPARATIONS AUTHORIZED FOR USE IN CANADA

Influenza vaccines authorized for use in Canada must meet predetermined immunogenicity and safety criteria or standards set by Health Canada. Influenza vaccine may be administered to anyone ≥6 months of age without contraindications. There are currently eight seasonal trivalent influenza vaccines authorized for use in Canada.

- Agriflu® (Novartis) (TIV)
- Fludad® (Novartis) (TIV)
- FluMist® (AstraZeneca) live attenuated vaccine (LAIV)
- Fluviral® (GlaxoSmithKline) (TIV)
- Fluzone® (Sanofi Pasteur) (TIV)
- Influvac® (Abbott) (TIV)
- Intanza® (Sanofi Pasteur) 9 µg and 15 µg formulations (TIV-ID)
- Vaxigrip® (Sanofi Pasteur) (TIV)

For information about the characteristics of influenza vaccines authorized in Canada refer to the most current Statement on Seasonal Influenza Vaccine. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-4/) For complete prescribing information, consult the product leaflet or information contained within the Health Canada’s authorized product monographs available through Health Canada’s Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Each province or territory will advise which vaccines will be made available for the publicly-funded program in their jurisdiction.

TRIVALENT INACTIVATED INFLUENZA VACCINE (TIV)

The seven TIV products currently authorized for use in Canada are a mix of split virus and subunit vaccines, which are standardized to contain the same HA content. In split virus vaccines, the virus has been disrupted by a detergent. In subunit vaccines, HA and NA have been further purified by removal of other viral components. The amount of NA in the vaccines is not standardized. Refer to Basic Immunology and Vaccinology in Part 1 for more information about inactivated vaccines.

One of the TIV products, Fludad®, contains the adjuvant MF59, which is an oil-in-water emulsion composed of squalene as the oil phase, stabilized with the surfactants polysorbate 80 and sorbitan triolate in citrate buffer. The other six TIV products do not contain an adjuvant.

One of the TIV products (Intanza®) is administered intra-dermally; the other six TIV products are administered intramuscularly.
LIVE ATTENUATED INFLUENZA VACCINE (LAIV)

FluMist® is a live attenuated influenza vaccine for administration by intranasal spray and authorized for use for persons 2-59 years of age. Each 0.2 mL dose of FluMist®, (given as 0.1 mL in each nostril) contains $10^{6.5-7.5}$ fluorescent focus units (FFU) of live attenuated virus reassortants of each of three strains propagated in pathogen-free eggs. The influenza strains in FluMist® are cold-adapted and temperature sensitive, so they replicate in the nasal mucosa rather than the lower respiratory tract, and they are attenuated so they do not produce classic influenza-like illness.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

Multiple studies show that influenza vaccine is efficacious with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes. In healthy children (equal to or younger than 18 or 16 years old) a systematic review and meta-analyses showed that efficacy of influenza vaccine against laboratory confirmed influenza ranged from 59% to 82%, efficacy against serologically-confirmed influenza ranged from 54% to 63% and efficacy against clinical illness ranged between 33% to 36%. In a systematic review, for healthy adults, inactivated influenza vaccine efficacy against laboratory-confirmed influenza was 80% (95% CI, 56 to 91) and vaccine effectiveness against influenza-like illness was 30% (95% CI, 17 to 41) when the vaccine strain matched the circulating strains and circulation was high. Another meta-analysis identified vaccine efficacy of 50% in healthy adults (95% CI, 27 to 65) during select seasons of vaccine mismatch, although mismatch is a relative term and the amount of cross-protection is expected to vary. In the elderly, vaccine effectiveness is about half of that of healthy adults and varies depending on the outcome and the study population.

In observational studies, immunization has been shown to reduce the number of physician visits, hospitalizations and deaths in high-risk persons 18 to 64 years of age, hospitalizations for cardiac disease and stroke in the elderly, and hospitalization and deaths in persons with diabetes mellitus 18 years of age and older.

For a summary of efficacy studies refer to the most recent NACI seasonal influenza statement.

IMMUNOGENICITY

The antigenic components of the vaccine may change each year. Because influenza viruses change over time, immunity conferred in one season will not reliably prevent infection by an antigenically drifted strain. Even if the vaccine strains have not changed, immunity generally wanes within a year of receiving the vaccine and re-immunization reinforces optimal protection for the coming influenza season.

The antibody response after vaccination depends on several factors, including the age of the recipient, prior and subsequent exposure to antigens and the presence of immune compromising conditions. Humoral antibody levels, which correlate with vaccine protection, are generally achieved by two weeks after immunization; however, there may be some protection afforded before that time.

RECOMMENDATIONS FOR USE

Influenza vaccine may be administered to anyone 6 months of age and older without contraindications. Decisions regarding the precise timing of vaccination in a given setting or geographic area should be made according to local epidemiologic factors (influenza activity, timing and intensity), opportune moments for vaccination, as well as programmatic issues.

With the variety of influenza vaccines that are now available, it is important for practitioners to note the specific differences in age indications, route of administration, dosage and schedule for the products that they will be using (Table 3). Characteristics of influenza vaccines authorized in Canada are available in Contents of Immunizing Agents Available for Use in Canada in Part and the most recent NACI seasonal influenza statement.
**RECOMMENDED RECIPIENTS OF INFLUENZA VACCINE**

To reduce the morbidity and mortality associated with influenza, immunization programs should focus on those at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications and those who provide essential community services (refer to Table 1). Healthy persons aged 5 to 64 years who do not have contraindications to influenza vaccine are also encouraged to receive influenza vaccine even if they are not in one of the recommended recipient groups.

<table>
<thead>
<tr>
<th>People at high risk of influenza-related complications or hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults (including pregnant women) and children with the following chronic health conditions:</td>
</tr>
<tr>
<td>o cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);</td>
</tr>
<tr>
<td>o diabetes mellitus and other metabolic diseases;</td>
</tr>
<tr>
<td>o cancer, immune compromising conditions (due to underlying disease and/or therapy);</td>
</tr>
<tr>
<td>o renal disease;</td>
</tr>
<tr>
<td>o anemia or hemoglobinopathy;</td>
</tr>
<tr>
<td>o conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;</td>
</tr>
<tr>
<td>o morbid obesity (BMI≥40); and</td>
</tr>
<tr>
<td>o children and adolescents with conditions treated for long periods with acetylsalicylic acid.</td>
</tr>
<tr>
<td>• People of any age who are residents of nursing homes and other chronic care facilities.</td>
</tr>
<tr>
<td>• People ≥65 years of age.</td>
</tr>
<tr>
<td>• All children 6 to 59 months of age.</td>
</tr>
<tr>
<td>• Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e. it is higher in the third than in the second trimester)</td>
</tr>
<tr>
<td>• Aboriginal peoples.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People capable of transmitting influenza to those at high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.</td>
</tr>
<tr>
<td>• Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):</td>
</tr>
<tr>
<td>o household contacts of individuals at high risk, as listed in the section above;</td>
</tr>
<tr>
<td>o household contacts of infants &lt;6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine; and</td>
</tr>
<tr>
<td>o members of a household expecting a newborn during the influenza season.</td>
</tr>
<tr>
<td>• Those providing regular child care to children ≤59 months of age, whether in or out of the home.</td>
</tr>
<tr>
<td>• Those who provide services within closed or relatively closed settings to persons at high risk (e.g. crew on a ship).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>• People who provide essential community services.</td>
</tr>
<tr>
<td>• People in direct contact during culling operations with poultry infected with avian influenza.</td>
</tr>
</tbody>
</table>

---

1 Healthy persons aged 5 to 64 years who do not have contraindications to influenza vaccine are also encouraged to receive influenza vaccine even if they are not in one of the recommended recipient groups.

**PREGNANCY AND BREASTFEEDING**

All pregnant women, at any stage of pregnancy, should be included among high priority recipients of influenza vaccine due to the risk of influenza-associated morbidity in pregnant women, evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy, evidence that vaccination of pregnant women protects their newborns from influenza and
influenza-related hospitalization, and evidence that infants born during influenza season to vaccinated women are less likely to be premature, small for gestational age, and low birth weight.

Both TIV and TIV-ID (9 µg) are available for use in pregnant women and there is no preference for the use of either product. Due to a lack of safety data at this time, LAIV, which is a live attenuated vaccine, should not be administered to pregnant women, but it can be administered to breastfeeding women. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional information.

IMMUNOCOMPROMISED PERSONS

Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune compromising conditions, including transplant recipients, those with proliferative diseases of the hematopoietic and lymphatic systems, and HIV-infected persons. Vaccine efficacy may be lower in persons with immune compromising conditions than in healthy adults. LAIV is not recommended for people with immune compromising conditions. If TIV-ID is being used for adults with immune compromising conditions, the 15 µg formulation should be considered to improve response.

Close contacts

LAIV recipients should avoid close association with persons with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least two weeks following vaccination, because of the theoretical risk for transmission. Refer to Immunization of Immunocompromised Persons in Part 3 for additional information.

TRAVELLERS

Influenza occurs year-round in the tropics. In temperate northern and southern countries, influenza activity peaks generally during the winter season (November to March in the Northern Hemisphere and April to October in the Southern Hemisphere). Influenza vaccination is recommended for travellers with a chronic health condition or other factors that would make them part of the recommended recipients of influenza vaccine due to increased risk of complications following influenza infection. In addition, influenza immunization is encouraged for all Canadians over 6 months of age which would also apply to travellers.

Vaccines prepared specifically for use in the Southern Hemisphere are not available in Canada, and the extent to which recommended vaccine components for the Southern Hemisphere may overlap with those in available Canadian formulations will vary. A decision in favour or against re-vaccination (i.e., boosting) of travellers to the Southern Hemisphere between April and October if they had already been vaccinated in the preceding fall/winter with the Northern Hemisphere vaccine depends on individual risk assessment, the similarity or differences between the Northern and Southern hemisphere vaccines, and the availability of a reliable and safe vaccine at the traveller's destination. For further information on advising travellers about influenza prevention, consult the Committee to Advise on Tropical Medicine and Travel (CATMAT) website. (http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/) Refer to Immunization of Travellers in Part 3 for additional general information.

CHOICE OF SEASONAL INFLUENZA VACCINE

With the recent authorization of a number of new vaccines, some of which are designed to enhance immunogenicity in specific age groups, the choice of product is no longer straightforward. The decision to include specific influenza vaccines as part of publicly-funded provincial/territorial programs depends on multiple factors such as cost-benefit evaluation and other programmatic and operational factors, such as shelf-life and implementation strategies. Not all products will be made available in all jurisdictions and availability of some products may be limited, vaccine providers should consult their province or territory for specifics on the products provided in their jurisdiction. Table 2 summarizes current recommendations for the choice(s) of influenza vaccine in specific age and risk groups.
Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)

<table>
<thead>
<tr>
<th>Recipient by age group</th>
<th>Vaccine types available for use</th>
<th>Preferred vaccine for healthy persons</th>
<th>Preferred vaccine for persons with chronic health conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6-23 months of age</td>
<td>TIV</td>
<td>-</td>
<td>-</td>
<td>Only TIV is available for this age group</td>
</tr>
<tr>
<td>Children 2-17 years of age</td>
<td>TIV, LAIV</td>
<td>LAIV&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No preference</td>
<td>Children with immune compromising conditions: LAIV not recommended</td>
</tr>
<tr>
<td>Adults 18-59 years of age</td>
<td>TIV, TIV-ID (9 µg), LAIV</td>
<td>No preference</td>
<td>TIV, TIV-ID (15 µg)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Adults with immune compromising conditions: LAIV not recommended</td>
</tr>
<tr>
<td>Adults 60-64 years of age</td>
<td>TIV, TIV-ID (15 µg)</td>
<td>No preference</td>
<td>No preference</td>
<td></td>
</tr>
<tr>
<td>Adults 65+ years of age</td>
<td>TIV, TIV-ID (15 µg), MF59-adjuvanted TIV</td>
<td>No preference</td>
<td>No preference</td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td>TIV, TIV-ID (9 µg)</td>
<td>No preference</td>
<td>No preference</td>
<td>LAIV not recommended</td>
</tr>
</tbody>
</table>

TIV = trivalent inactivated influenza vaccine (for IM administration)
TIV-ID = trivalent inactivated influenza vaccine for intradermal injection
LAIV = live attenuated influenza vaccine

<sup>1</sup> Unless contraindicated, there is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV, with weaker evidence of superior efficacy in older children. It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent.

<sup>2</sup> With TIV-ID, consider the 15 µg formulation for adults with immune compromising conditions.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

The recommended dosage schedule for the authorized products is presented in Table 3. Children 6 to 35 months of age should be given a full dose (0.5 mL) of TIV as is recommended for older children and adults. The first time children 6 months to less than 9 years of age receive seasonal influenza vaccine, whether TIV or LAIV, a two-dose schedule is required with a minimum interval of four weeks between doses. Pending further evidence, eligible children less than 9 years of age who have previously received one or more doses of seasonal influenza vaccine should receive one dose per influenza vaccination season thereafter.

The recommended injection site for TIV-ID, which is given intradermally using the supplied micro-injection device, is the deltoid region. LAIV is intended for intranasal administration only and should not be administered by the IM or ID route. It is supplied in a pre-filled single use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (one-half) is sprayed into the first nostril with the recipient upright, then the dose divider clip is removed and the remainder of the vaccine (0.1 mL) is sprayed into the other nostril. Refer to Vaccine Administration Practices in Part 1 and the manufacturer’s instructions available in the product leaflet and product monograph for additional information.
Table 3: Influenza vaccine: Recommended dosage and route, by age, for the 2013-2014 season

<table>
<thead>
<tr>
<th>Age group</th>
<th>TIV without adjuvant(^1) IM</th>
<th>MF59 -adjuvanted TIV (Fluaq(^8)) IM</th>
<th>TIV for intradermal use (Intanza(^9)) ID</th>
<th>LAIV (FluMist(^10)) IN</th>
<th>Number of doses required</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–23 months</td>
<td>0.5 mL(^3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 or 2(^4)</td>
</tr>
<tr>
<td>2–8 years</td>
<td>0.5 mL</td>
<td>-</td>
<td>-</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1 or 2(^4)</td>
</tr>
<tr>
<td>9–17 years</td>
<td>0.5 mL</td>
<td>-</td>
<td>-</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1</td>
</tr>
<tr>
<td>18–59 years</td>
<td>0.5 mL</td>
<td>0.1 mL (9 µg/strain)(^5)</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>60–64 years</td>
<td>0.5 mL</td>
<td>0.1 mL (15 µg/strain)</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.1 mL (15 µg/strain)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Influvac\(^8\) ≥18 years; Fluviral\(^8\) ≥6 months; Agriflu\(^8\) ≥6 months; Vaxigrip\(^8\) ≥6 months; and Fluzone\(^8\) ≥6 months

\(^2\) Unless contraindicated, there is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV, with weaker evidence of superior efficacy in older children. It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent.

\(^3\) This information differs from the product monograph. Recommendations for use and other information in this Guide may differ from that set out in the product monographs/leaflets of the Canadian manufacturers.

\(^4\) Children 6 months to less than 9 years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children less than 9 years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter.

\(^5\) For adults with immune compromising conditions, the 15µg formulation should be considered to improve response.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Booster doses are not recommended within the same influenza season.

**SEROLOGICAL TESTING**

Serologic testing is not recommended before or after receiving seasonal influenza vaccine.

**STORAGE REQUIREMENTS**

Influenza vaccine should be stored at +2°C to +8°C and should not be frozen. Refer to the individual product monographs for further details. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional information.
SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

All influenza vaccines, including LAIV, may be given concomitantly with or at any time before or after live attenuated vaccines or inactivated vaccines. When administering two or more parenteral vaccines, different administration sets (needle and syringe) should be used for each injection. Refer to Timing of Vaccine Administration in Part 1 for additional information.

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. Health care providers should take the opportunity to vaccinate eligible persons against pneumococcal disease when influenza vaccine is given.

VACCINE SAFETY AND ADVERSE EVENTS

Influenza vaccine is safe and well-tolerated and may be given to persons starting from six months of age (noting product-specific age indications and contraindications). Refer to Vaccine Safety Part 2 for additional information.

COMMON AND LOCAL ADVERSE EVENTS

TIV
With IM products, soreness at the injection site lasting up to two days is common in adults but rarely interferes with normal activities. Healthy adults receiving TIV show no increase in the frequency of fever or other systemic symptoms compared with those receiving placebo. TIV is safe and well tolerated in healthy children. Mild injection site reactions, primarily soreness at the vaccination site, occur in 7% or less of healthy children who are less than 3 years of age. Post-vaccination fever may be observed in 12% or less of immunized children 1 to 5 years of age.

MF59-adjuvanted TIV (Fluad®) produces injection site reactions (pain, erythema and induration) significantly more frequently than non-adjuvanted vaccines, but they are classified as mild and transient. Systemic reactions (myalgia, headache, fatigue and malaise) are comparable or more frequent with Fluad® compared to non-adjuvanted vaccines and are rated as mild to moderate and transient.

TIV-ID produces more frequent and more extensive erythema, swelling, induration and pruritus than vaccine given by the IM route. These reactions are generally mild and resolve spontaneously within a few days. Systemic reactions following TIV-ID are comparable to IM vaccine, except for myalgia which is less common with TIV-ID.

LAIV
The most common adverse events experienced by LAIV recipients are nasal congestion and runny nose.

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. Allergic responses to influenza vaccine are a rare consequence of hypersensitivity to some vaccine components. Refer to Contraindications and Precautions for additional information.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Guillain-Barré syndrome (GBS)
Recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines. Refer to Contraindications and Precautions for additional information.
Oculo-respiratory syndrome (ORS)
Oculo-respiratory syndrome (ORS), defined as the onset of bilateral red eyes and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) and/or facial swelling occurring within 24 hours of influenza immunization, was found during the 2000-2001 influenza season; few cases have been reported since then. It is not considered to be an allergic response.

Persons who have a recurrence of ORS upon revaccination do not necessarily experience further episodes with future vaccinations. Data on clinically significant adverse events do not support the preference of one vaccine product over another when revaccinating those who have previously experienced ORS. Refer to Contraindications and Precautions for additional information.

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. The following AEIFIs are of particular interest:

- Oculo-respiratory Syndrome (ORS)
- Guillain-Barré Syndrome (GBS) within 6 weeks following immunization


CONTRAINDICATIONS
Influenza vaccine should not be given to:

- people who have had an anaphylactic reaction to a previous dose; or
- people who have had an anaphylactic reaction to any of the vaccine components, with the exception of egg.

Refer to 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.

Additional LAIV - specific contraindications

LAIV should not be administered to:

- Children less than 24 months of age due to increased risk of wheezing.
- Individuals with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) or those with medically attended wheezing in the 7 days prior to vaccination.
- Children and adolescents (2 to 17 years of age) currently receiving aspirin or aspirin-containing therapy because of the association of Reye’s syndrome with aspirin and wild-type influenza infection. It is recommended that aspirin-containing products in children less than 18 years of age be delayed for four weeks after receipt of LAIV.
- Pregnant women, because it is a live attenuated vaccine and there is a lack of safety data at this time. However, it is not contraindicated in breastfeeding mothers.
- Persons with immune compromising conditions, due to underlying disease and/or therapy, as the vaccine contains live attenuated virus.
PRECAUTIONS

Allergic reactions to previous vaccine doses

Expert review of the risks and benefits of vaccination should be sought for those who have previously experienced severe lower respiratory symptoms (wheeze, chest tightness, difficulty breathing) within 24 hours of influenza vaccination, an apparent significant allergic reaction to the vaccine or any other symptoms (e.g., throat constriction, difficulty swallowing) that raise concern regarding the safety of re-immunization. This advice may be obtained from local medical officers of health or other experts in infectious disease, allergy/immunology and/or public health.

In view of the considerable morbidity and mortality associated with influenza, a diagnosis of influenza vaccine allergy should not be made without confirmation (which may involve skin testing) from an allergy/immunology expert. Individuals who have an allergy to substances that are not components of the influenza vaccine are not at increased risk of allergy to influenza vaccine.

Oculo-respiratory syndrome (ORS)

Individuals who have experienced ORS without lower respiratory tract symptoms - may be safely re-immunized with influenza vaccine. Persons who experienced ORS with lower respiratory tract symptoms should have an expert review. Health care providers who are unsure whether an individual previously experienced ORS versus an IgE-mediated hypersensitivity immune response should seek advice.

Guillain-Barré syndrome (GBS)

Although the evidence considering influenza vaccination and GBS was inadequate to accept or reject a causal relation between GBS in adults and seasonal influenza vaccination, avoiding subsequent influenza vaccination of persons known to have had GBS within six weeks of a previous influenza vaccination appears prudent at this time. However, the potential risk of GBS recurrence associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself.

Severe acute illness with or without fever

Administration of seasonal influenza vaccine should usually be postponed in persons with serious acute illness until their symptoms have abated. Immunization should not be delayed because of minor acute illness, with or without fever. If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, TIV can be administered or LAIV could be deferred until resolution of the illness.

Additional LAIV - specific precautions

LAIV recipients should avoid close association with persons with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least two weeks following vaccination, because of the theoretical risk for transmitting a vaccine virus and causing infection.

ADMINISTRATION OF INFLUENZA VACCINE TO EGG ALLERGIC PERSONS

All influenza vaccine products are manufactured by a process involving chicken eggs, which may result in the vaccine containing trace amounts of residual egg protein.

Egg-allergic individuals may be vaccinated against influenza using TIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg, with the following conditions. Those with mild reactions such as hives, or those who tolerate eggs in baked goods may be vaccinated in regular vaccination clinics. Those who have suffered from anaphylaxis with respiratory or cardiovascular symptoms should be vaccinated in a medical clinic, allergy office or hospital where appropriate expertise and equipment to manage respiratory or cardiovascular compromise is present. These individuals should always be kept under observation for 30 minutes.
Referral to a specialist with expertise in allergies may be necessary in occasional circumstances where there is strong concern about proceeding with the recommendation above and the individual is at risk of complications from influenza. If the individual is not in a high-risk group, the need for vaccination may be reassessed.

Data are not currently available to support this recommendation for LAIV.

Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.

**DRUG INTERACTIONS**

Although influenza vaccine can inhibit the clearance of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. It is recommended that LAIV not be administered until 48 hours after antiviral agents active against influenza (oseltamivir and zanamivir) are stopped, and that antiviral agents not be administered until two weeks after receipt of LAIV unless medically indicated. If antiviral agents are administered within this time frame (from 48 hours before to two weeks after LAIV is given), revaccination should take place at least 48 hours after the antivirals are stopped.

**SELECTED REFERENCES**


Institute of Medicine. *Immunization safety review: influenza vaccines and neurological complications.*


# JAPANESE ENCEPHALITIS VACCINE

- **Epidemiology**
- **Preparations Authorized for Use in Canada**
- **Efficacy, Effectiveness and Immunogenicity**
- **Recommendations for Use**
- **Vaccine Administration**
- **Serologic Testing**
- **Storage Requirements**
- **Simultaneous Administration with Other Vaccines**
- **Vaccine Safety and Adverse Events**
  - Common and local adverse events
  - Contraindications and precautions
- **Other Considerations**
- **Selected References**

## KEY INFORMATION (refer to text for details)

| What | Japanese encephalitis (JE) virus is transmitted to humans primarily through the bite of an infected mosquito.  
JE occurs in many areas of Asia, especially in the south east and in parts of the western Pacific, and is the leading cause of viral encephalitis in Asia.  
Transmission of JE virus occurs primarily in rural agricultural areas.  
The risk for acquiring JE is low for most travellers, particularly for short-term visitors to major urban areas.  
Most JE infections are asymptomatic. Only a small percentage of people infected with JE virus develop clinical disease.  
When encephalitis occurs, it is usually severe, with 20% to 30% mortality rates and residual neuropsychiatric problems in 30% to 50% of survivors.  
The most commonly reported adverse events following JE vaccination are injection site tenderness, redness and hardening; headache; myalgia; and fatigue. |
|---|---|
| Who | JE vaccine is recommended for adult travellers with a high exposure risk going to JE endemic/epidemic areas during the transmission season and for laboratory personnel who work with JE virus.  
JE vaccine is not authorized for use in children less than 18 years of age but may be considered in high risk circumstances. |
| How | Give JE vaccine as two separate 0.5 mL doses on days 0 and 28. |
| Why | When encephalitis occurs, it is usually severe, with 20% to 30% mortality rates and residual neuropsychiatric problems in 30% to 50% of survivors.  
Short-term (less than 1 month) travellers whose visits are restricted to major urban areas are at minimal risk for JE. |
Since the publication of 2006 Canadian Immunization Guide:

- An inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine with a revised dosing schedule has become available for persons 18 years of age and older.
- Inactivated mouse brain-derived JE vaccine (JE-VAX® [Sanofi Pasteur Ltd.]) is no longer available in Canada.
- In Canada, JE vaccine is not authorized for use in persons less than 18 years of age.

For additional information, refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) Statement on protection against Japanese encephalitis. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-4/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Japanese encephalitis (JE) is caused by a ribonucleic acid (RNA) virus from the family *Flaviviridae*.

Reservoir
The virus in primarily maintained in an enzootic cycle that typically involves the *Culex* mosquito and wild birds. Secondary epizootic cycles can lead to infections of humans, often with domestic pigs as an amplifying host.

Transmission
JE virus is transmitted to humans primarily through the bite of an infected mosquito. Mosquitoes acquire the virus from infected hosts (e.g., pigs and wild birds) and then transmit the virus to non-infected hosts (e.g., humans and horses). The principal vectors are *Culex* species mosquitoes that tend to bite in the evening and night. So called day-biting species predominate in some regions, but they not only bite in the day; they can also bite during the afternoon or evening.

Larvae of *Culex* mosquitoes develop in standing water, such as rice fields. Thus, transmission of JE virus occurs primarily in rural agricultural areas where flooding irrigation is practised; however, cases have been occasionally reported from urban areas.

Humans usually do not develop sufficient viremia to infect mosquitoes, and direct person-to-person spread of JE does not occur except, rarely, through intrauterine transmission. Based on experience with similar viruses, transmission could theoretically occur through blood transfusions or organ transplantation. The incubation period is 5 to 15 days.

Risk factors
A traveller’s risk for acquiring JE is determined by multiple factors, including immunization status, use of protective measures against mosquito bites, location of travel, duration of exposure, season, and activities while travelling. The risk for acquiring JE is low for most travellers, particularly for short-term visitors to major urban areas. Greater risk exists for travellers who are:

- visiting rural agricultural areas associated with rice production and flooding irrigation;
- staying for a long time; and
- participating in outdoor activities such as camping, hiking, cycling or fieldwork, especially during the evening or night.
Seasonal/temporal pattern
In most temperate areas of Asia, JE virus transmission is seasonal and disease usually peaks in summer and fall. In the subtropics and tropics, transmission patterns vary and cases can occur sporadically or year-round.

Spectrum of clinical illness
Most JE infections are asymptomatic. Only a small proportion of people infected with JE will develop clinical symptoms. Less than 1% of people infected with JE virus develop clinical disease. In endemic areas, disease occurs primarily in children.

Acute encephalitis is the most commonly identified clinical syndrome with JE virus infection. When encephalitis occurs, it is usually severe, with 20% to 30% mortality rates and residual neuropsychiatric problems in 30% to 50% of survivors. Milder forms of disease can occur and are reported more commonly among adults. JE acquired during pregnancy carries the risk of intrauterine infection and miscarriage.

DISEASE DISTRIBUTION

Incidence/prevalence

Global
JE occurs in many areas of Asia, especially in the south east and in parts of the western Pacific, and is an important cause of viral encephalitis in Asia. The World Health Organization (WHO) estimates that more than 50,000 JE cases occur annually, with 10,000 deaths and 15,000 cases of long-term neuropsychiatric sequelae. The incidence of JE varies widely from year to year and between regions within countries. In endemic areas, JE usually affects children living in rural areas. However, even in countries with effective childhood JE immunization programs, JE may present a risk to non-immune travellers because transmission is maintained in an enzootic (i.e., wildlife) cycle.

The overall risk for JE among persons from non-endemic countries travelling to Asia is estimated to be less than one case per 1 million travellers. However, the risk for JE among persons who stay for prolonged periods in rural areas with active JE virus transmission may reach levels similar to that of the susceptible resident population (1.2 to 2 cases per 100,000 per week). Short-term (less than 1 month) travellers whose visits are restricted to major urban areas are at minimal risk for JE although rare case reports suggest that even short-term, resort-based travellers can occasionally contract JE. There have been few cases of JE reported among Western travellers.

View a map of the areas at risk for JE transmission is available through the United States Centers for Disease Control and Prevention (CDC) (http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.htm) or the World Health Organization (WHO), (http://gamapserver.who.int/mapLibrary/Files/Maps/Global_JE_ITHRiskMap.png)

Japanese encephalitis has been known to occur in many countries, including China, India, Indonesia, Thailand and Vietnam. Risk can vary within areas and at time of year. In addition, JE risk may change over time. It is recommended that travel health practitioners access up-to-date risk information through the United States Centers for Disease Control and Prevention (CDC) Infectious Disease Related to Travel at: or the most current version of the CDC's Health Information for International Travel Yellow Book, (http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm)

National
To date, there has been one possible case of JE reported in a Canadian returning from Asia in 1982.
PREPARATIONS AVAILABLE FOR USE IN CANADA

JAPANESE ENCEPHALITIS VACCINE

- IXIARO® (inactivated, Japanese encephalitis vaccine, Vero cell culture-derived, adsorbed). Intercell AG (manufacturer), Novartis Pharmaceuticals Canada Inc.(distributor) (JE)

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
No efficacy or effectiveness data exist for the Vero cell culture-derived JE vaccine, IXIARO®. IXIARO® was authorized for use based on non-inferiority of serologic response compared to the previous mouse brain-derived JE vaccine and to the WHO threshold for protective antibody titre.

IMMUNOGENICITY
A single dose of JE vaccine induces sufficient protective antibodies in 30% of vaccinees at 10 days after vaccination and in 40% of vaccinees at 28 days post-vaccination. A second dose of vaccine given at 28 days after the first dose induces antibodies in about 95% of vaccinees at 28 days after the second dose. Vaccination with two doses of vaccine at the same time may increase the seroconversion rate to 60% at 10 days post-vaccination. The protective antibody concentration declines over time with 80% to 95% of fully immunized vaccinees maintaining an adequate concentration at 6 months after the first dose and 60% to 80% maintaining adequate antibodies at 12 months after the first dose. A booster dose of vaccine, among those who have completed a properly spaced primary series, induces an adequate antibody concentration in those who have lost protective antibodies at 12 months after their first dose.

RECOMMENDATIONS FOR USE

JE vaccine is only one part of the prevention strategy for Japanese encephalitis. All travellers going to JE endemic areas should be advised regarding personal protective measures. These measures may be sufficient to reduce an already small risk of JE to a level at which JE vaccine provides little added benefit. For additional information on alternative preventive tactics and strength of recommendations for vaccination, refer to CATMAT Statement on protection against Japanese encephalitis. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-4/index-eng.php)

INFANTS AND CHILDREN
JE vaccine is not authorized for use in persons less than 18 years of age due to little safety and efficacy data in this population. The pediatric traveller, especially the longer-term traveller, to areas endemic for JE may be at risk for JE infection and serious complications. If travel cannot be avoided or deferred, travellers less than 18 years of age should be advised to diligently use protective measures to prevent mosquito bites. When a child will be spending a prolonged period of time in an area at risk of acquisition, parents should be informed about the risk of disease occurring; the possibility of the child receiving a WHO approved JE vaccine at the destination should be explored; and the risk and benefits of receiving the vaccine “off-label” in Canada prior to departure presented. Data from a small study of children vaccinated with 2 doses of IXIARO® demonstrated protective antibody response similar to adults and without unexpected adverse events. Preliminary data suggest the use of a half adult dose in children less than 3 years of age.
ADULTS (18 years of age and older)
JE vaccine is recommended for travellers to JE endemic/epidemic areas during the transmission season who will:

- spend more than a cumulative total of 30 days in rural areas during the season of risk (or in urban areas known to be endemic or epidemic for JE); including longer-term travellers or expatriates who, while based in urban areas, anticipate making intermittent short trips to rural areas of risk.
- spend less than a cumulative total of 30 days in rural areas during the season of risk (or in urban areas known to be endemic or epidemic for JE) if substantial activity outdoors (or indoors if the indoor area does not exclude mosquitoes) is anticipated, especially during the evening/night.

JE vaccine is generally not recommended for travellers to JE endemic/epidemic areas during the transmission season whose:

- entire itinerary will be in urban areas (unless the urban areas are known to be endemic or epidemic for JE).
- visits to rural areas (or urban areas known to be endemic or epidemic for JE) will be during the daytime only.

JE vaccine is recommended for laboratory personnel who work with JE virus.

Refer to Schedule for additional information.

PREGNANCY AND BREASTFEEDING
There are no data related to safety or efficacy of JE vaccine in pregnant or lactating women. Pregnant or lactating women who must travel to areas where the risk of JE infection is high should be immunized only if the risk of disease outweighs the unknown risk of vaccination to the woman and/or her fetus/breastfeeding infant. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS
If travel must be undertaken, immunocompromised persons may be immunized with JE vaccine; however, the antibody response may be suboptimal and the person should be advised to be diligent about mosquito protection measures. When considering immunization of an immunocompromised person, consultation with the individual’s attending physician may be of assistance. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

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

WORKERS
Laboratory personnel who work with JE virus should receive JE vaccine. Refer to Immunization of Workers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose is 0.5 mL.

Route of administration
JE vaccine should be administered intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.
Schedule
A series of two doses given on days 0 and 28 should be administered. The immunization series should be completed 10 to 14 days before potential exposure to JE to develop an adequate antibody response. An accelerated schedule is not available. However, if there is insufficient time to administer the recommended two-dose schedule before entering a JE risk situation, a single dose of JE vaccine may be considered and the vaccinee advised that protection against JE may not be reliable. Alternatively, simultaneous administration of two doses of JE vaccine (given with separate injections at separate injection sites) may be considered; however, the risks and benefits of this approach must be critically evaluated.

BOOSTER DOSES AND RE-IMMUNIZATION
A booster dose (third dose) should be given one year after the second dose in the primary series, when there is a potential for re-exposure to JE virus. Persons at continuous risk for acquiring JE (laboratory personnel or persons residing in endemic areas) should receive a booster dose 12 months after primary immunization. Data on the need for further booster doses are not available. If a person received the previous mouse brain-derived JE vaccine more than 3 years ago and requires re-immunization, a two dose primary series of the currently available Vero cell culture-derived JE vaccine (IXIARO®) should be administered.

SEROLOGICAL TESTING
Serologic testing is not recommended before or after receiving JE vaccine.

STORAGE REQUIREMENTS
Store JE vaccine in a refrigerator at +2°C to +8°C. Do not freeze. Protect from light. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES
Data are limited regarding the safety and immunogenicity of JE vaccine when given concomitantly with other vaccines. In general, inactivated vaccines, such as JE vaccine, can be given concurrently with any other vaccine using different injection sites and separate needles and syringes. JE vaccine has been given concomitantly with hepatitis A vaccine without significant interference with safety and immunogenicity. There are no data available regarding possible interference between JE vaccine and yellow fever 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
Tenderness or pain (about 34.0%), redness (9.1%) and hardening (8.0%) are the most common vaccination site reactions following JE vaccination. Common systemic side effects include headache (19.2%), myalgia (13.4%), fatigue (9.5%) and influenza-like illness (8.8%). Other reactions, such as vaccination site swelling or itching, rash, fever, and nausea are reported in 1% to 5% of vaccinees.

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. Anaphylaxis following vaccination with JE vaccine may occur but is very rare. No serious hypersensitivity reactions or neurologic adverse events have been identified among JE vaccine recipients enrolled in clinical trials.
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) in Vaccine Safety in Part 2 for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS

JE 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. The vaccine does not contain any preservatives. Refer to Table 1 in Contents of Immunizing Agents Available in Canada in Part 1 for lists of all vaccines available for use in Canada and their contents.

Administration of JE 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

There are no data available regarding interchangeability of the currently available Vero cell culture-derived JE vaccine (IXIARO®) with the previous mouse brain-derived JE vaccine, either in primary series or in booster dosing. Refer to Booster doses and re-immunization for additional information. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

SELECTED REFERENCES


PART 4

MEASLES VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Immune Globulin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Measles occurs worldwide and is one of the most highly communicable diseases. Canada has imported cases and occasional outbreaks of measles. Measles vaccine is available as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine. MMR vaccine or human immune globulin (Ig) may be used for measles post-exposure immunization in non-immune persons. The efficacy of a single dose of measles vaccine given at 12 or 15 months of age is estimated to be 85% to 95%. With a second dose, efficacy is almost 100%. Reactions to MMR and MMRV vaccine are generally mild and transient and include pain and redness at the injection site, low-grade fever and rash. |
| Who | Measles-containing vaccine is recommended for routine immunization of children and for immunization of children and adolescents who missed measles immunization on the routine schedule. Measles-containing vaccine is recommended for susceptible adults born in 1970 or later. Adults born before 1970 can be presumed to have acquired natural immunity to measles; however, non-immune health care workers, travellers and military personnel should receive MMR vaccine, regardless of year of birth. |
| How | Routine childhood immunization: administer two doses of measles-containing vaccine (MMR or MMRV); the first dose at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter, but should be given not later than around school entry. Children and adolescents who are previously unimmunized: administer two doses of measles-containing vaccine. The minimum interval between doses of MMR vaccine is 4 weeks. MMRV vaccine may be used in healthy children aged 12 months to 12 years. The recommended interval between 2 doses of MMRV vaccine is at least 3 months; a minimum interval of 6 weeks between doses may be used if rapid, complete protection is required. Susceptible adults born in 1970 or later: administer one dose of MMR vaccine. Those who are at the greatest risk of measles exposure (travellers to destinations outside of North |
America, health care workers, students in post-secondary educational settings, and military personnel should receive two doses of MMR vaccine.

- **Non-immune health care workers and military personnel born before 1970:** administer two doses of MMR vaccine at least 4 weeks apart
- **Non-immune travellers born before 1970:** administer one dose of MMR vaccine.
- **Non-immune students born before 1970:** consider administering one dose of MMR vaccine

**Why**

- Measles occurs worldwide and is one of the most highly communicable infectious diseases.
- Complications of measles disease occur in about 10% of measles cases and death is estimated to occur in 1 to 2 of every 1,000 cases.
- MMR and MMRV vaccines are safe and effective.

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

- New recommendations have been made for measles vaccination of health care workers, travellers and military personnel.
- A new combined multivalent vaccine (measles-mumps-rubella-varicella vaccine [MMRV]) has become available for children aged 12 months to 12 years.


**EPIDEMIOLOGY**

**DISEASE DESCRIPTION**

**Infectious agent**

Measles (rubeola, red measles) is caused by measles virus, a member of the *Paramyxoviridae* family.

**Reservoir**

Humans

**Transmission**

Measles is one of the most highly communicable infectious diseases with greater than 90% secondary attack rates among susceptible persons. The virus is transmitted by the airborne route, respiratory droplets, or direct contact with nasal or throat secretions of infected persons. The incubation period is about 10 days (range, 7 to 18 days). The interval from exposure to appearance of rash averages 14 days. Cases are infectious from 1 day before the beginning of the prodromal period to 4 days after rash onset. People who recover from measles have permanent immunity to the disease.

**Risk factors**

All persons who have not had measles disease or who have not been successfully vaccinated are at risk of infection. In Canada, adults born before 1970 are generally presumed to have acquired natural immunity to measles. Individuals at greatest risk of exposure to measles include travellers to destinations outside of North America, health care workers, students in post-secondary educational settings, and military personnel.

**Seasonal/temporal patterns**

Historically, measles disease occurs primarily in late winter and spring in temperate zones. It is now restricted to sporadic cases and outbreaks.
Spectrum of clinical illness
Symptoms of measles include prodromal fever, cough, coryza, conjunctivitis, Koplik spots (white spots on the inner lining of the mouth) and a rash that typically begins on the face, advances to the trunk and then to the arms and legs. Complications such as otitis media and bronchopneumonia occur in about 10% of reported cases, even more commonly in those who are poorly nourished and chronically ill, and in infants less than 1 year of age. Measles encephalitis occurs in approximately 1 of every 1,000 reported cases and may result in permanent brain damage. Measles infection can cause subacute sclerosing panencephalitis (SSPE), a rare but fatal disease. In developed countries, death is estimated to occur in 1 to 2 of every 1,000 cases of measles. Measles during pregnancy results in a higher risk of premature labour, spontaneous abortion and low birth weight infants. Measles in an immunocompromised person may be severe.

DISEASE DISTRIBUTION

Incidence/prevalence

Global
Measles occurs worldwide and remains a serious and common disease in developing countries. According to the World Health Organization (WHO), measles is a leading cause of vaccine preventable deaths in children worldwide.

The global goal of reducing mortality due to measles by 90% by 2010 (compared with levels in 2000) was not reached. Measles was largely eliminated from the Western Hemisphere by 2002; however, in 2011 there were large measles outbreaks worldwide. There were over 26,000 cases in the WHO European Region with the highest number reported in France (more than 14,000 cases). Large outbreaks have also occurred in Africa, mostly in the Democratic Republic of the Congo, with more than 106,000 cases and 1,100 deaths.

National
Before the introduction of measles vaccine in 1963 to 1964, measles occurred in cycles with an increasing incidence every 2 to 5 years. At that time, an estimated 300,000 to 400,000 cases occurred annually. Since the introduction of vaccine, the incidence of measles has declined markedly in Canada (refer to Figure 1). Between 1989 and 1995, in spite of very high immunization coverage, there were many outbreaks involving predominately children who had received one dose of measles vaccine. It was estimated that 10% to 15% of immunized children remained unprotected after a single dose given at 12 months of age.

In 1996 to 1997, in an effort to reach the goal of measles elimination, every Canadian province and territory added a second dose of measles-containing vaccine to its routine immunization schedule, and most conducted catch-up programs in school-aged children with measles or measles-rubella vaccine. These interventions achieved immunization coverage for the second dose in excess of 85%, reducing the proportion of vulnerable children to a level that does not sustain endemic measles transmission. By 1998, endemic transmission of measles was interrupted.
**Figure 1: Reported incidence rate of confirmed measles cases, Canada 1924-2011**¹

Measles was not nationally reportable between 1959 and 1968. The incidence rate for 2011 is annualized to August 31, 2011.

**RECENT OUTBREAKS**

Since the introduction of the two dose measles-containing vaccine schedule, outbreaks in Canada have been a result of importation from other countries.

In 2007, there was an outbreak in Quebec with 94 confirmed measles cases. The laboratory results suggested there were two separate importations. More than one-half of cases were between the ages of 1 and 10 years. Where immunization status was known, nearly all of the cases were individuals who had not received two doses of measles-containing vaccine.

In 2008, there was an outbreak in Ontario of 53 confirmed measles cases. About one-third of the cases were less than 10 years of age. Where immunization status was known, nearly all of the cases were not immunized.

In the spring of 2010, an outbreak in British Columbia resulted in 77 confirmed measles cases. Infants and children under 5 years of age were disproportionately affected, as were adults aged 30 to 39 years. Where immunization status was known, 59% of cases had not been vaccinated, 29% had received one dose of measles-containing vaccine and 12% had received two doses of measles-containing vaccine.

In Canada in 2011, measles importations led to a large outbreak involving more than 700 cases, largely in Quebec. The majority of the cases were between the ages of 10 and 19 years old. Where immunization status was known, approximately 80% of cases were not adequately immunized for their age.
Refer to the Public health Agency of Canada Vaccine-Preventable Diseases webpage for the most recent information about the epidemiology of measles in Canada. (http://www.phac-aspc.gc.ca/im/vpd-mev/index-eng.php)

PREPARATIONS AVAILABLE FOR USE IN CANADA

MEASLES-CONTAINING VACCINES

- **M-M-R® II** (live, attenuated combined measles, mumps and rubella vaccine), Merck Canada Inc. (MMR)
- **PRIORIX®** (live, attenuated combined measles, mumps and rubella vaccine), GlaxoSmithKline Inc. (MMR)
- **PRIORIX-TETRA®** (live, attenuated combined measles, mumps, rubella and varicella vaccine), GlaxoSmithKline Inc. (MMRV)

In Canada, measles vaccine is only available in combination with mumps and rubella vaccine (MMR) or mumps, rubella and varicella vaccine (MMRV). In many countries outside of Canada measles vaccine alone is given.

HUMAN IMMUNE GLOBULIN

- **GamaSTAN® S/D** (immune globulin [human]), Grifols Therapeutics Inc. (Ig)

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

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

The efficacy of a single dose of measles-containing vaccine given at 12 or 15 months of age is estimated to be 85% to 95%. With a second dose, efficacy in children approaches 100%. However, measles outbreaks have occurred in populations with high immunization coverage rates. Due to the high infectivity of measles (each case may infect 12 to 18 others) at least 95% of the population needs to be immunized to develop herd immunity. There are no data regarding the efficacy of MMRV vaccine.

IMMUNOGENICITY

In clinical studies a single injection of MMR vaccine induced measles antibodies in 95%, mumps antibodies in 96%, and rubella antibodies in 99% of previously seronegative children.

In a study of 12 month old children, a single dose of MMRV vaccine resulted in a seroconversion rate for measles, mumps, rubella and varicella of 98%, 97%, 98% and 93%, respectively. The seroconversion rates and geometric mean titres for individual components were not significantly different from those achieved after MMR plus univalent varicella vaccines or MMR vaccine alone. A study of children receiving two doses of MMRV vaccine during the second year of life noted seropositivity for measles, mumps, rubella and varicella of 99%, 97.4%, 100% and 99.4% respectively by the third year post-vaccination. Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies following MMRV vaccinations are under evaluation.
RECOMMENDATIONS FOR USE

CHILDREN (12 months to 17 years of age)
Two doses of measles-containing vaccine should be given for routine immunization of children and for immunization of children and adolescents who have missed measles immunization on the routine schedule. MMRV vaccine may be used in children aged 12 months to 12 years. vaccine for varicella protection.

ADULTS (18 years of age and older)

Routine immunization: adults born before 1970 are generally presumed to have acquired natural immunity to measles; however, some of these individuals may be susceptible. Adults without contraindications, born in 1970 or later who do not have documented evidence of receiving measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles infection should be immunized with one dose of MMR vaccine.

Health care workers, regardless of their year of birth, who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive two doses of MMR vaccine. Refer to Workers.

Students in post-secondary educational settings, born in 1970 or later, who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive two doses of MMR vaccine. In students born before 1970, administration of one dose of MMR vaccine should be considered.

Military personnel, regardless of their year of birth, who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive two doses of MMR vaccine.

Travellers to destinations outside of North America, born in 1970 or later, who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive two doses of measles-containing vaccine. Travellers born before 1970 who do not have documented evidence of receiving a measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive one dose of MMR vaccine. Refer to Travellers.

Table 1 provides a summary of criteria for measles immunity. Refer to Schedule.
Table 1: Criteria for immunity to measles

<table>
<thead>
<tr>
<th>Routine</th>
<th>Health care workers</th>
<th>Travellers to destinations outside North America</th>
<th>Students in post-secondary educational settings</th>
<th>Military personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination with 2 doses(^1) (regardless of year of birth) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
</tr>
<tr>
<td></td>
<td>• Children 12 months to 17 years of age: 2 doses(^1)</td>
<td>• If born in 1970 or later: 2 doses(^1) OR • If born before 1970: 1 dose(^1) OR</td>
<td>• If born in 1970 or later: 2 doses(^1) OR • If born before 1970: 1 dose(^1) OR</td>
<td>• If born in 1970 or later: 2 doses(^1) (regardless of year of birth) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
</tr>
<tr>
<td></td>
<td>• Adults 18 years of age and older born in 1970 or later: 1 dose(^1,2) OR History of laboratory confirmed infection OR Laboratory evidence of immunity OR Born before 1970</td>
<td>• History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td>• History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td>• History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
</tr>
</tbody>
</table>

1 Measles-containing vaccine
2 Refer to additional recommendations for health care workers, travellers to destinations outside of North America, students in post-secondary educational settings and military personnel.

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, unless known to be immune based on laboratory testing. MMR or MMRV vaccine, as appropriate, may be given regardless of possible previous receipt of the vaccine because additional adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

Immunity to measles, mumps and rubella should be reviewed in women of reproductive age, and vaccination should be recommended to non-pregnant susceptible women. Ideally, the immunization status of women intending to become pregnant should be reviewed and vaccines updated as necessary prior to conception. Women should delay pregnancy by at least 28 days following vaccination with a live vaccine.

MMR and MMRV vaccines should generally not be given during pregnancy because of the theoretical risk of disease transmission to the fetus; however, there is no evidence demonstrating a teratogenic or other risk from such vaccines. There was no evidence of Congenital Rubella Syndrome in any of the offspring of 226 women inadvertently vaccinated during pregnancy. Inadvertent immunization with MMR vaccine is not a reason for pregnancy termination. In some situations, potential benefits of MMR vaccination may outweigh risks such as during measles or rubella outbreaks, in which case vaccination may be considered.

Women who are breastfeeding can be vaccinated with MMR vaccine.
Refer to Contraindications, Precautions. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised person with a live vaccine, approval from the individual’s attending physician should be obtained before vaccination. For complex cases, referral to a consultant with expertise in immunization or immunodeficiency is advised.

Family or medical history

People who have a suspicious history for immunodeficiency disorders (e.g., known or suspected family history of congenital immunodeficiency disorder or HIV infection, or history of failure to thrive and recurrent infections) should not be immunized with a live vaccine until they have been fully investigated and T cell dysfunction ruled out. Immunodeficiency states may be undiagnosed in young children presenting for routine immunizations, which include live vaccines. This is particularly important to consider in infants receiving live vaccines before 12 months of age. A history of negative prenatal screening of the infant’s mother for HIV should be obtained before administering a live vaccine. If a mother has not received routine prenatal care in Canada, the possibility of undiagnosed HIV infection should be considered.

Congenital (primary) immunodeficiency

Live vaccines are generally not recommended for people with congenital immunodeficiency states although some exceptions exist.

B cell deficiency

MMR vaccine, as appropriate for age, should be considered if the individual is not receiving regular immune globulin replacement therapy which may affect the efficacy of the vaccine.

T cell, natural killer T cell, and mixed cellular and antibody defects (e.g., Severe Combined Immune Deficiency [SCID])

All live vaccines, including MMR and MMRV, are contraindicated in people with defects in T cell function.

Phagocytic and neutrophil disorders (e.g., congenital neutropenia, leukocyte adhesion and migration defects, chronic granulomatous disease)

Children with phagocytic or neutrophil disorders may be vaccinated with MMR vaccine as appropriate for age.

Complement deficiency

There are no contraindications to the use of MMR vaccine in individuals with complement deficiency disorders. Immunity can decrease over time. Measurement of antibody titres and re-immunization, if needed, should be considered.

Acquired (secondary) immunodeficiency

Malignant hematologic disorders

MMR and MMRV vaccines are contraindicated in individuals with severe immunodeficiency due to blood dyscrasias, lymphomas, leukemias of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems and in people undergoing immunosuppressive treatment for malignancy. Children with Acute Lymphocytic Leukemia (ALL) may be vaccinated with MMR vaccine if the disease has been in remission for at least 12 months, the child’s total lymphocyte
count is at least $1.2 \times 10^9/L$, the child is not receiving radiation therapy, and maintenance chemotherapy can be withheld for at least 1 week before to 1 week after immunization.

**Malignant solid tumours**

MMR and MMRV vaccines are contraindicated in people undergoing immunosuppressive treatment for any malignant solid tumours.

**Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)**

- Pre-transplantation: People awaiting HSCT should not receive measles, mumps and rubella-containing vaccine. Vaccination of donors immediately before stem cell harvest is not recommended as there is no evidence that immunity can be transferred from the donor to the recipient and there are no safety data.
- Post-transplantation: Antibody titres to vaccine-preventable diseases decline after HSCT if the recipient is not re-vaccinated. Vaccination with MMR vaccine may be considered 24 months after transplantation provided there is no evidence of chronic graft-versus-host disease, immunosuppression has been discontinued for at least 3 months, and the person is considered immunocompetent by a transplant specialist. Serologic response should be checked after the first dose of MMR vaccine and a second dose should be given 3 months or more after the first dose if there is no seroconversion.

**Solid organ transplantation**

If possible, individuals being considered for solid organ transplantation should receive immunizations recommended for their age before the transplantation is performed. MMR vaccine may be given to infants as early as 6 months of age if transplantation is anticipated before 12 to 15 months of age. MMR vaccine should be given at least 4 weeks before solid organ transplantation and, in general, is not recommended after transplantation.

**Immunosuppressive therapy**

Vaccination status for measles, mumps and rubella should be reviewed for immunocompetent persons who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency. Refer to *Immunization of Immunocompromised Persons* in Part 3 for a list of immunosuppressive medications.

If indicated, MMR vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy to reduce the risk of disease caused by the vaccine strain. If MMR vaccine cannot be given prior to initiation of immunosuppressive therapy, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of live vaccines to reduce the risk of disease caused by the vaccine strain. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of MMR vaccine. The interval between discontinuation of immunosuppressive drugs and MMR vaccine administration may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.

If immunosuppressive therapy cannot be stopped, live vaccines are generally contraindicated, although the risk-to-benefit ratio may favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of development of disease. The safety and efficacy of live, attenuated vaccines during low dose intermittent or maintenance therapy with immunosuppressive drugs (other than corticosteroids) are unknown. Immunosuppressive drugs have been reported to cause reactivation of latent tuberculosis infection and predisposition to other opportunistic infections. Therefore, until additional information becomes available, avoidance of MMR vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent.
Corticosteroid therapy is not a contraindication to administering live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 2 mg/kg/day for a child or less than 20 mg/day of prednisone or its equivalent per day for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).

In general, live attenuated vaccines are contraindicated during monoclonal antibody treatment or in infants exposed to monoclonal antibodies. Monoclonal antibodies taken during pregnancy will be transferred to the fetus and their effects may persist after birth. Infants who have been exposed to monoclonal antibodies, either during pregnancy or from breastfeeding, should have B-cell enumeration. B cell enumeration should be normal before vaccination with live vaccines. Consultation with an immunologist is advised. Vaccination status should be reviewed prior to commencing monoclonal antibodies.

**HIV-infected**

An infectious disease specialist/immunologist should be consulted for advice on MMR immunization in HIV-infected people. There are no contraindications to the use of MMR vaccine early in the course of illness; however, MMR vaccine is contraindicated in persons with advanced HIV/AIDS. The safety and immunogenicity of MMRV vaccine in HIV-infected individuals has not been evaluated, and MMRV vaccine cannot be routinely recommended.

- **Children:** HIV-infected children 12 months of age and older, and with Centers for Disease Control and Prevention (CDC) clinical category N, A, or B and immunologic category 1 or 2 (i.e., CD4 counts ≥15%) may receive two doses of MMR vaccine 3 to 6 months apart. Univalent varicella vaccine may be administered concomitantly with MMR vaccine at different injection sites using separate needles and syringes.
- **Adolescents and adults:** immunization with two doses of MMR administered 3 months apart may be considered for susceptible HIV-infected adolescents and adults with CD4 cell count ≥200 x 10^6/L and CD4 percentage ≥15%.

**Household contacts**

Susceptible household contacts of immunocompromised people should receive a measles-containing vaccine as appropriate for age and risk factors.

Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional information.

**PERSONS WITH CHRONIC DISEASES**

**Hyposplenism or asplenia**

Hyposplenic or asplenic (congenital absence, surgical removal or functional [e.g., sickle cell disease]) individuals should be immune to measles, mumps and rubella or should receive MMR or MMRV vaccine as appropriate.

**Chronic renal disease/dialysis**

Individuals with chronic renal disease or undergoing dialysis should be immune to measles, mumps and rubella or should receive MMR or MMRV vaccine as appropriate.

**Neurologic disorders**

People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including MMR or MMRV vaccine as appropriate.
Autoimmune diseases
Individuals with autoimmune disease not being treated with immunosuppressive drugs are not considered significantly immunocompromised and should receive MMR immunization following consultation with their physician. Rheumatic disease modifying agents such as hydroxychloroquine, sulfasalazine, or auranofin are not generally identified as immunosuppressive.

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

TRAVELLERS
Protection against measles is especially important for people planning travel to destinations outside of North America. Travellers born in 1970 or later who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive two doses of measles-containing vaccine.

Measles vaccine should be given at an earlier age than usual for children travelling to countries outside of North America. MMR vaccine may be given as early as 6 months of age; however, two additional doses of measles-containing vaccine must be administered after the child is 12 months old to ensure long lasting immunity to measles.

Travellers born before 1970, who do not have documented evidence of receiving measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should receive one dose of MMR vaccine.

Measles is endemic in many countries. Refer to measles incidence rates in WHO member countries for additional information. (http://www.who.int/immunization/monitoring_surveillance/en/)

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. In many countries outside of Canada, mumps and rubella vaccines are in limited use and measles vaccine alone is given. A Canadian study showed that more than one-third of new immigrants and refugees, particularly women, were susceptible to measles, mumps, or rubella. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
It is recommended that all health care workers be immune to measles. Health care workers, regardless of their year of birth, who do not have documented evidence of receiving two doses of measles-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed measles disease should be vaccinated accordingly so that they have received two doses of MMR vaccine.

POST-EXPOSURE IMMUNIZATION
Measles may continue to be imported into Canada. Outbreaks may occur in susceptible populations. For practical purposes, all individuals attending the same school or facility should be considered contacts.

MMR vaccine
Susceptible, immunocompetent individuals 12 months of age and older who are exposed to measles may be protected from measles disease if they are given MMR vaccine within 72 hours of their exposure. MMR vaccine may be recommended for children between 6 months to less than 12 months of age for post-exposure management if it is given within 72 hours of exposure; however, two additional doses of measles-containing vaccine must be administered after the child is 12 months old (and at least 28 days from the previous dose) to ensure long lasting immunity to measles.
Human immune globulin (Ig)

Prophylactic use of Ig has been shown to be effective in modifying or preventing disease if administered within 6 days after exposure to measles, however, it should be given as soon as possible after exposure when indicated. Ig should be considered for contacts of measles who are:

1. susceptible pregnant women,
2. susceptible immunocompromised people, or
3. children less than 6 months of age.

Measles-containing vaccine is contraindicated in groups 1 and 2 and effectiveness and safety has not been established in group 3. Ig should also be considered for susceptible immunocompetent contacts of measles who are 6 months of age and older and who present more than 72 hours after exposure (when MMR vaccine no longer provides post-exposure protection) but within 6 days after exposure (when Ig may still provide post-exposure protection).

In HIV infected individuals, measles antibody titre is known to decline more rapidly over time as compared to those who are HIV uninfected. A dose of Ig should be considered in HIV infected individuals with severe immunosuppression after a known exposure to confirmed measles, even with documented previous MMR immunization. Regardless of vaccination status pre-transplant, Ig should also be considered for hematopoietic stem cell transplantation (HSCT) recipients, unless vaccinated post HSCT and known to have an adequate measles antibody titre.

In assessing the extent of measles exposure and deciding between MMR vaccine and Ig for post-exposure management, it is important to consider that Ig only provides short-term protection and requires postponing the administration of MMR vaccine for 5 to 6 months. If longer-term protection against measles is required because of ongoing measles transmission in the community, MMR vaccine may be the preferred choice. It is important to note that despite the use of MMR vaccine or Ig for post-exposure management, measles infection may still occur. Exposed individuals should be counseled regarding signs and symptoms of measles; counseling should include avoiding contact with others should they become ill with symptoms compatible with measles and the need to seek medical care, including advising health care workers of the possibility of measles before going to a health care setting so that appropriate precautions can be taken. For detailed information regarding infection prevention and control, refer to the Guidelines for the Prevention and Control of Measles Outbreaks in Canada. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-3/index-eng.php)

The recommended dose of Ig for healthy individuals exposed to measles is 0.25 mL/kg of body weight given by the IM route. The dose for exposed individuals who are immunocompromised is 0.5 mL/kg of body weight. A maximum dose of 15 mL should not be exceeded. For complete prescribing information, consult the product leaflet or information contained within the product monograph available through Health Canada’s Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php)

Individuals receiving replacement IVlg (400 mg/kg of body weight or higher) are considered protected and do not require Ig if the last dose of IVlg was received within the three weeks prior to measles exposure.

Unless it is contraindicated, individuals who receive Ig should receive measles-containing vaccine after specified intervals, once the measles antibodies administered passively have degraded. For recommendations on the interval between administration of an Ig preparation or blood product and vaccination with measles-containing vaccine, refer to Blood Products, Human Immune Globulin and Timing of Immunization in Part 1.

Refer to Passive Immunizing Agents in Part 5 for additional general information.
OUTBREAK CONTROL
Immunization with MMR vaccine is an integral element of a comprehensive measles outbreak prevention and management strategy. In a measles outbreak, MMR vaccine can be provided at any time starting from 6 months of age. However if given between 6 months and less than 12 months of age, two additional doses of measles-containing vaccine must be administered after the child is 12 months old (and at least 28 days from the previous dose) to ensure long lasting immunity to measles. For detailed information on outbreak control, refer to the Guidelines for the Prevention and Control of Measles Outbreaks in Canada. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-3/index-eng.php)

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose is 0.5 mL.

Route of administration
MMR vaccine should be administered subcutaneously; MMRV can be administered subcutaneously or intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Children (12 months to 12 years of age)
For routine immunization of children aged 12 months to 12 years, two doses of measles-containing vaccine (MMR or MMRV) should be administered. The first dose of measles-containing vaccine should be administered at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter, but should be given no later than around school entry.

The recommended minimum interval between doses of MMR vaccine is 4 weeks. Children who previously received a single dose of MMR vaccine should receive a second dose at least 4 weeks after the first dose. The recommended interval between two doses of MMRV vaccine is at least 3 months; a minimum interval of 6 weeks between doses may be used if rapid, complete protection is required.

Adolescents (13 to 17 years of age)
Measles-susceptible adolescents should receive two doses of MMR vaccine given at least 4 weeks apart.

Adults (18 years of age and older)
Measles-susceptible adults should receive one or two doses of MMR vaccine as appropriate for age and risk factors (refer to Table 1). If two doses are needed, MMR vaccine should be administered with a minimum interval of 4 weeks between doses.

BOOSTER DOSES AND RE-IMMUNIZATION
Re-immunization with measles-containing vaccine after age and risk appropriate vaccination is not necessary.

SEROLOGICAL TESTING
Serological testing may be indicated to confirm the diagnosis of measles or to determine immune status. Serologic testing is not recommended before or after receiving measles-containing vaccine. If serology is inadvertently done subsequent to appropriate measles immunization and does not demonstrate immunity, measles re-immunization is not necessary.
STORAGE REQUIREMENTS

M-M-R® II: Maintain vaccine at +10°C or colder during shipment. Freezing during shipment will not affect potency of the vaccine. Protect the vaccine from light. Before reconstitution, store the vial of vaccine at +2°C to +8°C or colder. The diluent may be stored in the refrigerator or at room temperature and must not be frozen.

PRIORIX®, PRIORIX-TETRA®: Store in a refrigerator at +2°C to +8°C. The diluent may be stored separately at room temperature. Protect from light.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information. Refer to Passive Immunizing Agents Part 5 for information regarding Ig storage requirements.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Live vaccines given by the parenteral route may be administered concomitantly with all other vaccines during the same visit using different injection sites and separate needles and syringes. In general, if two live parenteral vaccines are not administered concomitantly, there should be a period of at least 4 weeks before the second live parenteral vaccine is given. Exceptions are varicella-containing vaccines, such as MMRV vaccine:

- administer doses of varicella-containing vaccine at least 3 months apart for children 1 to 12 years of age. If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between 2 doses may be used for children 1 to 12 years of age.
- do not concomitantly administer varicella-containing vaccines with smallpox vaccine; administer varicella-containing vaccine and smallpox vaccine at least 4 weeks apart.

Oral and intranasal vaccines can be given at the same time as, or any time before or after any other live vaccine, regardless of the route of administration of the other live vaccine.

Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE AND IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

MMR vaccine

Adverse events following MMR immunization occur less frequently and are less severe than those associated with natural disease. Adverse reactions are less frequent after the second dose of vaccine and tend to occur only in those not protected by the first dose. Six to 23 days after MMR immunization, approximately 5% of immunized children experience malaise and fever (with or without rash) lasting up to 3 days. Parotitis, rash, lymphadenopathy, and joint symptoms also occur occasionally after MMR immunization.

MMRV vaccine

Pain and redness at the injection site or low-grade fever occur in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C) occur in 1% to less than 10% of vaccinees. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus, health care
providers should obtain specimens using viral transport media from a lesion to ensure varicella
disease is not confused with a reaction to vaccination.

Rubella-containing vaccines
Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with rubella-containing
vaccine, lasts for about 1 to 3 weeks, and rarely recurs. This is more common in post-pubertal
females, among whom arthralgia develops in 25% and arthritis in 10% after immunization with rubella-
containing vaccine. There is no evidence of increased risk of new onset, chronic arthropathies or
neurologic conditions.

Ig
Injection site pain and tenderness, urticaria, and angioedema may occur.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

MMR and MMRV vaccines
Serious adverse events are rare following immunization and, in most cases, data are insufficient to
determine a causal association. As with other vaccines, anaphylaxis following vaccination with MMR
or MMRV vaccine may occur but is very rare.

Immune Thrombocytopenic Purpura (ITP)
Rarely, ITP occurs within 6 weeks after immunization with MMR or MMRV vaccine. In most
children, post-immunization thrombocytopenia resolves within three months without serious
complications. In individuals who experienced ITP with the first dose of MMR or MMRV, serologic
status may be evaluated to determine whether an additional dose of vaccine is needed. The
potential risk to benefit ratio should be carefully evaluated before considering vaccination in such
cases.

Encephalitis
Encephalitis has been reported in association with administration of measles vaccine in
approximately 1 per million doses distributed in North America which is much lower than that
observed with natural measles disease (1 per 1,000 cases).

Febrile seizures
Recent studies have found a higher risk of febrile seizures with the first dose of a MMRV vaccine
(ProQuad®, not authorized for use in Canada) when compared to the concomitant administration of
MMR and univalent varicella vaccine. Data from the United States (US) estimated that the risk of
febrile seizures in the 5 to 12 days following the first dose of this MMRV vaccine is 1 for every
2,600 vaccinated children aged 12 to 23 months. Experience with the MMRV vaccine available in
Canada is more limited; however, one study showed an additional risk of febrile seizures with
MMRV vaccine compared to MMR and univalent varicella vaccines given as two separate products
administered concomitantly. The risk with the Canadian vaccine was smaller than the risk found
with the US product. Close surveillance and further investigation are underway.

Ig
Anaphylactic reactions, although rare, have been reported following the injection of human
immune globulin.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS
In the mid to late 1990s, researchers from the United Kingdom reported an association between MMR
vaccine and inflammatory bowel disease, and MMR vaccine and autism. Rigorous scientific studies and
reviews of the evidence have been done worldwide, and there is now considerable evidence to refute
those claims. In 2010, the original study suggesting a link between the MMR vaccine and autism was found to be fraudulent and was retracted.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with MMR or MMRV vaccine.
- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with MMRV vaccine.
- 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

MMR and MMRV vaccines and Ig are contraindicated in persons with a history of anaphylaxis after previous administration of the product and in persons with proven immediate or anaphylactic hypersensitivity to any component of the product (with the exception of egg allergy for MMR and MMRV vaccines [refer below], or its container. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for lists of vaccines and passive immunizing agents available for use in Canada and their contents. For measles-containing vaccines, potential allergens include:

- M-M-R®II: neomycin, phenol red, porcine gelatin, residual components of chick embryo cell cultures
- PRIORIX®: egg protein, neomycin
- PRIORIX-TETRA®: egg protein, neomycin

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.

The measles and mumps components of MMR and MMRV vaccines are produced in chick embryo cell culture and may contain traces of residual egg protein. The trace amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Prior egg ingestion is not a prerequisite for immunization with egg protein-containing vaccine. Skin testing is not recommended prior to vaccination as it does not predict reaction to the vaccine. MMR or MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens’ eggs. For all vaccines, immunization should always be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.

Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Refer to Immunocompromised persons.

MMR and MMRV vaccines are contraindicated during pregnancy. Refer to Pregnancy and breastfeeding.

MMR vaccine is contraindicated in individuals with active, untreated tuberculosis. While tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles-containing vaccines, such
as MMR or MMRV have such an effect.

A history of febrile seizures or a family history of convulsions is not a contraindication for the use of MMRV vaccine.

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

It is recommended to avoid the use of salicylates (e.g., acetylsalicylic acid [ASA]) for 6 weeks after immunization with MMRV vaccine because of an association between wild-type varicella, salicylate therapy and Reye’s syndrome.

Refer to Contraindications, Precautions and Concerns in Part 2 and Passive Immunizing Agents Part 5 for additional general information.

**DRUG INTERACTIONS**

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine such as MMRV. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of MMRV vaccine and should not restart antiviral therapy until 14 days after.

The measles component in measles-containing vaccines can temporarily suppress tuberculin reactivity, resulting in false-negative results. If tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) test is required, it should be done on the same day as immunization or delayed for at least 4 weeks after measles vaccination. Vaccination with measles-containing vaccine may take place at any time after tuberculin skin testing has been performed and/or read.

Passive immunization with human Ig or receipt of most blood products can interfere with the immune response to MMR and MMRV vaccines. These vaccines should be given at least 14 days prior to administration of an Ig preparation or blood product, or delayed until the antibodies in the Ig preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an Ig preparation or blood product is less than 14 days, the vaccine dose should be repeated after the recommended interval. The recommended interval between administration of an Ig preparation or blood product and subsequent immunization varies, depending on the Ig preparation or blood product. If the vaccine is given too early following Ig or blood product administration, it should be repeated after the appropriate interval has passed. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to MMR or MMRV vaccines. Refer to Blood Products, Human Immune Globulin and Timing of Immunization in Part 1 for additional general information.

**OTHER CONSIDERATIONS**

**INTERCHANGEABILITY OF VACCINES**

On the basis of expert opinion, the MMR vaccines authorized in Canada may be used interchangeably. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

**SELECTED REFERENCES**


of Pediatrics; 2009.


Bellini WJ, Rota JS, Lowe LE et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* 2005;192(10):1686-93.


PART 4
MENINGOCOCCAL VACCIN

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Almost all invasive meningococcal disease (IMD) is associated with <em>Neisseria meningitidis</em> serogroups A, B, C, Y, and W-135.</td>
<td></td>
</tr>
<tr>
<td>• Worldwide, IMD occurs sporadically and in focal epidemics. IMD is endemic in Canada but occurs at low rates.</td>
<td></td>
</tr>
<tr>
<td>• In Canada, the incidence of IMD is highest in infants and most cases are serogroup B for which there is no vaccine.</td>
<td></td>
</tr>
<tr>
<td>• Persons at higher risk of IMD include:</td>
<td></td>
</tr>
<tr>
<td>o persons with functional or anatomic asplenia</td>
<td></td>
</tr>
<tr>
<td>o persons with congenital complement, properdin, factor D or primary antibody deficiencies</td>
<td></td>
</tr>
<tr>
<td>o persons with acquired complement deficiencies (e.g., those receiving eculizumab (Soliris™))</td>
<td></td>
</tr>
<tr>
<td>o travellers to areas with high rates of endemic meningococcal infection or transmission, including travellers to the meningitis belt of sub-Saharan Africa and pilgrims to the Hajj in Mecca, Saudi Arabia</td>
<td></td>
</tr>
<tr>
<td>o research, industrial and clinical laboratory personnel who are potentially routinely exposed to <em>N. meningitidis</em></td>
<td></td>
</tr>
<tr>
<td>o military personnel who are at increased risk of meningococcal disease</td>
<td></td>
</tr>
<tr>
<td>o HIV positive individuals should be considered for vaccination, especially if HIV is congenitally acquired</td>
<td></td>
</tr>
<tr>
<td>• Meningococcal vaccines are initially highly effective; effectiveness wanes over time.</td>
<td></td>
</tr>
<tr>
<td>• Monovalent conjugate meningococcal vaccine (Men-C-C) effectiveness in infants is 97% within one year of vaccination. Vaccine effectiveness of the quadrivalent conjugate meningococcal vaccine Menactra™ in adolescents is 80% to 85% within 3 to 4 years of vaccination.</td>
<td></td>
</tr>
<tr>
<td>• There may be redness, swelling and soreness at the injection site.</td>
<td></td>
</tr>
</tbody>
</table>
### Who

- **Healthy children:** should be immunized with a Men-C-C vaccine routinely at 12 months of age; however, they may begin meningococcal immunization earlier depending on provincial/territorial schedules. If not previously immunized as infants or toddlers Men-C-C vaccine should be given to children less than 5 years of age and considered for children 5 to 11 years of age.
- **Adolescents and young adults:** either a Men-C-C or a quadrivalent conjugate meningococcal (Men-C-ACYW-135) vaccine (depending on local epidemiology and programmatic considerations) is recommended for adolescents (routinely at 12 years of age) and young adults even if previously vaccinated as an infant or toddler.
- **High risk individuals:** Men-C-ACYW-135 vaccine is recommended for children and adults with increased risk of IMD. The choice of vaccine and recommended schedule vary with age. Periodic booster doses are recommended.
- **Post-exposure management:** chemoprophylaxis is recommended for close contacts. If the serogroup is vaccine-preventable, immunoprophylaxis should also be considered depending on the exposure history. Recommendations for immunoprophylaxis in those previously vaccinated are provided.

### How

- **Routine infant immunization:** give Men-C-C vaccine to healthy infants according to provincial/territorial schedules.
- **12 months to 11 years of age:** give one dose of Men-C-C vaccine at 12 to 23 months of age (routinely at 12 months) whether immunized as an infant or not. For previously unimmunized children less than 5 years of age, give one dose of Men-C-C vaccine. Consider one dose of Men-C-C vaccine in children aged 5 to 11 years who were previously unimmunized.
- **12 to 24 years of age:** give adolescents (routinely at 12 years of age) and young adults one dose of either Men-C-C or Men-C-ACYW-135 vaccine, even if previously vaccinated as an infant or toddler.
- Men-C-C vaccine may be administered concomitantly with routine childhood vaccines and Men-C-ACYW-135 vaccine may be administered concomitantly with adolescent and adult age-appropriate vaccines at different injection sites using separate needles and syringes.
- Menveo™ can be administered with routine paediatric vaccines; however, further studies are needed with regard to concomitant administration with pneumococcal 13-valent conjugate vaccine.

### Why

- IMD mortality is approximately 10%.
- Of IMD survivors, 10% to 20% have long term sequelae which include hearing loss, neurologic disabilities, and digit or limb amputations.

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

- Two new quadrivalent conjugate meningococcal vaccines for serogroups A, C, Y, and W-135 have become available.
- Bivalent polysaccharide meningococcal vaccine is no longer available in Canada.
- Recommendations for routine vaccination have been modified.
- Schedules (including booster doses) have been revised for high risk individuals as has the list of high risk individuals.
- Recommendations for post-exposure immunoprophylaxis of close contacts of IMD who have been previously immunized have been provided.

For additional information, refer to the National Advisory Committee on Immunization (NACI) *Statement/Update on the Use of Quadrivalent Conjugate Meningococcal Vaccines,* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-3/index-eng.php)
EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Meningococcal disease is caused by an aerobic encapsulated diplococcus, *Neisseria meningitidis* (meningococcus). Meningococcal serogroups are classified according to the immunologic reactivity of the polysaccharide capsule. Almost all invasive meningococcal disease (IMD) is associated with serogroups A, B, C, Y, and W-135. Meningococcal serogroups A, B, and C cause the majority of disease worldwide and are responsible for most sporadic cases and outbreaks.

Reservoir
Humans are the only reservoir for *N. meningitidis*.

Transmission
Meningococci are transmitted person-to-person by mucosal contact with respiratory droplets from the nose and throat of infected persons. Most people who are colonized with meningococci are asymptomatic carriers. Meningococcal disease is characterized by a short incubation period (2 to 10 days, usually 3 to 4 days).

Risk factors
Risk factors for the development of IMD include: complement, properdin or factor D deficiencies; functional or anatomic asplenia (including sickle cell disease); certain genetic risk factors; household exposure to an infected person; concurrent respiratory tract infection; recent influenza; household crowding; and active and passive smoking. Persons with HIV infection may be at increased risk for meningococcal disease; especially if HIV is congenitally acquired.

Seasonal/temporal patterns
Although disease occurs year-round, there is seasonal variation with the majority of cases occurring in the winter-spring period in temperate climates and in the dry season in tropical climates. Most noteworthy is the “meningitis belt” of sub-Saharan Africa where the majority of cases occur from December to June. For further information, refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) website: about CATMAT. ([http://www.phac-aspc.gc.ca/tmp-pmv/catmat-cctmtmv/index-eng.php](http://www.phac-aspc.gc.ca/tmp-pmv/catmat-cctmtmv/index-eng.php))

Spectrum of clinical illness
Invasive meningococcal disease usually presents as an acute febrile illness with rapid onset and features of meningitis or septicemia (meningococcemia), or both, and a characteristic non-blanching petechial or purpuric rash. Symptoms of meningococcal meningitis include intense headache, fever, nausea, vomiting, photophobia and stiff neck. Meningococcemia is characterized by circulatory collapse, haemorrhagic skin rash and a high fatality rate. Overall mortality is approximately 10%, and 10% to 20% of survivors have long term sequelae which include hearing loss, neurologic disabilities, and digit or limb amputations.

DISEASE DISTRIBUTION

Incidence/prevalence

Global
Invasive meningococcal disease occurs sporadically worldwide and in focal epidemics. The traditional endemic areas of the world include the savannah areas of sub-Saharan Africa (known as the meningitis belt) extending from Gambia and Senegal in the west to Ethiopia and Western Eritrea in the east. Serogroup A disease predominates in Africa and Asia, while serogroup B
disease is predominant in Europe and most of the Americas. Meningococcal disease is also associated with the Hajj, an Islamic pilgrimage to Mecca, Saudi Arabia.

**National**

Invasive meningococcal disease is endemic in Canada, but rare. From 1985 to 2010, the overall incidence of IMD ranged between 0.4 to 1.6 cases per 100,000 population (refer to Figure 1). Incidence peaked in 1990 and again in 2001 due to localized outbreaks of serogroup C disease. Immunization campaigns using meningococcal serogroup C polysaccharide and conjugate vaccines were implemented in some regions during outbreaks from 1999 to 2001. Between 2002 and 2007, all Canadian provinces and territories implemented routine vaccination programs at various ages with monovalent meningococcal (serogroup C) conjugate vaccine, and since 2007 some have implemented routine adolescent quadrivalent meningococcal (serogroups A, C, Y, W-135) conjugate vaccination programs.

From 2005 to 2010, an average of 197 cases of IMD was reported annually in Canada, with an average incidence of 0.60 cases per 100,000 population. During this time period, incidence rates were highest among infants less than one year of age (average 7 cases per 100,000), followed by 1 to 4 year olds (1.81), and 15 to 19 year olds (1.18). As seen in Figure 2, the majority of cases with serogroup information from 2005 to 2010 were due to serogroup B (59%), which is not preventable by current vaccines. Serogroup C incidence has fallen dramatically to the extent that in 2010 its incidence fell to a level similar to that of serogroup W-135. Serogroup Y replaced C as the second most frequent serogroup by 2007. Cases caused by other serogroups were rare. The average number of cases caused by serogroups B, C, Y, and W-135 reported annually from 2005 to 2010 were 110, 29, 31, and 11, respectively. From 2005 to 2010, 6.7% of reported cases died. Case fatality ratios differed by serogroup, with serogroup C having the highest at 13% and serogroups B and W-135 having the lowest at around 4%.

**Figure 1: Reported cases and incidence (per 100,000) of invasive meningococcal disease in Canada, 1995 to 2010**

* Case data obtained from the National Enhanced Invasive Meningococcal Disease Surveillance System. Data for 2007 to 2010 are preliminary. Population data obtained from Statistics Canada annual estimates.
Figure 2: Incidence of invasive meningococcal disease per 100,000 population in Canada by serogroup and year, 1995 to 2010*

* Case data obtained from the National Enhanced Invasive Meningococcal Disease Surveillance System. Data for 2007 to 2010 are preliminary. Population data obtained from Statistics Canada annual estimates.

RECENT OUTBREAKS
Current meningococcal disease outbreak information is available from the World Health Organization (WHO) at: Global Alert and Response (GAR) Meningococcal Disease. (http://www.who.int/csr/don/archive/disease/ meningococcal_disease/en/)

PREPARATIONS AUTHORIZED FOR USE IN CANADA

MENINGOCOCCAL VACCINES

Monovalent conjugate meningococcal vaccines (Men-C-C)

- Meningitec® (meningococcal group C oligosaccharides conjugated to CRM₁₉₇ protein), Berna Biotech, AG (manufacturer), Pfizer Canada Inc. (distributor). (Men-C-C)
- Menjugate® (meningococcal group C oligosaccharide conjugated to CRM₁₉₇ protein), Novartis Vaccines and Diagnostics (sponsor), Novartis Pharmaceuticals Canada Ltd. (distributor). (Men-C-C)
- NeisVac-C® (meningococcal group C polysaccharide conjugated to tetanus toxoids), Baxter (manufacturer), GlaxoSmithKline Inc. (distributor). (Men-C-C)

Quadrivalent conjugate meningococcal vaccines (Men-C-ACYW-135)

- Menactra® (meningococcal groups A, C, Y, and W-135 polysaccharides conjugated to diphtheria toxoid protein), sanofi pasteur Ltd. (Men-C-ACYW-135)
- Menveo™ (meningococcal groups A, C, Y and W-135 oligosaccharide conjugated to CRM₁₉₇ protein), Novartis Vaccines and Diagnostics Inc. (Men-C-ACYW-135)
**Quadrivalent polysaccharide meningococcal vaccine (Men-P-ACYW-135)**

- **MENOMUNE® A/C/Y/W-135** (meningococcal groups A, C, Y and W-135 polysaccharide antigens), Sanofi Pasteur Inc. (manufacturer), sanofi pasteur Ltd. (distributor). (Men-P-ACYW-135).

Vaccines against meningococcal serogroup B disease are under development.

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**

A study of Men-C-C vaccine demonstrated effectiveness in infants of 97% within one year of vaccination, decreasing to 68% after 1 year. Longer term vaccine effectiveness requires receipt of a booster dose in the second year of life for those immunized in infancy. Vaccine effectiveness of Menactra® within 3 to 4 years of vaccination in adolescence is 80% to 85%; however, effectiveness wanes over time. There is no efficacy or effectiveness data available for Menveo™. Vaccine effectiveness measured at individual level may underestimate the impact of the program on meningococcal disease burden in the community due to the additional benefit conferred by herd immunity.

**Immunogenicity**

Men-C-C and Men-C-ACYW-135 vaccines are immunogenic in infants and toddlers but those vaccinated in infancy show a waning immune response. Vaccination with conjugate meningococcal vaccine primes the immune system for memory and induces good anamnestic responses; however, anamnestic response may not be sufficient to prevent disease after exposure and circulating antibodies are thought to be essential. In comparison to polysaccharide meningococcal vaccine, conjugate meningococcal vaccines demonstrate greater immunogenicity and induce better immunologic memory. Conjugate meningococcal vaccines do not result in hyporesponsiveness and have been shown to overcome the hyporesponsiveness evident with polysaccharide meningococcal vaccine usage.

**Recommendations for Use**

**Healthy Infants and Children (2 months to 11 years of age)**

Infants may receive Men-C-C vaccine beginning at 2 months of age depending on the provincial/territorial schedule and the incidence of meningococcal serogroup C disease in their jurisdiction. Men-C-C vaccine is recommended for all children at 12 to 23 months of age regardless of any doses given at less than 12 months of age. It is routinely given at 12 months and is recommended in unimmunized children less than 5 years of age. Men-C-C vaccine may be considered for children 5 to 11 years of age if not previously immunized as infants or toddlers.

**Healthy Adolescents and Your Adults (12 to 24 years of age)**

Either Men-C-C or Men-C-ACYW-135 vaccine (depending on local epidemiology and programmatic considerations) is recommended for adolescents (routinely at 12 years of age) and young adults, even if previously vaccinated as an infant or toddler.
HIGH RISK GROUPS

Underlying medical conditions
Individuals with increased risk of meningococcal disease because of underlying medical conditions are as follows:

- persons with functional or anatomic asplenia (including sickle cell disease)
- persons with congenital complement, properdin, factor D or primary antibody deficiencies
- persons with acquired complement deficiency due to receipt of the terminal complement inhibitor eculizumab (Soliris™)
- Men-C-ACYW-135 vaccine should be considered for individuals with HIV, especially if congenitally acquired.

Table 3 outlines the recommended schedule for vaccination of individuals who are at high risk due to underlying medical conditions. For those 1 year of age or older, two doses of Men-C-ACYW-135 vaccine, 8 weeks apart, are recommended.

There is limited evidence on the need for boosters. Based on expert opinion and the evidence to date, a booster dose for individuals in high risk groups is recommended every 3 to 5 years if vaccinated at 6 years of age and younger, and every 5 years for those vaccinated at 7 years of age and older. If a one dose primary series was used, give the second dose at the next available opportunity and then begin the booster doses based on the above intervals after the second dose.

Increased risk of exposure
Men-C-ACYW-135 vaccine is recommended for individuals at increased risk of exposure to meningococcal disease as follows:

- travellers (2 years of age and older) when meningococcal vaccine is recommended or required, including travellers to sub-Saharan Africa and pilgrims to the Hajj in Mecca, Saudi Arabia. Refer to Table 1 for recommendations for travellers 2 to 23 months of age.
- laboratory personnel who are potentially routinely exposed to N. meningitidis
- military personnel during recruit training and on certain deployments

A booster dose is recommended every 5 years if individuals in these groups remain at ongoing risk (every 3 to 5 years in children vaccinated at 6 years of age or younger). Refer to Travellers or Workers sections for additional information.

Meningococcal vaccine is also recommended for most close contacts of a case of IMD and for outbreak control, if the disease is caused by a serogroup contained in the vaccine. Refer to Post-exposure management and Outbreak control for additional information.

Age considerations for choice of vaccine for high risk groups

2 to 23 months of age
Based on available published data in this age group, Menveo™ should be used because it has been found to be safe and immunogenic. Routine meningococcal C conjugate vaccine does not need to be administered in addition to Menveo™.

24 months to 55 years of age
Either Men-C-ACYW-135 vaccine may be used.

56 years of age and older
Either Men-C-ACYW-135 vaccine should be considered.
Refer to Schedule for additional information, Table 1 for recommended vaccination for certain travellers and Table 3 for recommended vaccination of high risk individuals with underlying medical conditions.

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. Conjugate meningococcal vaccine, as appropriate for age, may be given regardless of possible previous receipt of the vaccine as adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Children and Adults with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING
Conjugate meningococcal vaccines have not been studied in pregnancy; however, there is no theoretical reason to suspect adverse events will occur and, in circumstances in which the benefits outweigh the risks, the use of conjugate meningococcal vaccines in pregnancy may be considered. Inactivated vaccines, such as conjugate meningococcal vaccines, may be administered to women who are breastfeeding. 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 conjugate meningococcal 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 meningococcal vaccine as appropriate for their risk factors. Refer to Immunization of Patients in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS
Quadrivalent conjugate meningococcal vaccine is recommended for certain high risk individuals as outlined under High risk groups above. 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 either or immunization and immunodeficiency is advised.

Congenital (primary) immunodeficiency
Persons with complement, properdin, factor D or primary antibody deficiencies should be vaccinated with Men-C-ACYW-135 vaccine. Refer to Table 3 for additional information.

Acquired (secondary) immunodeficiency
Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)
For children and adults, the effect of any previous meningococcal vaccine will be diminished following HSCT; therefore, HSCT recipients should be vaccinated as per recommendations for the previously unvaccinated based on their age or risk factors for IMD. If routinely indicated based on age or other risk factors, conjugate meningococcal vaccine can be given as early as 6 months after transplantation, unless needed earlier for management of a close contact or outbreak. However, if it is given earlier than 6 months after transplant the response may not be optimal and consideration should be given to repeating the dose at least 6 months after transplant (and at least 8 weeks after the previous dose) if ongoing protection is needed.
Solid organ transplantation

Conjugate meningococcal vaccine (type of vaccine as appropriate for age) is recommended to be given at least two weeks before transplantation if routinely indicated based on age or risk factors for IMD. If not given prior to transplant and routinely indicated based on age or other risk factors, meningococcal vaccine can be given any time after 6 months post-transplant and at least one month after discontinuation of treatment for acute rejection unless needed earlier for management of a close contact or outbreak. However, if it is given earlier than 6 months after transplant or earlier than 1 month after discontinuing treatment for acute rejection, the response may not be optimal and consideration should be given to repeating the dose at least 6 months after transplant and at least 1 month after discontinuing treatment for acute rejection (and at least 8 weeks after the previous dose) if ongoing protection is needed.

HIV-infected

Two doses of Men-C-ACYW-135 vaccine should be considered for individuals with HIV infection. Refer to Table 3 for additional information.

Acquired complement deficiency

People with conditions such as paroxysmal nocturnal hemoglobinuria who are receiving the terminal complement inhibitor eculizumab (Soliris™) should receive two doses of Men-C-ACYW-135 vaccine. They must be vaccinated at least two weeks prior to receiving the first dose of eculizumab, if possible, and every 5 years thereafter if they continue to use the drug. Refer to Table 3 for additional information.

Refer to Booster doses and re-immunization for additional information and Immunization of Immunocompromised Persons in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Asplenia

Two doses of Men-C-ACYW-135 vaccine are recommended for persons with anatomic or functional asplenia (including sickle cell disease). When elective splenectomy is planned, all recommended vaccines should ideally be completed at least 2 weeks before surgery; if only one dose can be given before surgery, the second dose should be given 8 weeks after the first dose (with a minimum interval of 4 weeks). In the case of an emergency splenectomy, two doses of vaccine should ideally be given beginning 2 weeks after surgery but can be given earlier, before discharge, if the person might not return for vaccination after discharge. Note that persons one year of age and older with asplenia who have not received Men-C-ACYW-135 vaccine should receive two doses administered 8 weeks apart (with a minimum interval of 4 weeks). Periodic booster doses are also recommended.

Refer to Table 3 for vaccination recommendations of high risk individuals due to underlying conditions based on age. Refer to Booster doses and re-immunization for additional information and Immunization of Persons with Chronic Diseases in Part 3 for additional general information.

TRAVELLERS

Travellers going to destinations where risk of meningococcal transmission is high should be vaccinated with Men-C-ACYW-135 vaccine. Men-C-C vaccine alone is not appropriate for protection of travellers as it does not protect against serogroup A, which is endemic in selected regions of the world, or serogroup W-135 disease. Current meningococcal disease outbreak information is available from the WHO at: Global Alert and Response (GAR) – Meningococcal Disease. (http://www.who.int/csr/don/archive/disease/meningococcal_disease/en/)

For travellers 2 months to 10 years of age, Men-C-ACYW-135 vaccine is indicated. For children 2 to 23 months, Mенвео™ is recommended based on expert opinion and clinical trial data; however, Mенвео™ is not authorized for use in this age group. For children 2 years to 10 years of age, Men-C-C vaccine should
already have been administered. If Men-C-C vaccine has not been given previously, it should be administered to children at least 4 weeks after the Men-C-ACYW-135 vaccine. Refer to Table 1 for recommended immunization for travellers to destinations where risk of meningococcal transmission is high.

Refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) information on assessing a traveller’s need for pre-travel vaccination. (http://www.phac-aspc.gc.ca/tmp-pmv/catmat-cctmv/)

Proof of meningococcal immunization may be required by certain countries. For example, Saudi Arabia requires proof of meningococcal immunization for pilgrims to the Hajj in Mecca. (http://www.hajinformation.com/main/p3001.htm) For travel to the Hajj, re-immunization at an interval of less than 5 years from the last dose may be required. Refer to Immunization of Travellers in Part 3 for additional general information.

Table 1: Recommended immunization for travellers to destinations where risk of meningococcal transmission is high, not previously immunized with Men-C-ACYW-135\(^1\) vaccine.

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended vaccine(s)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 11 months of age</td>
<td>Menveo™(^2)</td>
<td>2 or 3 doses given 8 weeks apart (with another dose between 12-23 months of age that is at least 8 weeks from the previous dose)(^3) and booster doses(^4)</td>
</tr>
<tr>
<td>12 to 23 months of age</td>
<td>Menveo™(^2)</td>
<td>2 doses at least 8 weeks apart(^3) and booster doses(^4)</td>
</tr>
<tr>
<td>24 months of age and older(^6)</td>
<td>Men-C-ACYW-135(^1)</td>
<td>1 dose(^5) and booster doses(^4)</td>
</tr>
</tbody>
</table>

\(^1\) Men-C-ACYW-135: Menactra\(^8\) or Menveo™

\(^2\) Menveo™ is not authorized for use in children less than 2 years of age; there are no authorized schedules for these children. The schedules in this table are based on those used in published clinical trials and the recommendation that a dose of meningococcal conjugate vaccine be given in the second year of life (12 to 23 months) for children vaccinated at less than 1 year of age.

\(^3\) Doses may be given a minimum of 4 weeks apart if accelerated immunization needed

\(^4\) A booster dose should be given every 3 to 5 years if vaccinated at 6 years of age or younger and every 5 years for those vaccinated at 7 years of age and older. Travellers to the Hajj should check recommendations for re-vaccination as more frequent re-vaccination may be required. (http://www.hajinformation.com/main/p3001.htm)

\(^5\) Children 2 to 10 years of age should have already received Men-C-C vaccine. If not, it should be administered 4 weeks after the Men-C-ACYW-135 vaccine.

\(^6\) Men-C-ACYW-135 vaccines are not authorized for use in those 56 years of age and older; however, based on limited evidence and expert opinion its use is considered appropriate.

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. Review of meningococcal vaccination status is particularly important for persons from areas of the world where sickle cell disease is present as persons with sickle cell disease are at risk of serious meningococcal infections. In many countries outside of Canada, conjugate meningococcal vaccines are in limited use. Information on vaccination schedules in other countries can be found on the following website:

WORKERS

Laboratory workers
Research, industrial and clinical laboratory personnel who are potentially routinely exposed to *N. meningitidis* should be offered one dose of Men-C-ACYW-135 vaccine. Re-vaccination is generally recommended every 5 years. Routine infection control precautions should be practiced at all times to minimize the risk of exposure in laboratory workers and post-exposure prophylaxis should be offered after recognized exposures. Refer to *Booster doses and re-immunization* for additional information.

Health care workers (HCW)
There is no evidence to recommend routine meningococcal immunization of HCW. Nosocomial transmission of IMD is very uncommon. HCW are considered as close contacts only if they have had intensive, unprotected contact (without wearing a mask) with infected patients (e.g., intubating, resuscitating or closely examining the oropharynx). It is recommended that HCW use barrier precautions to avoid direct contact with respiratory secretions of patients with meningococcal disease until the patient has completed 24 hours of effective antibiotic therapy.

Military personnel
Military personnel may be at increased risk when accommodated in close quarters or through deployment to endemic or epidemic countries.

Refer to *Immunization of Workers* in Part 3 for additional general information.

POST-EXPOSURE MANAGEMENT

Contacts of cases
Close contacts of individuals with meningococcal infections have an increased risk of developing IMD; this risk is greatest for household contacts. The increased risk of disease for household contacts persists for up to 1 year after disease in the index case and beyond any protection from antibiotic chemoprophylaxis. In general, this prolonged risk is not seen in contacts who do not have ongoing exposure.

Chemoprophylaxis should be offered to all persons having close contact with a case of IMD from 7 days before onset of symptoms in the case to 24 hours after onset of effective treatment in the case, regardless of their immunization status. Refer to the Public Health Agency of Canada *Guidelines for the Prevention and Control of Meningococcal Disease* for information about chemoprophylaxis in the management of close contacts of individuals with meningococcal infection. ([http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/31s1/index-eng.php](http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/31s1/index-eng.php))

Vaccination or re-vaccination of certain close contacts should be considered in addition to chemoprophylaxis when the serogroup is vaccine preventable as it may further reduce the risk of subsequent meningococcal disease.

*Close contacts requiring chemoprophylaxis and consideration for immunoprophylaxis*

The following individuals (regardless of immunization status) should receive chemoprophylaxis and, if the meningococcal serogroup identified in the case of IMD is vaccine preventable, should also be considered for immunoprophylaxis:

- Household contacts of a case of IMD
- Persons who share sleeping arrangements with a case of IMD
- Persons who have direct nose or mouth contamination with oral or nasal secretions of a case of IMD (e.g., kissing on the mouth, shared cigarettes, shared drinking bottles)
- Children and staff in contact with a case of IMD in child care or nursery school facilities
Refer to Table 2 for specific recommendations for immunoprophylaxis of close contacts of IMD cases according to the serogroup in the index case and the age and underlying conditions of the contact.

Re-vaccination criteria for those previously vaccinated against IMD

The following provides criteria for the re-vaccination of previously vaccinated close contacts when the index case has a vaccine preventable IMD serogroup or there is a vaccine preventable outbreak of IMD:

- Those previously vaccinated with a serogroup that differs from the index case or outbreak strain should be vaccinated immediately with the appropriate vaccine (as outlined in Table 2);
- Those previously vaccinated with a serogroup that is the same as the index case or outbreak strain should be re-vaccinated with the appropriate vaccine (as outlined in Table 2):
  - If they were less than 1 year of age at last meningococcal vaccination and more than 4 weeks has passed since their last meningococcal vaccine;
  - If they have an underlying medical condition that puts them at risk for meningococcal disease and more than 4 weeks has passed since their last meningococcal vaccine;
  - If more than a year has passed since their last meningococcal vaccine if they were not less than 1 year of age at the time of their last meningococcal vaccination and if they have no underlying medical condition that puts them at risk for meningococcal disease.

Close contacts requiring chemoprophylaxis only

The following individuals should receive chemoprophylaxis only, immunoprophylaxis is not necessary:

- Health care workers who have had intensive unprotected contact (without wearing a mask) with infected patients (i.e., intubating, resuscitating or closely examining the oropharynx).
- Airline passengers sitting immediately on either side of the case (but not across the aisle) when the total time spent aboard the aircraft was at least 8 hours.
- Close contacts of a case of IMD due to serogroups not present in meningococcal vaccines, or when the serogroup in the index case has not been determined.
- Previously vaccinated close contacts who do not meet the criteria for re-vaccination as outline above.

OUTBREAK CONTROL

Outbreaks of meningococcal disease

Consultation with either or public health officials and experts in communicable disease is important in the assessment and control of meningococcal disease outbreaks. Outbreaks may be controlled by the use of a conjugate meningococcal vaccine. The type of vaccine to use in an outbreak is dependent on the serogroup causing the outbreak and the age of those being vaccinated as outlined in Table 2. Re-vaccination criteria of previously vaccinated individuals are outlined above in Re-vaccination criteria for those previously vaccinated against IMD.
Table 2: Recommended vaccination of close contacts for post-exposure management and for outbreak control

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommended vaccine(s)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contacts and outbreak control of <strong>serogroup C</strong> invasive meningococcal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months to less than 12 months of age</td>
<td>Men-C-C&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Unvaccinated:</strong> 1 dose immediately after exposure then complete the routine series of Men-C-C</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Previously vaccinated:</strong> If previously vaccinated then re-vaccinate with Men-C-C if at least 4 weeks since last dose, then complete the routine series of Men-C-C if necessary</td>
</tr>
<tr>
<td>12 months – 10 years of age</td>
<td>Men-C-C&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Unvaccinated:</strong> 1 dose immediately after exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Previously vaccinated:</strong> If previously vaccinated at less than 1 year of age OR person is at high risk for IMD due to underlying medical conditions, then re-vaccinate with one dose of Men-C-C if at least 4 weeks since last dose; otherwise re-vaccinate if at least 1 year since last dose</td>
</tr>
<tr>
<td>11 years of age and older</td>
<td>Men-C-C&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Unvaccinated:</strong> 1 dose immediately after exposure</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Previously vaccinated:</strong> If previously vaccinated at less than 1 year of age OR person is at high risk for IMD due to underlying medical conditions, then re-vaccinate with one dose of vaccine of choice if at least 4 weeks since last dose; otherwise re-vaccinate if at least 1 year since last dose</td>
</tr>
<tr>
<td></td>
<td>Men-C-ACYW-135&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Close contacts and outbreak control of <strong>serogroup A, Y, or W-135</strong> invasive meningococcal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months to less than 12 months of age</td>
<td>Menveo™&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Unvaccinated:</strong> 2 or 3 doses given 8 weeks apart with another dose between 12 and 23 months and at least 8 weeks from the previous dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Previously vaccinated:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If previously vaccinated with only Men C-C, give Menveo™ as for unvaccinated persons, regardless of when Men-C-C was previously given&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If previously vaccinated with Men-C-ACYW-135, then re-vaccinate with one dose of Menveo™ if at least 4 weeks since last dose of Men-C-ACYW-135 vaccine; then complete series</td>
</tr>
<tr>
<td>Group</td>
<td>Recommended vaccine(s)</td>
<td>Schedule</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>12 to 23 months of age</td>
<td>Menveo™*</td>
<td><strong>Unvaccinated:</strong> 2 doses at least 8 weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Previously vaccinated:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If previously vaccinated with only Men C-C, give Menveo™ as for unvaccinated persons, regardless of when Men-C-C was previously given*5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If previously vaccinated with Men-C-ACYW-135 at less than 1 year of age OR if person is at high risk for IMD due to underlying medical conditions*2, then re-vaccinate with one dose of Menveo™ if at least 4 weeks since last dose of Men-C-ACYW-135; otherwise re-vaccinate with one dose of Menveo™ if at least 1 year since last dose of Men-C-ACYW-135</td>
</tr>
<tr>
<td>2 years and older</td>
<td>Men-C-ACYW-135*3</td>
<td><strong>Unvaccinated:</strong> 1 dose immediately after exposure*6</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Previously vaccinated:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If previously vaccinated with only Men C-C, give Men-C-ACYW-135 as for unvaccinated persons, regardless of when Men-C-C was previously given*5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If previously vaccinated with Men-C-ACYW-135 at less than 1 year of age OR if person is at high risk for IMD due to underlying medical conditions*2, then re-vaccinate with one dose of Men-C-ACYW-135 if at least 4 weeks since last dose of Men-C-ACYW-135; otherwise re-vaccinate with one dose of Men-C-ACYW-135 if at least 1 year since last dose of Men-C-ACYW-135</td>
</tr>
</tbody>
</table>

*1 Men-C-C: Meningitec® or Menjugate® or NeisVac-C®  
*2 At high risk due to underlying medical conditions - refer to Underlying medical conditions  
*3 Men-C-ACYW-135: Menactra® or Menveo™  
*4 Menveo™ is not authorized for use in children less than 2 years of age; there are no authorized schedules for these children. The schedules in this table are based on those used in published clinical trials and the recommendation that a dose of meningococcal conjugate vaccine be given in the second year of life (12 to 23 months) for children vaccinated at less than 1 year of age.  
*5 In general, a minimum four week interval is recommended between doses of conjugate meningococcal vaccines; however, in an outbreak or to manage a close contact of a case of IMD, the second dose of conjugate meningococcal vaccine may be given as soon as indicated to provide protection to a close contact who is unvaccinated for the implicated serogroup.  
*6 Individuals at high risk due to underlying medical conditions routinely need two doses of Men-C-ACYW-135.
VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

**Dose**
Each dose of meningococcal vaccine is 0.5 mL.

**Route of administration**
Conjugate meningococcal vaccine should be administered intramuscularly (IM). Refer to Vaccine Administration Practices in Part 1 for additional information.

**Schedule**
Recommended meningococcal immunization schedules and products vary across provinces/territories depending upon the epidemiology of meningococcal disease in the jurisdiction and other programmatic factors.

*Healthy infants and children (2 to 23 months of age)*
The manufacturer-recommended infant schedule varies with the Men-C-C vaccine used. For routine infant immunization, three doses of Menjugate® may be administered separated by at least 4 weeks, from 2 months of age. Two doses of NeisVac-C® or Meningitec® may be administered at least 2 months apart, from 2 months of age. **If Men-C-C vaccine is given to infants less than 12 months of age, a booster dose should be given between 12 to 23 months of age.** If the booster dose is missed, it can be given at the next vaccination opportunity.

*Healthy children, adolescents and young adults*
One dose of Men-C-C vaccine is recommended for previously unimmunized children 12 months to less than 5 years of age and may be considered for children 5 to 11 years of age. In addition to routine Men-C-C vaccine for infants and young children, adolescents and young adults (12 to 24 years of age) should receive one dose of either Men-C-C or Men-C-ACYW-135 vaccine, based on local epidemiology and programmatic considerations, with around 12 years being the preferred age for the routine dose.

*High risk individuals due to underlying medical conditions*
High risk individuals are those with underlying conditions that make them more likely to develop IMD. Schedule options for high risk individuals who have not previously received a quadrivalent conjugate meningococcal vaccine are included in Table 3. As noted in Table 3, previously unimmunized high risk persons 12 months of age and older should receive a two dose primary series administered 8 weeks apart (with a minimum interval of 4 weeks).
Table 3: Recommended immunization for high risk groups because of underlying medical conditions⁴ not previously immunized with Men-C-ACYW-135² vaccine

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended vaccine(s)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 11 months of age</td>
<td>Mencevo™³</td>
<td>2 or 3 doses given 8 weeks apart (with another dose between 12-23 months of age that is at least 8 weeks from the previous dose)⁴ and booster doses⁵</td>
</tr>
<tr>
<td>12 to 23 months of age</td>
<td>Mencevo™³</td>
<td>2 doses at least 8 weeks apart⁴ and booster doses⁵</td>
</tr>
<tr>
<td>24 months to 55 years of age</td>
<td>Men-C-ACYW-135</td>
<td>2 doses 8 weeks apart⁴ and booster doses⁵</td>
</tr>
<tr>
<td>56 years of age and older</td>
<td>Men-C-ACYW-135⁶</td>
<td>2 doses 8 weeks apart⁴ and booster doses⁵</td>
</tr>
</tbody>
</table>

¹ At high risk due to underlying medical conditions: refer to [Underlying medical conditions](#).
² Men-C-ACYW-135: Menactra® or Mencevo™
³ Mencevo™ is not authorized for use in children less than 2 years of age; there are no authorized schedules for these children. The schedules in this table are based on those used in published clinical trials and the recommendation that a dose of meningococcal conjugate vaccine be given in the second year of life (12 to 23 months) for children vaccinated at less than 1 year of age.
⁴ Doses may be given a minimum of 4 weeks apart if accelerated immunization needed
⁵ A booster dose should be given every 3 to 5 years if vaccinated at 6 years of age or younger and every 5 years for those vaccinated at 7 years of age and older.
⁶ Men-C-ACYW-135 vaccines are not authorized for use in those 56 years of age and older; however, based on limited evidence and expert opinion its use is considered appropriate.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Circulating antibodies are considered necessary to protect an individual against IMD. Re-vaccination is recommended as follows:

- Individuals at high risk of developing meningococcal disease due to underlying conditions as outlined in [Underlying medical conditions](#). Re-vaccination is recommended every 3 to 5 years for those vaccinated at 6 years of age and younger and every 5 years for those vaccinated at 7 years of age and older.
- When travelling to areas where meningococcal vaccine is recommended or required. Re-vaccination is recommended every 3 to 5 years of age if vaccinated at 6 years of age and younger, and every 5 years for those vaccinated at 7 years of age and older. Previously vaccinated travellers are advised to check requirements for re-vaccination with meningococcal vaccines prior to travel to the Hajj as more frequent vaccination may be required (refer to [Ministry of Hajj – Kingdom of Saudi Arabia](http://www.hajinformation.com/main/p3001.htm) and [Travellers](http://www.hajinformation.com/main/p3001.htm)).
- Military personnel who remain at risk due to travel or overcrowded conditions. A booster dose is recommended every 5 years if at ongoing risk
- At the time of exposure for contacts of a case of IMD in some circumstances. Refer to [Post-exposure management](#).
- During a community outbreak of IMD in some circumstances. Refer to [Post-exposure management](#).
- All laboratory personnel who are potentially routinely exposed to *N. meningitidis*. Booster doses should be given at routine 5 year intervals for those laboratory workers who remain at ongoing risk of exposure. Refer to [Workers](#).
People previously vaccinated with a polysaccharide meningococcal vaccine should be re-vaccinated with the appropriate conjugate meningococcal vaccine if they remain at ongoing risk for meningococcal disease, with at least a 6 month interval following vaccination with polysaccharide meningococcal vaccine.

**SEROLOGIC TESTING**

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

**STORAGE REQUIREMENTS**

Menactra®, Meningitec®, NeisVac-C®: Store in a refrigerator at +2ºC to +8ºC. Do not freeze.

Menjugate®, Menveo™: Store in a refrigerator at +2ºC to +8ºC. Do not freeze. Protect from light.

Refer to *Storage and Handling of Immunizing Agents* in Part 1 for additional general information.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**

Men-C-C vaccine may be administered concomitantly with routine childhood vaccines and Men-C-ACYW-135 vaccine may be administered concomitantly with adolescent and adult age appropriate vaccines at different injection sites using separate needles and syringes.

Menveo™ can be administered with routine paediatric vaccines; however, further studies are needed with regard to concomitant administration with pneumococcal 13-valent conjugate vaccine. Co-administration of Menveo™ and combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) may result in a lower immune response to the pertussis antigens than when Tdap vaccine is given alone; however, the clinical significance of this is unknown. Tdap vaccine given one month after Menveo™ induces the strongest immunologic response to pertussis antigens. 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**

**Conjugate meningococcal vaccines**

**Men-C-ACYW-135 vaccines**

Injection site reactions occur in up to 59% of vaccinees. Fever is reported in up to 5% of recipients and systemic reactions, such as headache and malaise, are reported in up to 60% of recipients.

**Men-C-C vaccines**

Mild reactions, including injection site reactions (redness, tenderness, and swelling), occur in up to 50% of vaccinees. Irritability occurs in up to 80% of infants and fever in up to 9% when other vaccines were administered. Headaches and malaise occur in up to 10% of older children and adults. These reactions last no more than a few days.
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. A concern regarding Guillain Barre Syndrome (GBS) following Menactra® was raised because of case reports to the United States Vaccine Adverse Event Reporting System (VAERS). Subsequently, two large epidemiologic studies were conducted. No cases of GBS were observed during the six weeks following over 2.2 million doses given to individuals aged 11 to 21 years. This evidence supports the conclusion that there is no increased risk of GBS following Menactra®.

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) (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php) in Canada and Vaccine Safety in Part 2 for additional information about AEFI reporting.

CONTRAINDICATIONS AND PRECAUTIONS
Meningococcal 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. Refer to Table 1 in Contents of Immunizing Agent Available for Use in Canada in Part 1 for lists of all vaccines available for use in Canada and their contents. For meningococcal vaccines, potential allergens include:

- Menactra®: diphtheria toxoid protein
- Meningitec®: latex in vial stopper, diphtheria CRM197 toxoid carrier protein Menjugate®: latex in tip cap of syringe, diphtheria CRM197 toxoid carrier protein
- Menomune®: thimerosal, latex
- Menveo™: diphtheria CRM197 toxoid carrier protein
- NeisVac-C®: tetanus toxoid protein

There are very few individuals who cannot receive meningococcal vaccines. 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. Menomune® may be considered in the rare circumstance that someone is allergic to components (other than latex) in the conjugate meningococcal vaccines.

Administration of meningococcal 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
There are no published data regarding the interchangeability of Men-C-C vaccines, but the vaccines have been safely interchanged without a noticeable decrease in efficacy. When possible, the infant series should be completed with the same vaccine. Either Men-C-ACYW-135 vaccine may be used for revaccination, regardless of which meningococcal vaccine was used for initial vaccination. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.
SELECTED REFERENCES


Richmond P, Borrow R, Miller E et al. Meningococcal serogroup C conjugate vaccine is immunogenic in...


PART 4

MUMPS VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th>Outbreaks of mumps continue to occur in Canada and the proportion of cases aged 20 years and older has increased.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complications such as orchitis/oophoritis are relatively frequent; permanent sequelae like deafness are rare.</td>
</tr>
<tr>
<td></td>
<td>Mumps vaccine is available as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine.</td>
</tr>
<tr>
<td></td>
<td>Mumps vaccine effectiveness has been estimated at 62% to 91% for one dose and 76% to 95% for two doses.</td>
</tr>
<tr>
<td></td>
<td>Reactions to MMR and MMRV vaccine are generally mild and transient and include pain and redness at the injection site, low-grade fever and rash.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Mumps-containing vaccine is recommended for routine immunization of children and for immunization of children and adolescents who missed mumps immunization on the routine schedule.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mumps-containing vaccine is recommended for susceptible adults born in 1970 or later.</td>
</tr>
<tr>
<td></td>
<td>Adults born before 1970 can be presumed to have acquired natural immunity to mumps; however, non-immune health care workers, travellers and military personnel should receive MMR vaccine, regardless of year of birth.</td>
</tr>
</tbody>
</table>
### How

<table>
<thead>
<tr>
<th>How</th>
<th>Routine childhood immunization: administer two doses of mumps-containing vaccine (MMR or MMRV); the first dose at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter, typically before school entry.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children and adolescents who are previously unimmunized: administer two doses of mumps-containing vaccine. The minimum interval between doses of MMR vaccine is 4 weeks. MMRV vaccine may be used in healthy children aged 12 months to 12 years. The recommended interval between 2 doses of MMRV vaccine is at least 3 months; a minimum interval of 6 weeks between doses may be used if rapid, complete protection is required.</td>
</tr>
<tr>
<td></td>
<td>Susceptible adults born in 1970 or later: administer one dose of MMR vaccine. Those who are at the greatest risk of mumps exposure (travellers to destinations outside of North America, health care workers, students in post-secondary educational settings, and military personnel) should receive two doses of MMR vaccine.</td>
</tr>
<tr>
<td></td>
<td>Non-immune health care workers and military personnel born before 1970: administer two doses of MMR vaccine at least 4 weeks apart.</td>
</tr>
<tr>
<td></td>
<td>Non-immune travellers born before 1970: administer one dose of MMR vaccine.</td>
</tr>
<tr>
<td></td>
<td>Non-immune students born before 1970: consider administering one dose of MMR vaccine.</td>
</tr>
</tbody>
</table>

### Why

<table>
<thead>
<tr>
<th>Why</th>
<th>Mumps occurs worldwide and outbreaks continue to occur.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complications of mumps disease are relatively frequent although permanent sequelae are rare.</td>
</tr>
<tr>
<td></td>
<td>MMR and MMRV vaccines are safe and effective.</td>
</tr>
</tbody>
</table>

Since the publication of the 2006 Canadian Immunization Guide:

- New recommendations have been made regarding a two dose mumps-containing vaccine vaccination schedule for children.
- New recommendations have been made regarding mumps vaccination in adults.
- A new combined multivalent vaccine (measles-mumps-rubella-varicella vaccine [MMRV]) has become available for children aged 12 months to 12 years.


### EPIDEMIOLOGY

### DISEASE DESCRIPTION

#### Infectious agent

Mumps virus is a member of the *Paramyxoviridae* family.

#### Reservoir

Humans

#### Transmission

Mumps virus is transmitted primarily by droplet spread as well as direct contact with saliva of an infected person. The incubation period is about 16 to 18 days. Virus has been isolated from saliva 7
days before to 9 days after the onset of parotitis with maximum infectiousness between 2 days before to 5 days after onset of symptoms.

**Risk factors**
In general, people who have not had mumps or who have not been successfully vaccinated are at risk of being infected. In Canada, adults born before 1970 can be presumed to have acquired natural immunity to mumps; however, some individuals may be susceptible. A second dose of mumps vaccination was routinely given along with measles and rubella (MMR) for measles control beginning in 1996 to 1997. Depending on the age the second dose was given, people born before 1996 may only have received one dose of mumps-containing vaccine and so may still be susceptible. In addition, people born between 1970 and approximately 1996 who received only one dose of mumps-containing vaccine may still be susceptible. Adolescents and adults who are at greatest risk of exposure to mumps include students in secondary and post-secondary educational settings, military personnel, health care workers and travellers to destinations outside of North America.

**Seasonal/temporal pattern**
Historically, the incidence of mumps peaked in the spring and winter months in temperate zones, but now there are sporadic cases and outbreaks.

**Spectrum of clinical illness**
About 40% of those infected with mumps develop acute parotitis, which is unilateral in about 25% of cases. Non-specific or primarily respiratory symptoms occur in about one-half of those infected. Subclinical infection is common. Although complications are relatively frequent, permanent sequelae are rare. Before the widespread use of vaccine, mumps was a major cause of viral meningitis. Mumps meningoencephalitis can, rarely, result in permanent neurologic sequelae, including paralysis, seizures, cranial nerve palsies and hydrocephalus. Permanent deafness may occur, at an estimated rate of 0.5 to 5.0 per 100,000 mumps cases. Orchitis occurs in 20% to 30% of post-pubertal male cases and oophoritis in 5% of post-pubertal female cases. Involvement of the reproductive organs is commonly unilateral; therefore, sterility is rare. Mumps infection in pregnancy has not been associated with congenital malformations, but mumps infection during the first trimester of pregnancy may increase spontaneous abortion.

**DISEASE DISTRIBUTION**

**Incidence/prevalence**

*Global*
Mumps occurs worldwide with cases reported throughout the year and epidemics occurring every two to five years. Mumps remains endemic in many countries, and mumps vaccine is used in only 59% of World Health Organization (WHO) member states.

Between 2004 and 2006, there was a large mumps outbreak in the United Kingdom (UK), with more than 70,000 cases. In 2006 there was a multi-state outbreak in the United States (US) with over 2,500 cases. In 2009 there were more than 7,400 cases of mumps in England and Wales, mostly among unvaccinated young adults. In June 2009, a large outbreak of mumps occurred in New York and New Jersey in the US. The outbreak mainly affected school age males from a faith-based community. Of those with known vaccination status, 88% had received at least one dose of mumps-containing vaccine before the outbreak and 75% had received two doses.

*National*
Since the approval of mumps vaccine in 1969, the number of reported mumps cases has decreased by more than 99% from an average of 34,000 cases reported per year in the early 1950s to fewer than 400 cases per year in the early 1990s. A further reduction in incidence was observed following the introduction of the routine second dose of MMR vaccine in 1996 to 1997. The annual number of cases has continued to decrease; during the period 2000 to 2006, an average of 81 cases were reported.
annually, ranging from 28 (2003) to 201 cases (2002). However, in 2007 there were over 1,000 cases and in 2008 there were almost 750 reported cases, mainly as a result of outbreaks in several provinces.

The age distribution of mumps in Canada has changed. While the total number of reported cases decreased, the proportion of reported cases aged 20 years and older increased from 14% in 1988-1990 to 64% in 2003-2005. Conversely, the proportion of cases aged 1 to 9 years fell from 49% to 17% during the same period.

RECENT OUTBREAKS
In Canada, large outbreaks of mumps have been rare in recent years. In 2007, large outbreaks occurred in Nova Scotia, New Brunswick and Alberta with a total of 1,159 confirmed cases, accounting for 90% of the total cases in Canada that year. The majority (58%) of cases occurred in persons aged 20 to 29 years, many of who were college or university students. Immunization history was known for less than one-half of the mumps cases. Of those known, 8% had received two or more doses, 73% had received one dose, and 19% had received no mumps immunization. The viral strain in the 2007 outbreaks was identical to the strain (genotype G) detected in the previous Nova Scotia outbreaks, the 2006 US multi-state outbreak, and the UK epidemic.

In 2008, large outbreaks occurred in Alberta, Ontario and British Columbia (BC). In Alberta, the 2007 outbreak continued with an additional 280 cases in 2008. In Ontario, a total of 324 outbreak cases were reported, of which 289 were confirmed. The cases ranged in age from less than 1 year to 45 years (average age 11) with no gender difference. The majority of cases (95.7%) occurred in unimmunized individuals. The BC outbreak included 183 reported cases, of which 133 were confirmed. The outbreak started in a largely unimmunized faith-based community. One-half of the cases were in the 0 to 19 year old age group. Nearly one-half of the cases (46%) were unimmunized and 28% of the cases had unknown immunization history.

Beginning in October 2009, an outbreak of mumps occurred among a faith-based community in Quebec with 23 confirmed cases. The outbreak was linked to a large mumps outbreak in New York and New Jersey in the US. All cases were male and aged 8 to 47 years.

PREPARATIONS AVAILABLE FOR USE IN CANADA

MUMPS-CONTAINING VACCINES

- **M-M-R® II** (live, attenuated combined measles, mumps and rubella vaccine), Merck Canada Inc. (MMR)
- **PRIORIX®** (live, attenuated combined measles, mumps and rubella vaccine), GlaxoSmithKline Inc. (MMR)
- **PRIORIX-TETRA®** (live, attenuated combined measles, mumps, rubella and varicella vaccine), GlaxoSmithKline Inc. (MMRV)

In Canada, mumps vaccine is only available in combination with measles and rubella vaccine (MMR) or measles, rubella and varicella vaccine (MMRV). In many countries outside of Canada, measles vaccine alone is given and mumps vaccination is not offered.

For complete prescribing information, consult the product leaflet or information contained within the product monograph available through the Health Canada’s Drug Product Database. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of vaccines available for use in Canada and their contents.
EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS
Mumps vaccine effectiveness has been estimated at 62% to 91% for one dose and 76% to 95% for two doses. Mumps outbreaks have been reported in populations with greater than 95% coverage with single dose mumps-containing vaccine, suggesting that one dose of mumps-containing vaccine is not sufficient to prevent mumps outbreaks. In some instances, outbreaks have arisen in settings with high two-dose coverage. Waning immunity contributes to the risk of mumps in vaccinated individuals. There are no data regarding the efficacy of MMRV vaccine.

IMMUNOGENICITY
In clinical studies a single injection of MMR vaccine induced measles antibodies in 95%, mumps antibodies in 96%, and rubella antibodies in 99% of previously seronegative children.

In a study of 12 month old children, a single dose of MMRV vaccine resulted in a seroconversion rate for measles, mumps, rubella and varicella of 96%, 97%, 98% and 93%, respectively. The seroconversion rates and geometric mean titres for individual components were not significantly different from those achieved after MMR vaccine alone. A study of children receiving two doses of MMRV vaccine during the second year of life noted seropositivity for measles, mumps, rubella and varicella of 99%, 97.4%, 100% and 99.4% respectively by the third year post-vaccination. Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies following MMRV vaccinations are under evaluation.

RECOMMENDATIONS FOR USE

CHILDREN (12 months to 17 years of age)
Two doses of mumps-containing vaccine should be given for routine immunization of children and for immunization of children and adolescents who missed mumps immunization on the routine schedule. MMRV vaccine may be used in children aged 12 months to 12 years.

Students in secondary educational settings should have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease.

ADULTS (18 years of age and older)
Routine immunization: adults born before 1970 are generally presumed to have acquired natural immunity to mumps; however, some of these individuals may be susceptible. Adults without contraindications, born in 1970 or later who do not have documented evidence of receiving mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps infection should be immunized with one dose of MMR vaccine.

Health care workers, regardless of their year of birth, who do not have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive two doses of MMR vaccine. Refer to Workers.

Students in post-secondary educational settings, born in 1970 or later, who do not have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive two doses of MMR vaccine. In students born before 1970, administration of one dose of MMR vaccine should be considered.
Military personnel, regardless of their year of birth, who do not have documented evidence of receiving two doses of a mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive two doses of MMR vaccine.

Travellers to destinations outside of North America, born in 1970 or later, who do not have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive two doses of mumps-containing vaccine. Travellers born before 1970 who do not have documented evidence of receiving a mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive one dose of MMR vaccine. Refer to Travellers.

Table 1 provides a summary of criteria for mumps immunity. Refer to Schedule.

### Table 1: Criteria for immunity to mumps

<table>
<thead>
<tr>
<th>Routine</th>
<th>Health care workers</th>
<th>Travellers to destinations outside North America</th>
<th>Students in secondary or post-secondary educational settings</th>
<th>Military personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination with 2 doses(^1) (regardless of year of birth) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination:</td>
<td>Documentation of vaccination with 2 doses(^1) (regardless of year of birth) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
</tr>
<tr>
<td>- Children 12 months to 17 years of age: 2 doses(^1)</td>
<td>OR History of laboratory confirmed infection</td>
<td>If born in 1970 or later: 2 doses(^1) OR If born before 1970: 1 dose(^1) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td>If born in 1970 or later: 2 doses(^1) OR If born before 1970: consider 1 dose(^1) if no documentation of receipt of mumps-containing vaccine OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td></td>
</tr>
<tr>
<td>- Adults born in 1970 or later: 1 dose(^1,2) OR History of laboratory confirmed infection OR Laboratory evidence of immunity</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>- Born before 1970</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Mumps-containing vaccine
\(^2\) Refer to additional recommendations for health care workers, travellers to destinations outside of North America, students in post-secondary educational settings and military personnel.

### 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, unless known to be immune based on laboratory testing. MMR or MMRV vaccine, as appropriate, may be given regardless of possible previous receipt of the vaccine because additional adverse events associated with repeated
immunization have not been demonstrated. Refer to **Immunization of Persons with Inadequate Immunization Records** in Part 3 for additional general information.

**PREGNANCY AND BREASTFEEDING**

Immunity to measles, mumps and rubella should be reviewed in women of reproductive age, and vaccination should be recommended to non-pregnant susceptible women. Ideally, the immunization status of women intending to become pregnant should be reviewed and vaccines updated as necessary prior to conception. Women should delay pregnancy by at least 28 days following vaccination with a live vaccine.

MMR and MMRV vaccines should generally not be given during pregnancy because of the theoretical risk of disease transmission to the fetus; however, there is no evidence demonstrating a teratogenic or other risk from such vaccines. There was no evidence of Congenital Rubella Syndrome in any of the offspring of 226 women inadvertently vaccinated during pregnancy. Inadvertent immunization with MMR vaccine is not a reason for pregnancy termination. In some situations, potential benefits of MMR vaccination may outweigh risks such as during measles or rubella outbreaks, in which case vaccination may be considered.

Women who are breastfeeding can be vaccinated with MMR vaccine.

Refer to **Contraindications and Precautions**. Refer to **Immunization in Pregnancy and Breastfeeding** in Part 3 for additional general information.

**IMMUNOCOMPROMISED PERSONS**

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised person with a live vaccine, **approval from the individual’s attending physician should be obtained before vaccination**. For complex cases, referral to a physician with expertise in immunization or immunodeficiency or both is advised. Refer to **Immunocompromised persons** in the **Measles Vaccine** in Part 4 for additional information.

- **Household contacts**
  
  Susceptible household contacts of immunocompromised people should receive a mumps-containing vaccine as appropriate for age and risk factors.

  Refer to **Contraindications and Precautions**. Refer to **Immunization of Immunocompromised Persons** in Part 3 for additional information.

**PERSONS WITH CHRONIC DISEASES**

- **Neurologic disorders**
  
  People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including MMR or MMRV vaccine. Refer to **Immunization of Persons with Chronic Diseases** in Part 3 for additional general information.

**TRAVELLERS**

Protection against mumps is especially important for people planning travel to destinations outside of North America. Travellers born in 1970 or later, who do not have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive two doses of mumps-containing vaccine.
Travellers born before 1970, who do not have documented evidence of receiving mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should receive one dose of MMR vaccine.

Mumps is endemic in many countries. Refer to mumps incidence rates in WHO member countries for additional information. (http://www.who.int/immunization_monitoring/diseases/en/)

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. In many countries outside of Canada, mumps and rubella vaccines are in limited use and measles vaccine alone is given. A Canadian study showed that more than one-third of new immigrants and refugees, particularly women, were susceptible to measles, mumps, or rubella. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS

It is recommended that all health care workers be immune to mumps. Health care workers, regardless of their year of birth, who do not have documented evidence of receiving two doses of mumps-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed mumps disease should be vaccinated accordingly so that they have received two doses of MMR vaccine. Refer to Immunization of Workers in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION

Post-exposure MMR vaccination does not prevent or alter the clinical severity of mumps. It may be considered if repeated exposure to mumps is anticipated. If exposure to mumps does not cause infection, post-exposure vaccination with MMR vaccine should induce protection against subsequent infection. There is no evidence of increased risk of adverse reactions from immunization with MMR vaccine if an individual is already immune to one or more components of the vaccine or infected by mumps virus. There are no data on the use of MMRV vaccine in post-exposure situations. Passive immunization with human immune globulin (Ig) is not effective in preventing mumps.

OUTBREAK CONTROL

With the implementation of a two dose schedule for mumps vaccine, it is expected that large outbreaks of mumps will occur less frequently. However, cases that do occur may result in transmission of mumps, usually among unvaccinated children and young adults who have not received two doses of vaccine and who were born after wide circulation of natural mumps disease was common. Outbreaks have also occurred in populations who are predominantly vaccinated with two doses of mumps-containing vaccines. In outbreak situations, a dose of mumps-containing vaccine is, recommended for those born in or after 1970 who received only one dose of a mumps-containing vaccine. At-risk populations will need to be further defined by the age groups and settings involved in the outbreak. For further information regarding mumps outbreak control refer to the Public Health Agency of Canada’s (PHAC) Supplement: Guidelines for the Prevention and Control of Mumps Outbreaks in Canada. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/36s1/index-eng.php)

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose is 0.5 mL.
Route of administration
MMR vaccine should be administered subcutaneously; MMRV can be administered subcutaneously or intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Children (12 months to 12 years of age)
For routine immunization of children aged 12 months to 12 years, two doses of mumps-containing vaccine (MMR or MMRV) should be administered. The first dose of mumps-containing vaccine should be administered at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter, typically before school entry.

The recommended minimum interval between doses of MMR vaccine is 4 weeks. Children who previously received a single dose of MMR vaccine should receive a second dose at least 4 weeks after the first dose. The recommended interval between two doses of MMRV vaccine is at least 3 months; a minimum interval of 6 weeks between doses may be used if rapid, complete protection is required.

Adolescents (13 to 17 years of age)
Mumps-susceptible adolescents should receive two doses of MMR vaccine given at least 4 weeks apart.

Adults (18 years of age and older)
Mumps-susceptible adults should receive one or two doses of MMR vaccine as appropriate for age and risk factors (refer to Table 1). If two doses are needed, MMR vaccine is administered with a minimum interval of 4 weeks between doses.

BOOSTER DOSES AND RE-IMMUNIZATION
Re-immunization with mumps-containing vaccine after age and risk appropriate vaccination is not necessary.

SEROLOGICAL TESTING
Serologic testing is not recommended before or after receiving mumps-containing vaccine. Although generally used as criteria for immunity, the presence of mumps-specific IgG, as determined by enzyme immunoassay (EIA), does not necessarily predict the presence of neutralizing antibodies and, thus, immunity. Conversely, the absence of detectable mumps-specific IgG does not mean the person is susceptible. For further information regarding mumps serology refer to the PHAC Supplement: Guidelines for the Prevention and Control of Mumps Outbreaks in Canada. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10pdf/36s1-eng.pdf)

STORAGE REQUIREMENTS
M-M-R® II: Maintain vaccine at +10°C or colder during shipment. Freezing during shipment will not affect potency of the vaccine. Protect the vaccine from light. Before reconstitution, store the vial of vaccine at +2°C to +8°C or colder. The diluent may be stored in the refrigerator or at room temperature and must not be frozen.

PRIORIX®: Store in a refrigerator at +2°C to +8°C. The diluent may be stored separately at room temperature. Protect from light.

PRIORIX-TETRA®: Store the vaccine and diluent in a refrigerator at +2°C to +8°C and do not freeze. Protect the vaccine from light.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.
SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Live vaccines given by the parenteral route may be administered concomitantly with all other vaccines during the same visit using different injection sites and separate needles and syringes. In general, if two live parenteral vaccines are not administered concomitantly, there should be a period of at least 4 weeks before the second live parenteral vaccine is given. Exceptions are varicella-containing vaccines, such as MMRV vaccine:

- administer doses of varicella-containing vaccine at least 3 months apart for children 1 to 12 years of age. If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between doses may be used for children 1 to 12 years of age.
- do not concomitantly administer varicella-containing vaccines with smallpox vaccine; administer varicella-containing vaccine and smallpox vaccine at least 4 weeks apart.

Oral and intranasal vaccines can be given at the same time as, or any time before or after any other live vaccine, regardless of the route of administration of the other live 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

**MMR vaccine**

Adverse events following MMR immunization occur less frequently and are less severe than those associated with natural disease. Adverse reactions are less frequent after the second dose of vaccine and tend to occur only in those not protected by the first dose. Six to 23 days after MMR immunization, approximately 5% of immunized children experience malaise and fever (with or without rash) lasting up to 3 days. Parotitis, rash, lymphadenophy, and joint symptoms also occur occasionally after MMR immunization.

**MMRV vaccine**

Pain and redness at the injection site or low-grade fever or both occur in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C) occur in 1% to less than 10% of vaccinees. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus, health care providers should obtain specimens using viral transport media from a lesion of the vaccinee to ensure varicella disease is not confused with a reaction to vaccination.

**Rubella-containing vaccines**

Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with rubella-containing vaccine; it lasts for about 1 to 3 weeks, and rarely recurs. This is more common in post-pubertal females, among whom arthralgia develops in 25% and arthritis in 10% after immunization with rubella-containing vaccine. There is no evidence of increased risk of new onset, chronic arthropathies or neurologic conditions.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

**MMR and MMRV vaccines**

Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. As with other vaccines, anaphylaxis following vaccination with MMR or MMRV vaccine may occur but is very rare.
Immune Thrombocytopenic Purpura (ITP)

Rarely, ITP occurs within 6 weeks after immunization with MMR or MMRV vaccine. In most children, post-immunization thrombocytopenia resolves within three months without serious complications. In individuals who experienced ITP with the first dose of MMR or MMRV vaccine, serologic status may be evaluated to determine whether an additional dose of vaccine is needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases.

Encephalitis

Encephalitis has been reported in association with administration of measles vaccine in approximately 1 per million doses distributed in North America which is much lower than that observed with natural measles disease (1 per 1,000 cases).

Febrile seizures

Recent studies have found a higher risk of febrile seizures with the first dose of a MMRV vaccine (ProQuad®, not authorized for use in Canada) when compared to the concomitant administration of MMR and univalent varicella vaccine. Data from the US estimated that the risk of febrile seizures in the 5 to 12 days following the first dose of this MMRV vaccine is 1 for every 2,600 vaccinated children aged 12 to 23 months. Experience with the MMRV vaccine available in Canada is more limited; however, one study showed an additional risk of febrile seizures with MMRV vaccine compared to MMR and univalent varicella vaccines given as two separate products administered concomitantly. The risk with the Canadian vaccine was smaller than the risk found with the US product. Close surveillance and further investigation are underway.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

In the mid to late 1990s, researchers from the UK reported an association between MMR vaccine and inflammatory bowel disease, and MMR vaccine and autism. Rigorous scientific studies and reviews of the evidence have been done worldwide, and there is now considerable evidence to refute those claims. In 2010, the original study suggesting a link between the MMR vaccine and autism was retracted.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with MMR or MMRV vaccine.
- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with MMRV vaccine.
- 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

MMR and MMRV 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 (with the exception of egg allergy [refer below]) or its container. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of vaccines available for use in Canada and their contents. For mumps-containing vaccines, potential allergens include:
- M-M-R®II: neomycin, phenol red, porcine gelatin, residual components of chick embryo cell cultures
- PRIORIX®: egg protein, neomycin
- PRIORIX-TETRA®: neomycin

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.

The measles and mumps components of MMR and MMRV vaccines are produced in chick embryo cell culture and may contain traces of residual egg and chicken protein. The trace amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is not recommended prior to vaccination as it does not predict reaction to the vaccine. MMR or MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens’ eggs. Prior egg ingestion is not a prerequisite for immunization with egg protein-containing vaccine. For all vaccines, immunization should always be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.

Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Refer to Immunocompromised persons.

MMR and MMRV vaccines are contraindicated during pregnancy. Refer to Pregnancy and breastfeeding.

MMR vaccine is contraindicated in individuals with active, untreated tuberculosis. While tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles-containing vaccines, such as MMR or MMRV have such an effect.

A history of febrile convulsions or a family history of convulsions is not a contraindication for the use of MMRV vaccine.

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

It is recommended to avoid the use of salicylates (e.g., acetylsalicylic acid [ASA]) for 6 weeks after immunization with MMRV vaccine because of an association between wild-type varicella, salicylate therapy and Reye’s syndrome.

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

DRUG INTERACTIONS

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine such as MMRV. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible from at least 24 hours before administration of MMRV vaccine and should not restart antiviral therapy until 14 days after.

The measles component in measles-containing vaccines can temporarily suppress tuberculin reactivity, resulting in false-negative results. If tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) test is required, it should be done on the same day as immunization or delayed for at least 4 weeks after measles vaccination. Vaccination with measles-containing vaccine may take place at any time after tuberculin skin testing has been performed and/or read.
Passive immunization with human immune globulin (Ig) or receipt of most blood products can interfere with the immune response to MMR and MMRV vaccines. These vaccines should be given at least 14 days prior to administration of an Ig preparation or blood product, or delayed until the antibodies in the Ig preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an Ig preparation or blood product is less than 14 days or before the antibody has degraded, repeat the vaccine dose after the recommended interval. The recommended interval between administration of an Ig preparation or blood product and subsequent immunization varies, depending on the Ig preparation or blood product. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to MMR or MMRV vaccines. Refer toBlood Products, Human Immune Globulin and Timing of Immunization in Part 1 for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

On the basis of expert opinion, the MMR vaccines authorized in Canada may be used interchangeably. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

SELECTED REFERENCES


PART 4
PERTUSSIS VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Pertussis (whooping cough) is a highly communicable bacterial illness. |
|      | Its severity is greatest among infants who are too young to be protected by a complete vaccine series. |
|      | Acellular pertussis vaccines have an estimated effectiveness of 80% to 85% following 3 doses. |
|      | Acellular pertussis vaccine is only available as a combination vaccine. |
|      | Redness, swelling and pain at the injection site are the most common adverse reactions to acellular pertussis-containing vaccines. |

| Who | Acellular pertussis-containing vaccine is recommended for: |
|     | - routine immunization of infants and children, including an adolescent booster dose |
|     | - immunization of children who missed pertussis immunization on the routine schedule |
|     | - adults who have not previously received a dose of pertussis-containing vaccine in adulthood |

| How | Routine pertussis immunization of infants, children and adolescents: 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: administer one dose of Tdap vaccine if not previously received in adulthood (18 years of age and older). Adults of any age, who have not received a dose of Tdap vaccine in adulthood and who are in contact or anticipate contact with infants (e.g., parents, grandparents, childcare providers) should be prioritized for pertussis vaccination. |
|     | Acellular pertussis-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes. |
Why

- One to three deaths related to pertussis occur each year in Canada, particularly in infants who are too young to be immunized, or unimmunized or partially immunized children.
- Adolescents and adults who have not received a booster vaccination are at risk of infection and are often the source of infection in infants.

Significant revisions since the last chapter update are highlighted in the CIG Summary Table of Changes available on the PHAC website. (http://www.phac-aspc.gc.ca/publicat/cig-gci/errarta-eng.php)


EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis*.

Reservoir
Humans. Adolescents and adults are often the source of infection in infants.

Transmission
Pertussis is highly communicable with studies showing 80% secondary attack rates among susceptible household contacts. Transmission is less likely from vaccinated cases and to vaccinated contacts. Pertussis is usually transmitted by the respiratory route through contact with respiratory droplets; indirect spread through contaminated objects occurs rarely, if at all. The incubation period is 9 to 10 days (range, 6 to 20 days), and may rarely be as long as 42 days. Infectiousness is greatest during the catarrhal period and during the first 2 weeks after cough onset. Patients are no longer contagious after 5 days of appropriate antibiotic treatment.

Risk factors
Pertussis can affect individuals of any age; however, severity is greatest among infants who are too young to be protected by a complete vaccine series. Young infants are also at highest risk of pertussis-associated complications. Immunity to pertussis from childhood vaccination and natural disease wanes with time; therefore, adolescents and adults who have not received a booster vaccination are at risk of infection and its consequent transmission to others.

Seasonal/temporal patterns
Pertussis is an endemic disease common to children (especially young children) everywhere, regardless of ethnicity, climate or geographic location.

Spectrum of clinical illness
The clinical course of pertussis is divided into three stages. The initial catarrhal stage is characterized by runny nose, sneezing, low-grade fever, and a mild cough, similar to a cold. After 1 to 2 weeks of gradually worsening cough, the paroxysmal stage begins. The paroxysmal stage is characterized by bursts of rapid coughing, ending with a inspiratory whoop and sometimes post-tussive vomiting. This
stage lasts from 1 to 6 weeks but may persist for up to 10 weeks. In the convalescent stage, recovery is gradual and may take weeks to months.

The clinical course varies with age. In young infants, who are at the highest risk, clinical symptoms are frequently atypical. Whoop and post-tussive vomiting may be absent. The presentation may be characterized solely by episodes of apnea. Serious complications occur mainly in infants and may include pneumonia, atelectasis, seizures, encephalopathy, hernias and death.

Pertussis may be milder in adolescents and adults but symptoms can range from asymptomatic infection to a very prolonged, debilitating cough. Pertussis is a common and often unrecognized cause of cough persisting for over 2 weeks in adolescents and adults. Complications in adolescents and adults include sleep disturbance, rib fractures, subconjunctival haemorrhages, rectal prolapse, and urinary incontinence, all from intense and persistent coughing. Adolescents and adults with a cough, and less so in those who are asymptomatic, are a source of infection for those most at risk, namely infants.

Mortality is rare in industrialized countries. Pneumonia is the most common cause of death, typically in infants less than 6 months of age. One to three deaths related to pertussis occur each year in Canada, particularly in infants who are too young to be immunized or unimmunized or partially immunized children.

DISEASE DISTRIBUTION


PREPARATIONS AVAILABLE FOR USE IN CANADA

PERTUSSIS-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 combined 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)
Pertussis vaccine is only available as an acellular preparation in a combination vaccine. The amount of acellular pertussis antigen present varies by product. Preparations containing higher concentrations of acellular pertussis antigen (designated as “aP”) are administered for primary immunization of infants and young children less than 7 years of age (pediatric formulation) and may be administered as a booster for children 4 years to less than 7 years of age. Preparations containing a lower concentration (designated as “ap” and referred to as “reduced”) may also 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).

For complete prescribing information, consult the product leaflet or information contained within Health Canada’s authorized product monographs available through the Drug Product Database. Refer to Table 1 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**
The vaccine efficacy following the primary series with acellular pertussis vaccines is estimated to be about 85%, and approximately 90% following booster immunization. Although the duration of protection afforded by acellular pertussis vaccine is unknown, available data suggests that protection does not significantly decline between the first booster (18 months) and second booster (4-6 years) with an acellular pertussis vaccine. However, a progressive decline in protection has been observed following the second booster dose. NACI will be assessing the implications of this finding.

**IMMUNOGENICITY**
Immunologic correlates of protection against pertussis are not well-defined, but higher levels of anti-pertussis antibodies seem to be associated with greater protection. In general, acellular pertussis-containing combination vaccines have demonstrated good immunogenicity of their component antigens. Consistently high response to pertussis vaccine has been observed after booster vaccination.

**RECOMMENDATIONS FOR USE**

**INFANTS AND CHILDREN (2 months to 17 years of age)**
Acellular pertussis 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) for primary immunization or booster doses 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)**
All adults should receive one dose of Tdap vaccine if they have not previously received pertussis-containing vaccines in adulthood. In particular, adults who have not previously received pertussis-containing vaccines in adulthood, and who anticipate having regular contact with an infant, should be prioritized to receive a dose of Tdap vaccine, ideally administered at least 2 weeks before contact with the infant.

Persons who have had pertussis infection should receive pertussis-containing vaccines as recommended
because infection does not confer long term immunity.

Refer to Schedule and Booster doses and re-immunization. Refer to Diphtheria Toxoid, Tetanus Toxoid, 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. There are no established serologic correlates for protection against pertussis. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

Immunization with Tdap to date has been shown to be safe in pregnant women and allows high levels of antibody to be transferred to newborns during the first two months of life when the morbidity and mortality from pertussis infection is the highest. All pregnant women following 26 weeks of pregnancy who have not received a dose of a pertussis-containing vaccine in adulthood should be encouraged to receive Tdap vaccination. In special circumstances, such as an outbreak situation, all pregnant women who are 26 weeks gestation or greater may be offered Tdap vaccination irrespective of their immunization history. 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 pertussis-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 acellular pertussis-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 in Immunocompromised persons in Diphtheria Toxoid in Part 4. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

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 are at risk of added morbidity and mortality from pertussis disease. Persons with neurological disorders with onset preceding immunization should receive all routinely recommended immunizations, including pertussis-containing vaccine.

Cases of Guillain Barré Syndrome (GBS) have been reported very rarely following administration of a tetanus toxoid-containing vaccine. Refer to Contraindications and Precautions for additional information. Refer to Tetanus Toxoid in Part 4 for additional information.
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 acellular pertussis-containing combination vaccines. 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. Children who have received one or more doses of diphtheria-tetanus-whole cell pertussis (DPT) vaccine before arriving in Canada should have their vaccine series completed with acellular pertussis-containing vaccine (DTaP or Tdap) as appropriate for age. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
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.

OUTBREAK CONTROL
Acellular pertussis vaccine has been used for the control of pertussis outbreaks in defined populations, such as in schools or hospitals, although data supporting its effectiveness are lacking. Children exposed to a case of pertussis should have their immunization status reviewed and updated as required. In an outbreak, public health officials may recommend that pregnant women be offered Tdap vaccination after 26 weeks of gestation irrespective of their immunization history.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose of pertussis-containing vaccine is 0.5 mL

Route of administration
Pertussis-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 pertussis 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; DTaP-IPV-Hib vaccine provided at 12 to 23 months of age may be used to complete the primary series of DTaP-HB-IPV-Hib vaccine administered at 2, 4 and 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 on 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 acellular pertussis-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 acellular pertussis-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 Tdap vaccine in adulthood 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.

BOOSTER DOES AND RE-IMMUNIZATION

The preschool booster dose of either DTaP-IPV or Tdap-IPV vaccine should be administered at 4 to 6 years of age. Adolescents should routinely receive a booster dose of Tdap vaccine at 14 to 16 years of age. Adults who have not previously received Tdap vaccine in adulthood should receive one dose of Tdap vaccine regardless of the interval since the last dose of tetanus or diphtheria toxoid-containing vaccine.

SEROLOGICAL TESTING

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

STORAGE REQUIREMENTS

Store pertussis-containing vaccines in a refrigerator at +2ºC to +8ºC and do not freeze. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Pertussis-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 IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS

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

COMMON AND LOCAL ADVERSE EVENTS

Redness, swelling and pain at the injection site are the most common adverse reactions to childhood pertussis-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 pertussis-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. 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.

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. Anaphylaxis following vaccination with pertussis-containing vaccine may occur but is very rare.

Hypotonic hyporesponsive episodes (HHE) and seizures may occur following immunization with pertussis-containing vaccine. The WHO case definition of HHE includes sudden onset of hypotonia (muscle limpness), hyporesponsiveness (reduced responsiveness or unresponsiveness), and pallor or cyanosis. However, there is evidence that there are no adverse consequences to these events and the adverse consequences of being incompletely immunized have been well documented. HHE occur less frequently following receipt of acellular pertussis-containing vaccine than following whole cell pertussis-containing vaccines which are no longer in use in Canada. High fever and convulsions, both febrile and afebrile, are rarely reported and are not contraindications to further immunization with acellular pertussis-containing vaccine. Encephalopathy with onset temporally related to pertussis immunization is very rare and an alternative etiology is usually established. Encephalopathy itself, from whatever cause, is not a contraindication to pertussis immunization. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Epidemiological studies do not support allegations of a causal relationship between pertussis-containing vaccines and permanent neurological injury.
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) (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

Pertussis-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 pertussis-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

There are no currently known potential allergens in ADACEL® vaccine.

With respect to Infanrix hexa™, 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.

It is prudent to not administer further doses of tetanus-toxoid containing vaccine to persons who develop Guillain-Barre Syndrome (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. Refer to Tetanus Toxoid in Part 4 for additional information.

Administration of pertussis-containing vaccine should be postponed in persons suffering from severe acute illness. Immunization should not be delayed because of minor acute illness, with or without fever. Refer to General Contraindications and Precautions in Part 2 for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

The primary series of three doses of pertussis-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.
SELECTED REFERENCES


Gautret P, Wilder-Smith A. Vaccination against tetanus, diphtheria, pertussis and poliomyelitis in adult travellers. Travel Med Infect Dis 2010;8:155-60.


Sanofi Pasteur Ltd. Product Monograph - ADACEL®, August 2009.

Sanofi Pasteur Ltd. Product Monograph - ADACEL®-POLIO, October 2010.


Stehr K, Cherry J, Heininger U et al. A comparative efficacy trial in Germany in infants who received either the Lederle-Takeda acellular pertussis component DTP (DTap) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics 1998;101(1 Pt 1):1-11.


PART 4

PNEUMOCOCCAL VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and Precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th>Streptococcus pneumoniae infections are a major cause of illness and death worldwide.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invasive pneumococcal disease (IPD) is most common in the very young, the elderly and persons at high risk (such as those with functional or anatomic asplenia; congenital or acquired immunodeficiency).</td>
</tr>
<tr>
<td></td>
<td>In children, efficacy of pneumococcal conjugate 7-valent (Pneu-C-7) vaccine against IPD due to serotypes contained in the vaccine is estimated to range from 89% to 97%. There are no efficacy data available for other pneumococcal conjugate vaccines.</td>
</tr>
<tr>
<td></td>
<td>Pneu-P-23 vaccine efficacy against IPD is estimated to be 50% to 80% among the elderly and in specific groups.</td>
</tr>
<tr>
<td></td>
<td>There may be redness, swelling and soreness at the injection site following pneumococcal immunization.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Routine pneumococcal immunization is recommended for all children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults and children considered to be at increased risk from IPD should be vaccinated using the pneumococcal vaccine and schedule recommended for their age group and specific risk condition.</td>
</tr>
</tbody>
</table>
### Pneu-C-13 vaccine

- **Routine infant immunization**: administer three doses of Pneu-C-13 vaccine at minimum 8-week intervals beginning at 2 months of age, followed by a fourth dose at 12 to 15 months of age. For healthy infants, a three-dose schedule may be used with doses at 2 months, 4 months, and 12 months of age.
- **12 to 23 months of age**: administer two doses of Pneu-C-13 vaccine at least 8 weeks apart to children not previously vaccinated with a conjugate pneumococcal vaccine or who received only 1 dose before 12 months of age
- **24 to 35 months of age**: administer one dose of Pneu-C-13 vaccine to children with no or incomplete vaccination schedules with any conjugate pneumococcal vaccine.
- **36 to 59 months of age**: administer one dose of Pneu-C-13 vaccine to:
  - Healthy children who are of aboriginal origin or who attend group child care who have received age-appropriate pneumococcal conjugate vaccination but have not received Pneu-C-13 vaccine. Consider one dose of Pneu-C-13 vaccine for other healthy children.
  - Children at high risk of IPD who have received age-appropriate pneumococcal conjugate vaccination but have not received Pneu-C-13 vaccine.
  - Children with no or incomplete vaccination schedules with any conjugate pneumococcal vaccine.
- **60 months to 17 years of age**: administer one dose of Pneu-C-13 vaccine to children and adolescents at high risk of IPD who have not previously received Pneu-C-13 vaccine.
- **Adults with immunocompromising conditions (except hematopoietic stem cell transplant (HSCT))**: administer one dose of Pneu-C-13 followed 8 weeks later by one dose of Pneu-P-23 (if not previously immunized with Pneu-P-23). The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. A single re-immunization with Pneu-P-23 is recommended.
- **Adults with hematopoietic stem cell transplantation (HSCT)**: administer three doses of Pneu-C-13 starting 3-9 months after transplant. These doses should be administered at least 4 weeks apart, followed by a dose of Pneu-P-23 12 to 18 months post transplant (6 to 12 months after the last dose of Pneu-C-13). A single re-immunization with Pneu-P-23 is recommended.

### Pneu-P-23 vaccine

- Administer one dose of Pneu-P-23 vaccine after pneumococcal conjugate vaccine to children 24 months of age and older, adolescents and adults who are at high risk of IPD.
- Administer one dose of Pneu-P-23 vaccine to immunocompetent adults 65 years of age and older and to immunocompetent residents of long-term care facilities without contraindications. Immunocompromised adults should be immunized with Pneu-C-13 and Pneu-P-23 as indicated above.
- One lifetime re-immunization with Pneu-P-23 vaccine is recommended for those at highest risk of IPD.

### Why

- *S. pneumoniae* is a common cause of invasive disease, such as pneumonia, bacteremia, and meningitis.
- The case fatality rate of bacteremic pneumococcal pneumonia is 5% to 7% and is higher among elderly persons.

For additional information, refer to the National Advisory Committee on Immunization (NACI) Statements:  
*Statement on the recommended use of pneumococcal 23-valent polysaccharide vaccine in homeless persons and injection drug users* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-5/index-eng.php);  
*Update on pediatric invasive pneumococcal disease and recommended use of conjugate pneumococcal vaccines* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-3/index-eng.php);  
*Update on the use of conjugate pneumococcal vaccines in childhood* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-12/index-eng.php);  
*Statement on the Use of Conjugate Pneumococcal Vaccines*.

Significant revisions since the last chapter update are highlighted in the CIG Summary Table of Changes available on the PHAC website. (http://www.phac-aspc.gc.ca/publicat/cig-gci/errata-eng.php)

**EPIDEMIOLOGY**

**DISEASE DESCRIPTION**

**Infectious agent**

Pneumococcal disease is caused by a bacterium, *Streptococcus pneumoniae* (S. pneumoniae or pneumococcus) of which 15 serotypes cause the majority of disease.

**Reservoir**

Humans carry *S.pneumoniae* in their nasopharynx.

**Transmission**

*S. pneumoniae* is transmitted by direct oral contact, respiratory droplets, or indirect contact with respiratory secretions of infected or colonized persons. A person can transmit the infection as long as nasal and throat secretions contain pneumococci in large numbers; usually until 24 hours following appropriate antibiotic treatment. The incubation period has not been clearly defined and may be as short as 1 to 3 days.

**Risk factors**

IPD is most common in the very young, the elderly and groups at high risk (Table 1). Persons with a cochlear implant appear to be at increased risk of pneumococcal meningitis. Attendance at a child care center has been shown to increase the risk of IPD and acute otitis media (AOM) 2-fold to 3-fold among children under 5 years of age. Homeless populations have high rates of respiratory infections, including those caused by *S. pneumoniae*. 
Table 1: Conditions resulting in high risk of IPD

<table>
<thead>
<tr>
<th>Conditions without immunocompromising conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cerebral spinal fluid (CSF) leak</td>
</tr>
<tr>
<td>Chronic neurologic condition that may impair clearance of oral secretions</td>
</tr>
<tr>
<td>Cochlear implants (including those children who are to receive implants)</td>
</tr>
<tr>
<td>Chronic cardiac or pulmonary disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Chronic liver disease (including hepatic cirrhosis due to any cause)</td>
</tr>
<tr>
<td>Asthma that required medical care in the preceding 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions with immunocompromising conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease or other hemoglobinopathies*</td>
</tr>
<tr>
<td>Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions</td>
</tr>
<tr>
<td>Asplenia (functional or anatomic)*</td>
</tr>
<tr>
<td>Immunocompromising therapy including use of long-term corticosteroids, chemotherapy, radiation therapy, post-organ transplant therapy, and certain anti-rheumatic drugs</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant (recipient)</td>
</tr>
<tr>
<td>Malignant neoplasms including leukemia and lymphoma</td>
</tr>
<tr>
<td>Solid organ or islet transplant (candidate or recipient)</td>
</tr>
</tbody>
</table>

* Generally asplenia (functional or anatomic), sickle cell disease and other hemoglobinopathies are not considered immunocompromising conditions, but for the purposes of pneumococcal vaccine recommendations they are included in this category.

Seasonal/temporal pattern

IPD is more common in the winter and spring in temperate climates.

Spectrum of clinical illness

Pneumonia with secondary bacteremia, bacteremia, and meningitis are the most common IPDs. Bacteremia is the most common manifestation of IPD among children 2 years of age and younger. Bacteremic pneumococcal pneumonia is the most common presentation among adults and is a common complication following influenza. The case fatality rate of bacteremic pneumococcal pneumonia is 5% to 7% and is higher among elderly persons. Bacterial spread within the respiratory tract may result in AOM, sinusitis or recurrent bronchitis.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

Pneumococcal infections are a major cause of morbidity and mortality worldwide and pneumonia is the most common cause of pneumococcal-attributed death. Each year, an estimated 1 million children under five years of age die due to S. pneumoniae respiratory infections, most in developing countries. In Europe and the United States (US), pneumococcal pneumonia is the most common community-
acquired bacterial pneumonia, estimated to affect approximately 100 of every 100,000 adults each year. Bacteremia affects approximately 15 to 19 of every 100,000 adults and meningitis affects about 1 to 2 of every 100,000 adults each year.

**National**

IPD has been nationally notifiable since 2000. In Canada between 2005 to 2008, incidence rates per 100,000 population per year of IPD were 26.6 among infants less than 1 year of age, 16.9 among children 1 to 4 years, and 20.4 among adults 60 years of age and older. Children under 1 year of age accounted for 3% of cases, those aged 1 to 4 years accounted for 8%, and adults 60 years of age and older accounted for 40% of IPD cases.

Pneu-C-7 vaccine was incorporated into routine childhood immunization schedules in all Canadian jurisdictions by 2006. Pneu-C-10 came on the market in 2009 and Pneu-C-13 replaced Pneu-C-7 vaccine in 2010. A population-based study has shown a greater than 80% decline in the incidence of pediatric IPD following Pneu-C-7 vaccine implementation. However, the incidence of IPD caused by serotypes not protected by Pneu-C-7 increased, resulting in a decreased impact of the vaccination program.

Canada does not currently have a national surveillance system that links epidemiological and serological data. However, data from regional surveillance systems in British Columbia, Alberta, Quebec, Ontario and Northern Canada provide information on IPD incidence rates by serotype. In 2008, among children under 5 years of age, the incidence of IPD varied by serotype grouping and by surveillance system. The incidence rate of IPD caused by serotypes covered by Pneu-C-7 vaccine was estimated to range from 0.0 to 7.8 per 100,000. Compared to Pneu-C-7 vaccine, the incidence rate of IPD additionally covered by Pneu-C-10 vaccine ranged from 0.0 to 2.1 cases per 100,000 and the incidence rate of IPD additionally covered by Pneu-C-13 vaccine ranged from 3.7 to 31.2 per 100,000 individuals.

From 2006 to 2009, Immunization Monitoring Program, ACTive (IMPACT) data suggest that the number of IPD cases due to serotypes contained in Pneu-C-7 vaccine decreased, but the number of cases due to other serotypes increased in children aged 0 to 4 years. Refer to Figure 1 and Table 2. Other studies have shown that there was also a decline in the incidence of IPD caused by serotypes contained in Pneu-C-7 vaccine among adults 65 years of age and older, likely due to the indirect effect of conjugate pneumococcal vaccines decreasing carriage in children and subsequent transmission to older adults, rather than a direct effect of Pneu-P-23 vaccine.

In particular, the incidence of disease due to strains of *S. pneumoniae* serotype 19A has increased in Canada and other countries (refer to Figure 1). Data on the effectiveness of the new Pneu-C-13 vaccine that covers this serotype are pending.
Figure 1: Number of pneumococcal cases among children less than 5 years of age by year and serotype category, Canada, 2006-2009

Data from the Immunization Monitoring Program ACTive (IMPACT) hospital-based surveillance network.

**Pneu-C-7**: cases of pneumococcal disease caused by serotypes contained in Pneu-C-7 vaccine

**Additional in Pneu-C-10**: cases of pneumococcal disease caused by the three additional serotypes contained in Pneu-C-10 vaccine, compared to Pneu-C-7 vaccine

**Additional in Pneu-C-13**: cases of pneumococcal disease caused by the three additional serotypes contained in Pneu-C-13 vaccine, compared to Pneu-C-10 vaccine

**Non-vaccine**: cases of pneumococcal disease caused by serotypes that are not contained in a conjugate pneumococcal vaccine.

**Cases of IPD**: patients with clinical evidence of invasive disease with isolation of *S. pneumoniae*, or demonstration of *S. pneumoniae* DNA from a normally sterile site (excluding the middle ear [mastoiditis] and pleural cavity [pneumonia, pleural effusion or empyema]).

**RECENT OUTBREAKS**

Between 2004 and 2008, a widespread community-based outbreak of *S. pneumoniae* serotype 5 occurred, principally in homeless adults and intravenous drug users, in British Columbia, Alberta, Saskatchewan and Manitoba, with 1,002 cases reported as of December 31, 2008.
PREPARATIONS AUTHORIZED FOR USE IN CANADA

PNEUMOCOCCAL VACCINES

Conjugate pneumococcal vaccines

- **Prevnar®13** (pneumococcal 13-valent conjugate vaccine, CRM197 protein), Pfizer Canada Inc. (licensee) (Pneu-C-13)
- **SYNFLORIX™** (pneumococcal 10-valent conjugate vaccine, non-typeable Haemophilus influenzae protein D, diphtheria or tetanus toxoid conjugates adsorbed), GlaxoSmithKline Inc. (Pneu-C-10).

The tetanus, diphtheria and non-typeable *Haemophilus influenzae* carrier proteins used in conjugate pneumococcal vaccines do not confer protection against diphtheria, tetanus or *Haemophilus influenzae* type b disease.

Pneumococcal 23-valent polysaccharide vaccines

- **PNEUMOVAX® 23** (pneumococcal 23-valent polysaccharide vaccine), Merck Canada Inc. (Pneu-P-23)
- **PNEUMO 23®** (pneumococcal 23-valent polysaccharide vaccine), Sanofi Pasteur SA (manufacturer), sanofi pasteur Ltd. (distributor) (Pneu-P-23)

Table 2: *S. pneumoniae* serotypes included in pneumococcal vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>4</th>
<th>9V</th>
<th>6B</th>
<th>14</th>
<th>18C</th>
<th>19F</th>
<th>23F</th>
<th>1</th>
<th>5</th>
<th>7F</th>
<th>3</th>
<th>6A</th>
<th>19A</th>
<th>2</th>
<th>8</th>
<th>9N</th>
<th>10A</th>
<th>11A</th>
<th>12F</th>
<th>15B</th>
<th>17F</th>
<th>20</th>
<th>22F</th>
<th>33F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneu-C-7*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneu-C-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneu-C-13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneu-P-23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pneu-C-7 vaccine is no longer available.*

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

Conjugate pneumococcal vaccines

In children, the efficacy of Pneu-C-7 vaccine is 89% to 97% against IPD serotypes whose antigens are contained in the vaccine. Pneu-C-7 vaccine provides a 54% reduction in AOM and a 20% reduction in tympanostomy tube placement due to vaccine serotypes. There are no efficacy data available for Pneu-C-13 vaccine for any indication and no efficacy data available for Pneu-C-10 vaccine for its primary indication against IPD. However, preliminary estimates from an unpublished case control study that was conducted in the US suggest 79% to 95% vaccine effectiveness among 2-59 month old children against Pneu-C-13 serotype IPD.
Pneumococcal polysaccharide vaccines
Pneu-P-23 vaccine efficacy is more than 80% against IPD among healthy young adults and ranges from 50% to 80% among the elderly and in high-risk groups. Effectiveness in preventing community-acquired pneumonia in the elderly remains a challenge. Immunogenicity and efficacy are decreased in certain groups at particularly high risk of pneumococcal infection, such as persons with renal failure, sickle cell anemia, or impaired immune responsiveness, including HIV infection. Following immunization with Pneu-P-23 vaccine, antibody levels decline after 5 to 10 years and decrease more rapidly in some groups than others. The duration of immunity is not known.

IMMUNOGENICITY

Conjugate pneumococcal vaccines
Infants immunized with Pneu-C-7 vaccine develop a 3.4-fold to 20-fold increase in serum antibodies against vaccine serotypes. Anamnestic responses are induced upon boosting with either conjugate pneumococcal or Pneu-P-23 vaccines. The immunogenicity of Pneu-C-7 vaccine has been demonstrated in children with immunodeficiency.

New conjugate pneumococcal vaccines Pneu-C-10 and Pneu-C-13 were authorized based on identifying an immune response to all serotypes in the vaccine and demonstrating non-inferiority to each of the 7 serotypes common to the new vaccine and Pneu-C-7 vaccine. Studies on Pneu-C-10 vaccine demonstrated an antibody response to all 10 serotypes. Studies on Pneu-C-13 vaccine demonstrated an antibody response to all 13 serotypes. There are no studies comparing the immunogenicity of Pneu-C-10 and Pneu-C-13 vaccines.

Pneumococcal polysaccharide vaccines
In healthy young adults, a single dose of pneumococcal polysaccharide vaccine stimulates an antibody response to each of the serotypes in the vaccine. Polysaccharide vaccine is less immunogenic in children than the conjugate pneumococcal vaccine.

RECOMMENDATIONS FOR USE

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

Routine infant immunization (2 to 11 months of age)
Conjugate pneumococcal vaccine is recommended for routine infant immunization. Pneu-C-13 vaccine is recommended as the product of choice.

Children (12 to 23 months of age)
Assess children with no pneumococcal vaccinations or interrupted or incomplete vaccination schedules to determine the number of doses required to complete the series; children who have received complete, age-appropriate pneumococcal vaccination but have not received Pneu-C-13 vaccine should receive one dose of Pneu-C-13 vaccine (refer to Table 3). Children at high risk of IPD (refer to Table 1) should also receive one dose of Pneu-P-23 vaccine when they reach 24 months of age.

Children (24 to 35 months of age)
One dose of Pneu-C-13 vaccine is recommended for:

- Children with no pneumococcal vaccinations or incomplete vaccination schedules with any conjugate pneumococcal vaccine product.
- Children who have received complete, age-appropriate pneumococcal vaccination but have not received Pneu-C-13 vaccine.
Children at high risk of IPD (refer to Table 1) should also receive one dose of Pneu-P-23 vaccine, at least 8 weeks after Pneu-C-13 vaccine.

**Children** (36 to 59 months of age)

One dose of Pneu-C-13 vaccine is recommended for:

- Healthy children who have received age-appropriate pneumococcal vaccination but have not received Pneu-C-13 vaccine and who are of aboriginal origin or who attend group child care.
- Children at high risk of IPD (refer to Table 1) who have received age-appropriate pneumococcal vaccination but have not received Pneu-C-13 vaccine.
- Children with no or incomplete vaccination schedules with any conjugate pneumococcal vaccine product (refer to Table 3).
- Other healthy children who have received age-appropriate pneumococcal vaccination but have not received Pneu-C-13 vaccine, one dose of Pneu-C-13 vaccine may be considered. The age of the child (incidence of IPD declines from 24 to 59 months of age), the degree of exposure to other young children, and the local epidemiology of IPD need to be considered.

If a child at high risk of IPD has not previously received Pneu-P-23 vaccine, one dose of Pneu-P-23 vaccine should also be administered 8 weeks after Pneu-C-13 vaccine. Refer to Booster doses and re-immunization for re-immunization recommendations.

**Children** (60 months to 17 years of age)

Children and adolescents at high risk of IPD (refer to Table 1) who have not previously received Pneu-C-13 vaccine should receive one dose of Pneu-C-13 vaccine. If a child or adolescent at high risk of IPD has not previously received Pneu-P-23 vaccine, one dose of Pneu-P-23 vaccine should also be administered, at least 8 weeks after the Pneu-C-13 vaccine. Refer to Schedule and Booster doses and re-immunization.

**HEALTHY CHILDREN AND ADOLESCENTS IN THIS AGE GROUP DO NOT NEED PNEUMOCOCCAL VACCINE**

**Adults** (18 years of age and older)

One dose of Pneu-P-23 vaccine is recommended for all immunocompetent adults 65 years of age and older, and for immunocompetent adults less than 65 years of age in long-term care facilities or who have conditions putting them at increased risk of pneumococcal disease (Table 1). In addition, the following adults who are immunocompetent are recommended for vaccination with Pneu-P-23 vaccine:

- Persons with alcoholism,
- Smokers,
- Persons who are homeless, and
- Individuals who use illicit drugs should also be considered for vaccination.

Immunization with Pneu-C-13 vaccine is recommended for adults with immunocompromising conditions (Table 1). Adults with immunocompromising conditions (except HSCT) should receive one dose of Pneu-C-13 followed 8 weeks later by one dose of Pneu-P-23 (if not previously immunized with Pneu-P-23). The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. Adults with HSCT should receive three doses of Pneu-C-13 starting 3-9 months after transplant. These doses should be administered at least 4 weeks apart, followed by a booster dose of Pneu-P-23 12 to 18 months post-transplant (6 to 12 months after the last dose of Pneu-C-13).

There is currently no evidence that a Pneu-C-13 booster dose adds any benefit. Refer to Booster doses and re-immunization for re-immunization recommendations for Pneu-P-23. Individuals who have previously received Pneu-P-23 vaccine and require re-immunization following immunization with Pneu-C-13 vaccine, should receive Pneu-P-23 no sooner than 8 weeks after Pneu-C-13 vaccine and no sooner than 3 to 5 years after the initial dose of Pneu-P-23, depending on the age of the initial Pneu-P-23.
Some experts suggest that a conjugate pneumococcal vaccine may be given as the initial dose, followed by the Pneu-P-23 vaccine for immunocompetent adults at increased risk of IPD, as this may theoretically improve antibody response and immunologic memory. If this strategy is chosen, Pneu-C-13 vaccine should be administered first, followed at least 8 weeks later by Pneu-P-23 vaccine. However, Pneu-P-23 vaccine is the vaccine of choice for these individuals, and if only one vaccine can be provided, it should be Pneu-P-23 vaccine, because of the greater number of serotypes prevented by the vaccine. Refer to Booster doses and re-immunization.

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. Conjugate and polysaccharide pneumococcal vaccine, as appropriate for age and risk condition, may be given, regardless of possible previous receipt of the vaccine, as adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING
Pneu-P-23 and/or Pneu-C-13 vaccines are recommended for pregnant women who are at high risk of IPD (refer to Recommendations for Use - Adults). There is no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with inactivated vaccines. Women who are breastfeeding can be vaccinated with Pneu-P-23 or Pneu-C-13 vaccine. 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 conjugate pneumococcal 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.

PERSONS/RESIDENTS IN HEALTH CARE INSTITUTIONS
Residents of long-term care facilities should receive Pneu-P-23 vaccine. For adults with immunocompromising conditions, Pneu-C-13 is also recommended with the Pneu-C-13 administered first, if possible. A single re-immunization of Pneu-P-23 is recommended for some conditions. Refer to Booster doses and re-immunization.

IMMUNOCOMPROMISED PERSONS
Conjugate pneumococcal vaccine (Pneu-C-13) followed by polysaccharide pneumococcal vaccine (Pneu-P-23) is recommended for individuals aged 2 years and over with immunocompromising conditions due to underlying disease or therapy (refer to Table 1). Immunologic abnormalities may decrease the protection provided by either type of pneumococcal vaccine and those at highest risk should be counselled regarding the risk of fulminant pneumococcal sepsis, which may occur despite immunization. When considering immunization of an immunocompromised person, consultation with the individual’s attending physicians may be of assistance in addition to the guidance provided below. For complex cases, referral to a physician with expertise in immunization or immunodeficiency is advised.

Congenital (primary) immunodeficiency
Individuals with congenital immunodeficiencies involving any part of the immune system should be immunized against pneumococcal disease. Both Pneu-C-13 and Pneu-P-23 vaccines are recommended along with a single re-immunization with Pneu-P-23 (refer to Table 3 and Table 4).
Acquired (secondary) immunodeficiency

Hematopoietic stem cell transplantation (HSCT-autologous or allogeneic)

Hematopoietic stem cell transplant recipients are at increased risk of pneumococcal diseases and pneumococcal vaccine is recommended for all persons. Regardless of age, pneumococcal vaccination should be started at 3 to 9 months after HSCT with three doses of Pneu-C-13 vaccine provided at least 4 weeks apart, followed by a dose of Pneu-P-23 vaccine 6 to 12 months later or when recipient reaches age 2 years. Because antibody response to pneumococcal vaccination is known to be poor in these persons, some experts recommend that all transplant recipients over 2 years of age receive a booster dose of Pneu-P-23 vaccine 1 year after their initial Pneu-P-23 immunization.

Solid organ transplantation

If possible, individuals being considered for solid organ transplantation should receive age-appropriate pneumococcal vaccines at least 2 weeks before transplantation. If the vaccination was not completed prior to transplant, in general, it should not be re-initiated until at least 3 to 6 months after transplantation. Both Pneu-C-13 and Pneu-P-23 vaccines are recommended along with a single re-immunization with Pneu-P-23 (refer to Table 3 and Table 4).

Immunocompromising therapy

Vaccination status for pneumococcal disease should be reviewed for immunocompetent persons who might be anticipating initiation of immunocompromising treatments or who have diseases that might lead to immunodeficiency. Although pneumococcal vaccine can be safely administered at any time before, during or after immunosuppression, all attempts should be made to time vaccination so that optimal immunogenicity is achieved.

If indicated, pneumococcal vaccine should be administered at least 14 days before the initiation of immunocompromising therapy including use of long-term corticosteroids (e.g., high-dose systemic corticosteroids [≥2 mg/kg per day for a child or ≥20 mg/day for an adult of prednisone or its equivalent] for 14 days or more), chemotherapy, radiation therapy, post-organ-transplant therapy, biologic and non-biologic immunocompromising therapies for rheumatologic and other inflammatory diseases. If this process cannot be completed, a period of 3 months should elapse after immunocompromising drugs (except high-dose systemic corticosteroids) have been stopped before administration of pneumococcal vaccine to ensure immunogenicity. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and administration of pneumococcal vaccines. The interval between discontinuation of immunocompromising drugs and pneumococcal vaccine may vary with the intensity of the immunocompromising therapy, underlying disease and other factors.

If immunocompromising therapy cannot be stopped, pneumococcal vaccine should be given when the person is least immunosuppressed. Both Pneu-C-13 and Pneu-P-23 vaccines are recommended along with a single re-immunization with Pneu-P-23 (refer to Table 3 and Table 4).

HIV-infected

When possible, pneumococcal vaccine should be given early in the course of HIV infection; however, there is no contraindication to the use of pneumococcal vaccines at any time. Both Pneu-C-13 and Pneu-P-23 vaccines are recommended along with a single re-immunization with Pneu-P-23 (refer to Table 3 and Table 4).

Refer to Booster doses and re-immunization for reason and schedule for re-vaccination. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.
PERSONS WITH CHRONIC DISEASES

Hyposplenism or asplenia
Hyposplenic or asplenic individuals should receive pneumococcal vaccine as they are at risk of serious pneumococcal infections. When elective splenectomy is planned, all recommended vaccines should ideally be administered 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). Both Pneu-C-13 and Pneu-P-23 vaccines are recommended along with a single re-immunization with Pneu-P-23 (refer to Table 3 and Table 4).

Chronic renal disease/dialysis
Individuals with chronic renal disease or on dialysis should be vaccinated using the pneumococcal vaccine (conjugate vs. polysaccharide) and schedule recommended for their age. Children and adolescents less than 18 years of age should receive both Pneu-C-13 and Pneu-P-23. For adults, only Pneu-P-23 is generally recommended. Due to the decreased immunogenicity and efficacy of polysaccharide vaccine in people with chronic renal failure, a single re-immunization is recommended. Refer to Booster doses and re-immunization for schedule for re-vaccination.

Asthma
Individuals who required medical attention for asthma in the past 12 months should be vaccinated using the pneumococcal vaccine (conjugate vs. polysaccharide) and schedule recommended for their age group. Children and adolescents less than 18 years of age should receive both Pneu-C-13 and Pneu-P-23. For adults, only Pneu-P-23 is generally recommended. No re-immunization is recommended.

Neurologic disorders
Persons with chronic CSF leak or chronic neurologic conditions that may impair clearance of oral secretions should be vaccinated using the pneumococcal vaccine (conjugate vs. polysaccharide) and schedule recommended for their age group. Children and adolescents less than 18 years of age should receive both Pneu-C-13 and Pneu-P-23. For adults, only Pneu-P-23 is generally recommended. No re-immunization is recommended.

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

TRAVELLERS
The primary series of conjugate pneumococcal vaccine may be started at 6 weeks of age for infants who will be travelling. 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. Review of pneumococcal vaccination status is particularly important for persons from areas of the world where sickle cell disease is present as persons with sickle cell disease are at risk of serious pneumococcal infections. Information on vaccination schedules in other countries is available at: http://www.who.int/vaccines/GlobalSummary/Immunization/ScheduleSelect.cfm.

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

OUTBREAK CONTROL
During outbreaks of pneumococcal infection due to Pneu-C-13 vaccine serotypes, immunization with Pneu-C-13 vaccine is recommended for children who have not previously received adequate vaccination with Pneu-C-13. Pneu-P-23 vaccine has also been used to control outbreaks of pneumococcal infection due to Pneu-P-23 vaccine serotypes in adults. Pneu-C-10 or Pneu-13 vaccine could be used in adults if the serotype of the outbreak is covered by the vaccine.
VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose of pneumococcal vaccine is 0.5 mL.

Route of administration
Conjugate pneumococcal vaccine should be administered intramuscularly (IM). Pneu-P-23 vaccine may be given either IM or subcutaneously (SC). Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule
Infants and children: For routine infant immunization, three doses of conjugate pneumococcal vaccine with a minimum of 8 weeks intervals beginning at 2 months of age, followed by a fourth dose (booster) at 12 to 15 months of age should be administered. Pneu-C-13 vaccine is recommended as the product of choice. For healthy infants, a 3-dose schedule may be used, with doses given at 2, 4, and 12 months of age. A 4-dose schedule is recommended for immunization of infants at high risk of IPD.

Infants 7 to 11 months of age who have not been previously immunized against IPD should receive two doses of conjugate pneumococcal vaccine at least 8 weeks apart followed by a third dose after 12 months of age, at least 8 weeks after the second dose.

Children between 12 and 23 months require two doses of Pneu-C-13 at least 8 weeks apart. Older children who are recommended to receive pneumococcal vaccine (see Recommendations for Use) require only one dose Pneu-C-13.

The number of doses required to complete a vaccination series for children with interrupted or incomplete schedules varies with the age of the child. Infants who are less than 12 months of age when they re-present should complete their immunization schedule as if no interruption had occurred. Older children with interrupted or incomplete vaccination schedules should be assessed to determine the number of doses required to complete the series (refer to Table 3).

Children who are at high risk of IPD should also receive one dose of Pneu-P-23 vaccine at 24 months of age with possible re-immunization depending on the condition (refer to Booster doses and re-immunization). Refer to Table 3 and Recommendations for Use.
**Table 3: Recommended schedules for conjugate pneumococcal vaccine for children 2 months up to and including 17 years of age, by conjugate pneumococcal vaccination history**

<table>
<thead>
<tr>
<th>Age at presentation for immunization</th>
<th>Number of doses of Pneu-C-7, Pneu-C-10 or Pneu-C-13 previously received</th>
<th>Recommended schedule for Pneu-C-13*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6 months†, **</td>
<td>0 dose</td>
<td>2 or 3 doses† + booster at 12–15 months of age</td>
</tr>
<tr>
<td></td>
<td>1 dose</td>
<td>1 or 2 doses† + booster at 12–15 months of age</td>
</tr>
<tr>
<td></td>
<td>2 doses</td>
<td>0 or 1 dose† + booster at 12–15 months of age</td>
</tr>
<tr>
<td>7-11 months§</td>
<td>0 doses</td>
<td>2 doses + booster at 12-15 months of age</td>
</tr>
<tr>
<td></td>
<td>1 dose</td>
<td>1 dose at 7-11 months + booster at 12-15 months of age</td>
</tr>
<tr>
<td></td>
<td>2 doses</td>
<td>booster at 12-15 months of age</td>
</tr>
<tr>
<td>12-23 months, healthy or high risk of IPD†</td>
<td>0 dose or incomplete vaccination schedule with any product</td>
<td>2 doses</td>
</tr>
<tr>
<td></td>
<td>1 dose at less than 12 months of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 or more doses at less than 12 months of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 dose at 12 months of age or older</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (0 doses Pneu-C-13)</td>
<td>1 dose</td>
</tr>
<tr>
<td>24-35 months, healthy or high risk of IPD†</td>
<td>0 dose or incomplete vaccination schedule with any product</td>
<td>1 dose</td>
</tr>
<tr>
<td></td>
<td>Complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (0 doses Pneu-C-13)</td>
<td></td>
</tr>
<tr>
<td>36-59 months, healthy</td>
<td>0 dose or incomplete vaccination schedule with any product</td>
<td>1 dose</td>
</tr>
<tr>
<td></td>
<td>Complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (0 doses Pneu-C-13)</td>
<td>● If of aboriginal origin or attending group child care, 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● All other children, consider 1 dose</td>
</tr>
<tr>
<td>36-59 months, high risk of IPD§</td>
<td>0 dose or incomplete vaccination schedule with any product</td>
<td>1 dose</td>
</tr>
<tr>
<td></td>
<td>Complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (0 doses Pneu-C-13)</td>
<td></td>
</tr>
<tr>
<td>60 months – 17 years, high risk of IPD§</td>
<td>0 dose Pneu-C-13</td>
<td>1 dose.</td>
</tr>
</tbody>
</table>
* The minimum interval between doses of conjugate pneumococcal vaccine is 8 weeks.
** Children at high risk of IPD should follow the 4-dose schedule and also receive one dose of Pneu-P-23 at 24 months of age. A single re-immunization with Pneu-P-23 is recommended for some conditions (refer Booster doses and re-immunization),
† Follow relevant provincial/territorial schedule.
◦ Programs using a 3-dose schedule should offer the third dose early in the second year of life (at 12 months of age) to allow for early complete protection.
▼ Children at high risk of IPD should also receive one dose of Pneu-P-23 at 24 months of age. When both Pneu-C-13 and Pneu-P-23 need to be given, the conjugate vaccine should be given first. A single re-immunization with Pneu-P-23 is recommended for some conditions (refer to Booster doses and re-immunization).

**Adults:** Immunocompetent adults who are at high risk of IPD (refer to Table 1), immunocompetent residents of long-term care facilities and all adults 65 years of age and older without contraindications should receive one dose of Pneu-P-23 vaccine. Adults with immunocompromising conditions require Pneu-C-13 and Pneu-P-23 with the Pneu-C-13 given first (refer to Table 4). A single re-immunization with Pneu-P-23 is recommended for some conditions (refer to Booster doses and re-immunization).

### Table 4: Recommended schedules for adult (18 years of age and over) immunization with pneumococcal vaccine

<table>
<thead>
<tr>
<th>Age, underlying condition</th>
<th>Type of vaccine</th>
<th>Number of doses and recommended schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>At high risk of IPD and without immunocompromising conditions</td>
<td>Pneu-P-23*</td>
<td>1 dose - a single re-immunization with Pneu-P-23 recommended 5 years later for some conditions</td>
</tr>
<tr>
<td>Resident of long-term care facility and without immunocompromising conditions and without conditions that increase the risk of IPD</td>
<td>Pneu-P-23</td>
<td>1 dose</td>
</tr>
<tr>
<td>65 years or greater, without immunocompromising conditions and without conditions that increase the risk of IPD</td>
<td>Pneu-P-23</td>
<td>1 dose</td>
</tr>
<tr>
<td>Immunocompromising condition (other than HSCT)</td>
<td>Pneu-C-13; Pneu-P-23</td>
<td>- 1 dose of Pneu-C-13** - 1 dose of Pneu-P-23 at least 8 weeks after Pneu-C-13 - a single re-immunization with Pneu-P-23 recommended 5 years later</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant (HSCT)</td>
<td>Pneu-C-13; Pneu-P-23</td>
<td>- 3 doses of Pneu-C-13 starting 3-9 months after transplant, administered at least 4 weeks apart - 1 dose of Pneu-P-23 12 to 18 months post-transplant (6 to 12 months after the last dose of Pneu-C-13) - a single re-immunization with Pneu-P-23 recommended as early as 1 year later by some experts</td>
</tr>
</tbody>
</table>
Some experts suggest that a conjugate pneumococcal vaccine may be given as the initial dose followed by the Pneu-P-23 vaccine for immunocompetent adults at increased risk of IPD, as this may theoretically improve antibody response and immunologic memory. If this strategy is chosen, Pneu-C-13 vaccine should be administered first, followed at least 8 weeks later by Pneu-P-23 vaccine. However, Pneu-P-23 vaccine is the vaccine of choice for these individuals, and if only one vaccine can be provided, it should be Pneu-P-23 vaccine.

The Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23.

BOOSTER DOSES AND RE-IMMUNIZATION

Conjugate Pneumococcal Vaccine
Re-immunization with conjugate pneumococcal vaccine after age and risk appropriate childhood vaccination is not necessary.

Pneumococcal Polysaccharide Vaccine
Immunity induced by Pneu-P-23 vaccine decreases over time. Routine re-immunization of healthy individuals who have been vaccinated with Pneu-P-23 vaccine is not recommended. However, re-immunization is recommended for those of any age at highest risk of IPD, including those with functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure; nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy. For solid organ transplant recipients, there is evidence that antibody titers decline after 3 years. Experience with re-immunization after solid organ transplant is limited.

If re-immunization is carried out, a single re-immunization after 5 years is recommended in persons who were 11 years of age or over at the time of initial immunization with Pneu-P-23 vaccine. A single re-immunization after 3 years is recommended for those who were 10 years of age or younger at the time of initial immunization with Pneu-P-23 vaccine. Because there are insufficient data to recommend repeated administration of Pneu-P-23 vaccine, re-vaccination following a second dose is not routinely recommended.

Individuals who have previously received Pneu-P-23 vaccine and require re-immunization following immunization with Pneu-C-13 vaccine, should receive Pneu-P-23 no sooner than 8 weeks after Pneu-C-13 vaccine and no sooner than 3 to 5 years after the initial dose of Pneu-P-23, depending on the age of the initial Pneu-P-23.

Refer to Immunocompromised persons for considerations for persons undergoing HSCT.

SEROLOGICAL TESTING
Serologic testing is not recommended before or after receiving pneumococcal vaccine.

STORAGE REQUIREMENTS
Pneu-C-13: Store in a refrigerator at +2ºC to +8ºC. Do not freeze.

Pneu-C-10: Store in a refrigerator at +2ºC to +8ºC. Protect from light. Do not freeze.

PNEUMOVAX® 23: Store at +2ºC to +8ºC.

PNEUMO® 23: Store at +2ºC to +8ºC. Do not freeze.

Refer to Storage and Handling of Immunizing Agents in Part 1.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES
Conjugate pneumococcal vaccine may be administered concomitantly with routine childhood vaccines at different injection sites using separate needles and syringes.
Conjugate pneumococcal vaccine and Pneu-P23 vaccine should be administered at least 8 weeks apart. However, for adults, Pneu-C-13 dose should be administered at least one year after any previous dose of Pneu-P-23. Pneumococcal 23-valent polysaccharide vaccine and HZ vaccine may be administered together.

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 information.

**COMMON AND LOCAL ADVERSE EVENTS**

**Conjugate pneumococcal vaccine**

Clinical trials of Pneu-C-10 vaccine have found that irritability; decreased appetite; drowsiness; pain, swelling and redness at the injection site; or low-grade fever occur in 29% to 37% of vaccinees. Fever above 39°C occurs in 2% to 3% of vaccines. An increase in reactogenicity was reported after booster vaccination compared to the doses of the primary series.

Studies of Pneu-C-13 vaccine indicate that irritability, decreased appetite, increased or decreased sleep, pain, swelling and redness at the injection site (after the toddler dose and in older children), are common adverse events. Low-grade fever occurs in 20% to 30% or more of vaccinees. In adults over 50 years of age, the most commonly reported adverse events include pain at the injection site, fatigue, headache and new onset myalgia, with fever above 38°C occurring in approximately 3% of vaccine recipients.

**Pneumococcal polysaccharide vaccine**

Reactions to Pneu-P-23 vaccine are usually mild. Soreness, redness and swelling at the injection site occur in 30% to 60% of vaccinees and more commonly follow SC administration than IM administration. Occasionally, low grade fever may occur. Re-immunization of healthy adults less than 2 years after the initial dose is associated with increased local injection site and systemic reactions. Studies have suggested that re-vaccination after an interval of at least 4 years is not associated with an increased incidence of adverse side effects. However, severe local reactions including reports of injection site cellulitis and peripheral edema in the injected extremity have been documented rarely with Pneu-P-23 vaccine in post-marketing surveillance, even with the first dose. Multiple re-vaccinations are not recommended. Refer to *Booster doses and re-immunization*.

**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. Few serious adverse events were reported in clinical trials with any of the pneumococcal vaccines, and consisted mainly of reports of afebrile and febrile seizure. Arthus-like reactions (causing a local vasculitis from deposition of immune complexes) are very rare and mainly occur in persons with high initial pneumococcal antibody levels. Anaphylaxis following vaccination with pneumococcal vaccine may occur but is very rare. Refer to *Vaccine Safety* in Part 2 for additional general information.

**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) or consult *Vaccine Safety* in Part 2 for additional information about AEFI reporting.
CONTRAINDICATIONS AND PRECAUTIONS

Pneumococcal 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. For pneumococcal vaccines, potential allergens include:

- **Prevnar®13**: diphtheria CRM₁₉₇ carrier protein
- **SYNFLORIX™**: latex in plunger stopper of pre-filled syringe, diphtheria toxoid carrier protein, tetanus toxoid carrier protein, non-typeable *Haemophilus influenzae* protein D carrier protein

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 pneumococcal vaccine should be postponed in persons suffering from severe acute illness. Immunization should not be delayed because of minor acute illness, with or without fever.

There are currently no data available regarding safety for children below the age of 6 weeks of age. There are limited safety and immunogenicity data on Pnu-C-13 vaccine for children or adults in groups at higher risk for IPD (e.g., children or adults with splenic dysfunction, HIV infection, malignancy, nephrotic syndrome).

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

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

Infants who have started an immunization schedule with one conjugate pneumococcal vaccine may continue their immunization schedule with a different conjugate pneumococcal vaccine. For example, infants who started a series with Pnu-C-7 or Pnu-C-10 vaccine can complete it with Pnu-C-13 vaccine. Refer to *Principles of Vaccine Interchangeability* in Part 1 for additional general information.

SELECTED REFERENCES


## PART 4
### POLIOMYELITIS VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

### KEY INFORMATION (refer to text for details)

| What | Polio remains endemic in three countries - Afghanistan, Nigeria and Pakistan; additional countries are known or suspected of having re-established transmission of poliovirus. Several other countries have ongoing outbreaks due to importations of poliovirus.  
Children less than five years of age are more susceptible to polio infection.  
Inactivated poliomyelitis vaccine (IPV)-containing vaccines produce immunity in over 95% of vaccinees after three doses and in close to 100% following a booster dose.  
Adverse events following IPV vaccine are usually limited to mild injection site reactions. |
|---|---|
| Who | IPV-containing vaccine is recommended for:  
  o routine immunization of infants and children  
  o children who missed polio immunization on the routine schedule  
  o unimmunized adults  
  o as a booster dose for adults previously immunized against polio and at increased risk of polio exposure |
| How | **Routine polio 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).  
**Adults previously unimmunized with polio vaccine:** administer a primary series of IPV-containing vaccine if a primary series of tetanus toxoid-containing vaccine is being given or if the adult is at increased risk for exposure to poliovirus, otherwise administer polio with routine tetanus and diphtheria booster doses.  
**Adults previously immunized with polio vaccine:** for those at increased risk of exposure to polio (e.g., those travelling to, or planning to work in areas that have wild polio or vaccine-derived polio outbreaks) a single lifetime booster dose of IPV-containing vaccine is recommended.  
IPV-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes. |
**Why**

- Until polio eradication has been achieved globally, there remains a small risk of contracting polio with travel to polio-endemic countries and importation of polio into Canada.
- The case fatality rate for paralytic polio is 2% to 5% among children and 15% to 30% for adults.

* Refer to [Poliomyelitis-containing vaccines](#) for complete vaccine description.

Since the publication of the 2006 Canadian Immunization Guide:

- Two new combination vaccines containing tetanus toxoid, reduced diphtheria toxoid, reduced acellular pertussis, and inactivated poliomyelitis vaccines (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.
- Recommendations for polio vaccination of unimmunized adults have been revised.

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**

Polio is caused by poliovirus, a member of the enterovirus subgroup of the *Picornaviridae* family.

**Reservoir**

Humans

**Transmission**

Transmission of poliovirus occurs predominantly through the fecal-oral route. Respiratory spread may rarely occur. The incubation period for polio is generally 6 to 20 days (range, 3 to 35 days). Communicability is greatest around the onset of illness when the virus is present in high concentrations in the throat and feces. Poliovirus can remain in feces for 3 to 6 weeks. In persons who have received oral polio vaccine (OPV), poliovirus can be present in the throat for 1 to 2 weeks following immunization and can remain in feces for several weeks. In rare cases, including immunocompromised persons, poliovirus (from natural infection or OPV vaccine) can be excreted for prolonged periods of time (from greater than 6 months to a number of years).

**Risk factors**

Polio infections are more common in children less than five years of age; however, any person who is not immune to poliovirus, regardless of age, can become infected.

**Seasonal/temporal pattern**

In temperate climates, polio infection generally increases in the late summer and autumn months.

**Spectrum of clinical illness**
Most polio infections (90% to 95%) are asymptomatic. In symptomatic persons, initial symptoms occur on average 7 to 14 days after infection and include fever, fatigue, headache and vomiting. With increased disease severity, severe muscle pain and stiffness of the neck and back with or without paralysis may occur. Although paralysis is the most visible sign of polio infection, less than 1% of cases result in paralysis. The case fatality ratio for paralytic polio ranges from 2% to 5% among children and 15% to 30% for adults.

DISEASE DISTRIBUTION

Incidence/prevalence

**Global**

Since global eradication efforts began in 1988, the annual global incidence of polio has decreased by over 99% and the number of countries in which polio remains endemic has decreased from 125 to three. Polio remains endemic in Afghanistan, Nigeria and Pakistan. An additional three countries (Angola, Chad and Democratic Republic of the Congo) are known to have and one country (Sudan) is suspected of having re-established transmission of poliovirus. Several more countries had ongoing outbreaks in 2010 and 2011 due to importations of poliovirus. A [list of countries with confirmed cases of wild polio](http://www.phac-aspc.gc.ca/tmp-pmv/info/polio-eng.php) can be viewed through the Public Health Agency of Canada.

**National**

The incidence of polio in Canada was dramatically reduced by the introduction of immunization programs in the 1950s (refer to Figure 1). The last indigenous case of wild poliovirus in Canada was in 1977. In 1994, Canada was certified as being free of wild poliovirus by the World Health Organization. More recent cases of paralytic polio in Canada have been associated with importations of wild poliovirus and the use of OPV vaccine. Between 1980 and 1995, 11 cases of paralytic polio associated with OPV vaccine use were reported in Canada. Vaccine programs switched from OPV vaccine to inactivated poliomyelitis vaccines (IPV) in 1995/1996. As recently as 2007 and 2009, Canada has seen isolated cases of polio or asymptomatic importations of vaccine associated poliovirus related to immunization with OPV vaccine in other countries.

Until polio eradication has been achieved globally, there remains a small risk of importation of polio into Canada. To ensure that Canada remains polio-free, the Public Health Agency of Canada, in conjunction with the Canadian Paediatric Society, conducts surveillance of cases of acute flaccid paralysis (AFP) in children less than 15 years of age. Since 1996, between 27 and 64 AFP cases in children less than 15 years of age have been reported each year, none attributed to wild or vaccine-derived poliovirus.
PREPARATIONS AVAILABLE FOR USE IN CANADA

POLIOMYELITIS-CONTAINING VACCINES

- **ADACEL®-POLIO** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine combined with inactivated poliomyelitis vaccine)., sanofi pasteur Ltd. (TdIPV)
- **BOOSTRIX®-POLIO** (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine combined with inactivated poliomyelitis vaccine)., GlaxoSmithKline Inc. (Tdap-IPV)
- **IMOVAX® Polio** (inactivated poliomyelitis vaccine (vero cell origin), sanofi pasteur SA (manufacturer), sanofi pasteur Ltd. (distributor). (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. (TDaP-IPV)
- **Td POLIO ADSORBED** (adsorbed vaccine containing tetanus and reduced diphtheria toxoids and inactivated poliomyelitis vaccine)., sanofi pasteur Ltd. (Td-IPV)

Poliomyelitis vaccine contains three types of wild poliovirus and is available as trivalent inactivated polio vaccine (IPV) or in a combination vaccine. Live attenuated oral polio vaccine (OPV) is no longer recommended or available in Canada because most cases of paralytic polio from 1980 to 1995 were associated with OPV vaccine. OPV vaccine continues to be widely used internationally.
Efficacy, Effectiveness, and Immunogenicity

IPV-containing vaccines produce immunity to all three types of poliovirus in over 95% of vaccinees following three doses of vaccine, and in close to 100% following a booster dose. Seroconversion rates are lower if the minimum age and minimum intervals for vaccine administration are used in infants less than 6 months of age.

Recommendations for Use

Infants and Children (2 months to 17 years of age)

An IPV-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 IPV vaccine or the adolescent/adult formulation of the diphtheria-tetanus-pertussis-polio-containing vaccine (Tdap-IPV). Tdap-IPV vaccine contains less diphtheria toxoid than vaccines given to younger children and is less likely to cause reactions in older children. Tdap vaccine is generally administered to adolescents at 14 to 16 years of age as the first 10-year booster dose however, Tdap-IPV vaccine should be used if IPV vaccine is also indicated.

Adults (18 years of age and older)

Similar to vaccination of children, vaccination of adults is recommended to prevent the introduction and circulation of polio. A complete series of IPV-containing vaccine is recommended for previously unimmunized adults who are also receiving a primary series of tetanus toxoid-containing vaccine. For other adults who are unvaccinated against polio, vaccination efforts should be focused on those who are at increased risk of exposure to polioviruses (refer to Table 1). Adults who are unvaccinated against polio but who do not need a primary series of tetanus and diphtheria toxoid-containing vaccine and who are not at increased risk of exposure can be provided with polio vaccinations when tetanus and diphtheria toxoid-containing vaccine booster doses are due.

Adults previously immunized with polio vaccine: for those at increased risk of exposure to polio (e.g., those travelling to, or planning to work in areas that have wild polio or vaccine-derived polio outbreaks) a single lifetime booster dose of IPV-containing vaccine is recommended (refer to Table 1).

Table 1: Persons at increased risk of exposure to poliovirus

<table>
<thead>
<tr>
<th>Category</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travellers to, or persons receiving travellers from, areas where poliovirus is known or suspected to be circulating</td>
<td></td>
</tr>
<tr>
<td>Members of communities or specific population groups with disease caused by polio</td>
<td></td>
</tr>
<tr>
<td>Health care workers who have close contact with patients who might be excreting wild type or vaccine type poliovirus</td>
<td></td>
</tr>
<tr>
<td>People who come in close contact with those who may be excreting poliovirus (e.g., people working with refugees, or the military and people on humanitarian missions in endemic countries)</td>
<td></td>
</tr>
<tr>
<td>Laboratory workers handling specimens that may contain poliovirus</td>
<td></td>
</tr>
<tr>
<td>Family or close contacts of internationally adopted infants who may have been or will be vaccinated with OPV vaccine</td>
<td></td>
</tr>
</tbody>
</table>
Refer to Schedule, Travellers and Booster doses and re-immunization. Refer to Diphtheria Toxoid, Tetanus Toxoid, Pertussis Toxoid, 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. IPV 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 Diphtheria Toxoid in Part 4 for additional information. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

IPV vaccine may be considered for pregnant women who require immediate protection and are at increased risk of exposure to wild poliovirus (refer to Table 1). There is no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with inactivated vaccines, such as IPV vaccine. 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 an IPV-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 IPV-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 in Immunocompromised persons and in Diphtheria Toxoid in Part 4. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

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

Refer to Tetanus Toxoid and Pertussis Vaccine in Part 4 for information regarding other components in IPV-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 an IPV-containing vaccine as appropriate for age, particularly if they are children, or if they are adults and are travelling to areas where poliovirus is known or suspected to be circulating. Previously unimmunized children travelling to areas where poliovirus is known or suspected to be circulating should start a primary series of an IPV-containing
vaccine, with consideration given to an accelerated schedule (refer to Schedule). 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. If IPV vaccine is not available in the region to which the child is travelling, children may complete their series with OPV vaccine while travelling. Parents of children receiving OPV vaccine should be informed that infants can excrete poliovirus for up to 5 days following vaccination, so household contacts and caregivers of these infants should have up-to-date polio immunization. People should be instructed to wash their hands carefully after changing diapers. There is also a small risk of OPV vaccine-associated paralytic polio (approximately 1 per 2.4 million doses distributed).

Children with a complete primary series do not require additional doses of IPV vaccine before travelling. For adults previously immunized against polio, a single lifetime dose of polio-containing vaccine is recommended for certain travellers at increased risk of exposure to polio (e.g., military personnel, workers in refugee camps in endemic areas, or travellers to areas where there are polio epidemics) (refer to Table 1). Refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) Poliomyelitis vaccination for International Travellers for more information. (http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php)

Refer to Diphtheria Toxoid 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. Children who have received one or more doses of polio vaccine before arriving in Canada should have their vaccine series completed with IPV-containing vaccine as appropriate for age. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
Workers who need a primary series of tetanus and diphtheria toxoid-containing vaccine should also receive IPV-containing vaccine if unvaccinated against polio. For other workers who are unvaccinated against polio, vaccination efforts should be focused on those who are at increased risk of exposure to polioviruses as identified in Table 1. If previously vaccinated with a primary series of tetanus and diphtheria toxoid-containing vaccine and not in an increased risk group (refer to Table 1), adults unvaccinated against polio can receive IPV-containing vaccine when due for their next tetanus and diphtheria booster. Refer to Immunization of Workers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

**Dose**
Each dose of IPV-containing vaccine is 0.5 mL.

**Route of administration**
Combination vaccines containing IPV vaccine must be administered intramuscularly. IPV vaccine when given as a separate vaccine should be administered subcutaneously. Refer to Vaccine Administration Practices in Part 1 for additional information.

**Schedule**

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

Routine polio 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.

A dose of IPV-containing vaccine is not required at 6 months of age for a complete primary series of polio vaccine; however, it is acceptable to give the additional dose of IPV vaccine in a combination vaccine for convenience of administration.

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 with imminent exposure to circulating poliovirus (e.g., during an outbreak or because of travel), 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 (4 years of age and older) not immunized against polio in infancy and not requiring the additional antigens in combination vaccine should receive two doses of IPV vaccine, given 4 to 8 weeks apart, followed by a third dose administered 6 to 12 months after the second dose.

Children who received a primary series of IPV-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). The booster dose at 4 to 6 years of age is not required if the third dose of IPV-containing vaccine was administered after the fourth birthday. A dose of IPV-containing vaccine should be administered at 4 to 6 years of age regardless of the number doses of IPV and/or OPV vaccine administered prior to 4 years of age.

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

For children and adolescents not previously immunized with tetanus, diphtheria and polio, refer to Tetanus Toxoid or Diphtheria Toxoid in Part 4. Children 7 years of age and older only needing polio protection, should receive two doses of IPV-containing vaccine, given 4 to 8 weeks apart, followed by a third dose administered 6 to 12 months after the second dose.

Adults (18 years of age and older)
For adults not previously immunized with tetanus, diphtheria and polio, refer to Tetanus Toxoid or Diphtheria Toxoid in Part 4. Adults at increased risk for polio who only need polio protection, should receive two doses of IPV-containing vaccine given 4 to 8 weeks apart, followed by a third dose 6 to 12 months after the second dose. Adults who are unimmunized against polio but are not at increased risk and have had a primary series of tetanus and diphtheria containing vaccine, should receive polio containing vaccine as part of their next tetanus and diphtheria booster.

**BOOSTER DOSES AND RE-IMMUNIZATION**
For adults previously immunized against polio, a single lifetime booster dose of polio-containing vaccine is recommended for those at increased risk of exposure to polio (e.g., military personnel, workers in refugee camps in endemic areas, travellers to areas where there are polio epidemics) (refer to Table 1).

**SEROLOGICAL TESTING**
Serologic testing is not recommended before or after receiving IPV vaccine.

**STORAGE REQUIREMENTS**
Store IPV-containing vaccines in a refrigerator at +2ºC to +8ºC and do not freeze.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**
IPV-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 Part 2 for additional general information. Refer to Diphtheria Toxoid, Tetanus Toxoid, Pertussis Vaccine, Haemophilus influenzae type b Vaccine and Hepatitis B Vaccine in Part 4 for additional information regarding other components in IPV-containing combination vaccines.

**COMMON AND LOCAL ADVERSE EVENTS**
Adverse events following IPV vaccine are usually limited to mild injection site reactions.

**LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS**
Serious adverse events are rare following immunization with IPV-containing vaccine and, in most cases, data are insufficient to determine a causal association. Anaphylaxis following vaccination with IPV-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 AEFI.

CONTRAINDICATIONS AND PRECAUTIONS
IPV-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 IPV-containing vaccines, potential allergens include:

- ADACEL®-POLIO: neomycin, polymyxin B, streptomycin
- BOOSTRIX®-POLIO: latex in plunger stopper of pre-filled syringe, neomycin, polymyxin B
- IMOVAX®- POLIO: neomycin, polymyxin B, streptomycin
- 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

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 IPV-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 three doses of IPV-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.

SELECTED REFERENCES


Gautret P, Wilder-Smith A. *Vaccination against tetanus, diphtheria, pertussis and poliomyelitis in adult travellers.* Travel Med Infect Dis 2010;8:155-60.


PART 4

RABIES VACCINE

- Epidemiology
- Preparations Available for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccines and Immune Globulin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th>Rabies is a rare viral central nervous system infection most often transmitted to humans through the bite of an infected mammal.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transmission of rabies from saliva contamination of scratches, broken skin or the mucous membranes without a bite is rare.</td>
</tr>
<tr>
<td></td>
<td>Pre-exposure immunization for high risk persons produces rabies neutralizing antibodies.</td>
</tr>
<tr>
<td></td>
<td>Post-exposure prophylaxis is highly effective in preventing rabies.</td>
</tr>
<tr>
<td></td>
<td>Adverse reactions for rabies vaccines include injection site reactions, such as pain, erythema, swelling and itching.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Pre-exposure immunization is given to people at high risk of close contact with rabid animals or the rabies virus (e.g., people with occupational exposure to animals; laboratory workers handling the rabies virus; certain travellers; hunters and trappers in areas with confirmed rabies; and spelunkers).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evaluation of an individual’s need for post-exposure prophylaxis includes risk assessment related to the exposure to the potentially rabid animal.</td>
</tr>
</tbody>
</table>
How

- Pre-exposure immunization: three 1.0 mL intramuscular (IM) or 0.1 mL intradermal (ID) doses of rabies vaccine given on days 0, 7 and any time between days 21 to 28. Rabies vaccine must never be given into the gluteal muscle due to the risk of decreased absorption.
- If exposure to potentially rabid animals can be avoided, delay pre-exposure immunization of immunocompromised individuals until they are likely to mount an optimal response.
- The ID route should not be used for post-exposure prophylaxis or for pre-exposure prophylaxis in those who are immunocompromised or are taking chloroquine.
- Post-exposure management requires consideration of: the exposure to the potentially rabid animal; management of the potentially rabid animal; and management of the exposed person.
- Thorough cleaning and flushing the wound with soap and water is the most important post-exposure measure.
- If indicated, initiate post-exposure prophylaxis as soon as possible but administer regardless of the time interval since exposure.
- Post-exposure prophylaxis of immunocompetent persons who have not been previously immunized with rabies vaccine consists of: local wound treatment; rabies immune globulin (20 IU/kg body weight) given on day 0 with as much as possible infiltrated into and around the wound; and four 1.0 mL IM doses of rabies vaccine given on days 0, 3, 7 and 14. In those who have not previously been immunized and are immunocompromised or are taking antimalarials, a fifth dose of vaccine should be given on day 28.
- Post-exposure prophylaxis of persons previously appropriately immunized with rabies vaccine consists of: local wound treatment and two 1.0 mL IM doses of rabies vaccine given on days 0 and 3. Rabies immune globulin should not be given to persons who have previously received appropriate rabies vaccinations.
- There are no definite contraindications to rabies vaccine after significant exposure to a proven rabid animal.
- Hypersensitivity to eggs may be a concern when using PCECV vaccine.
- Vaccination schedules for post-exposure prophylaxis should be adhered to as closely as possible; it is essential that all doses be received.
- Post-vaccination serology is recommended after pre-exposure immunization using the ID route; following immunization of immunocompromised individuals or people taking chloroquine; or if there has been a significant deviation from the recommended vaccination schedule.

Why

- Human rabies occurs very rarely in Canada, but if not prevented, is almost always fatal once symptoms develop. Recent cases have been due to bat exposures.
- Pre-exposure immunization and post-exposure prophylaxis result in antibodies to prevent the virus from entering the peripheral nervous system.
- A thorough risk assessment will determine the appropriate post-exposure management to prevent human rabies.

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

- The recommended number of vaccine doses for post-exposure prophylaxis of immunocompetent persons previously unimmunized with rabies vaccine has been reduced from five to four.
- New recommendations have been made regarding management of encounters with bats.

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Rabies virus is a ribonucleic acid (RNA) virus of the Rhabdoviridae family. There are different antigenic variants of rabies virus distinguished by laboratory testing. Specific variants tend to occur in specific species of animals, although these variants can be found in other species as well. The virus is easily killed by sunlight, soap and drying.

Reservoir

Rabies is a disease of mammals, both domestic and wild. Dogs are the main carriers of the disease in Asia and Africa. In Canada and the US, foxes, skunks, raccoons and bats may be reservoirs capable of transmitting infection to dogs, cats, livestock and people.

Transmission

Rabies is spread to humans when virus in the saliva of an infected animal enters through a bite, scratch, broken skin, the mucous membranes or the respiratory tract. The virus then gains access to the central nervous system through peripheral nerves. Bites from an infected animal are the main route of exposure. Transmission also occurs through transplantation of organs from undiagnosed infected persons. The usual incubation period is 3 to 8 weeks, although it may vary from several days to years.

Risk factors

People who work in close contact with animals, such as veterinarians and veterinary staff, animal control and wildlife workers, and laboratory workers who handle the rabies virus are at higher risk for exposure to rabies. Individuals who engage in activities such as hunting and trapping or cave exploration (spelunkers) which place them in close contact with potentially rabid animals like bats, foxes, skunks and raccoons, in areas where rabies is found, may also be considered at higher risk of rabies exposure.

Children are considered at higher risk for exposure to rabies because they often play with animals and are less likely to report bites or scratches. Additionally, bites in children are usually higher on the trunk or face, and are often more severe.

Risk to travellers varies depending on itinerary, purpose and duration of the trip, as well as activities and access to medical care.

Spectrum of clinical illness

Rabies is an almost always fatal viral infection of the central nervous system. Early symptoms of rabies may include headache, malaise, fever and fatigue. There may be discomfort or pain at the exposure site (i.e., the site where the person was bitten). Symptoms progress quickly as the central nervous system is attacked, and the illness generally presents in one of two ways. The more common, agitated (furious) form presents with the classic symptoms of hydrophobia and aerophobia (severe laryngeal or diaphragmatic spasms and a sensation of choking when attempting to drink or when air is blown in the face) with a rapidly progressing encephalitis and death. The paralytic form of the disease manifests in progressive flaccid paralysis, has a more protracted course, and is more difficult to diagnose. A more detailed description of the clinical signs of rabies in animals is available at: Fact Sheet: Rabies. (http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/rabies/fact-sheet/eng/1356155202013/1356155379445)
DISEASE DISTRIBUTION

Incidence/prevalence of human rabies

Global

Rabies occurs worldwide, although most human deaths occur in Asia and Africa. In recent years, bat-related rabies has become a public health concern in the Americas and the Caribbean. A map of the areas where rabies transmission occurs is available from the World Health Organization (WHO) website: Rabies countries or areas at risk. (http://www.who.int/rabies/Global_Rabies_ITH_2008.png)

National

Human rabies occurs very rarely in Canada. Between 1924 and 2009, 24 people in six provinces died of rabies (Figure 1): Quebec (12), Ontario (6), Saskatchewan (2), Alberta (2), British Columbia (1) and Nova Scotia (1). The three most recent human cases in Canada were bat-related; the cases occurred in Quebec in 2000, British Columbia in 2003 and Alberta in 2007.

Rabies incidence rates are similar in Canada and the US and are reported in cases per billion person-years because of the extremely low number of cases. Between 1990 and September 2007, 36 bat-related human rabies cases were identified in Canada (3 cases) and the US (33 cases) resulting in an incidence rate of 6.7 cases per billion person-years. Of these 36 bat-related human cases, the types of exposures reported were as follows:

- Direct contact with a bat: 52.8%
  - With recognized bite: 27.8%
  - Without recognized bite: 25%
- History of household exposure to a bat: 16.7%
- No history of exposure to a bat: 30.5%

Figure 1: Rabies – Number of Deaths in Canada, 1924-2009
Incidence/prevalence of animal rabies
Rabies testing of animals is carried out mainly when there has been a possible exposure involving a human or other animal, or for special studies. Therefore, the incidence/prevalence data for animal rabies are influenced by the likelihood that an animal will have these types of encounters in the different jurisdictions and that the animal will be captured and submitted for testing. The number of rabid animals detected in Canada has decreased considerably from 670 in 2000 to 145 in 2009. Part of this decline is related to wildlife rabies control measures, such as oral rabies vaccinations delivered through baiting programs and trap-vaccinate-release programs.

There are regional differences in the prevalence of animal rabies and the specific species infected in each region vary over time. Therefore, it is important for health care providers to consult local public health departments regarding local epidemiology and for public health officials to remain current based on information from the Canadian Food Inspection Agency (CFIA) website: Positive rabies in Canada. (http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/rabies/positive-rabies/eng/1356156989919/1356157139999)

Between 2006 and 2010, a total of 1005 cases of confirmed animal rabies were reported in Canada. Four provinces accounted for the majority of these cases: Ontario (35%), Manitoba (22%), Quebec (16%) and Saskatchewan (13%). North West Territories had 66 cases (6.5%), British Columbia 54 cases (5%), and Alberta 11 (11%). Nova Scotia reported 3 cases, New Brunswick 2 cases and Prince Edward Island 1 case. The Yukon and Newfoundland/Labrador had no reported cases of animal rabies.

Over the same time period, skunks accounted for 37% of reported cases, followed by bats (33%), raccoons (9%) and foxes (6%). Dogs accounted for 4% and cats accounted for 2% of animal rabies cases. The species most commonly identified as having rabies by region, based on total numbers of positive test results, were as follows: foxes in the Northwest Territories/Nunavut (70%), skunks in Manitoba (75%) and Saskatchewan (70%), and bats in British Columbia (99%), Alberta (81%), Quebec (70% since 2008 when raccoon rabies was last detected) and Ontario (56%); In Ontario, the second most affected species was skunks (27%).

Raccoon rabies arrived in Canada from the US in 1999 and was found mainly in Ontario, New Brunswick, and Quebec. A small number of rabid raccoons were also found in Manitoba and Saskatchewan. An active eradication program was put in place and, based on reports to September 2011 no rabid raccoons have been detected in Canada since 2008.

Rabies occurs in larger rodents such as ground hogs/woodchucks and beavers in some areas of the US. Rabies in these animals is rare in Canada with only three rabid ground hogs/woodchucks detected from 1998 to mid-2011, two in Manitoba in 1999 and one in Ontario in 2000.

Rabid bats have been found in most regions across Canada. The prevalence of rabies in wild bats is generally unknown, although older studies suggest a prevalence of between less than 1% and 4.1%. In 2006, the CFIA tested 2,150 bats, 3.3% of which were positive.

Bat strains of rabies virus have occasionally been identified in other animals such as foxes, cows, horses, squirrels, skunks, dogs and cats. No human cases of rabies associated with bat strains have been known to be transmitted from exposure to other animals.

PREPARATIONS AVAILABLE IN CANADA

RABIES VACCINES (Rab)

- IMOVAX® Rabies (inactivated, human diploid cell rabies vaccine), sanofi pasteur Ltd. (HDCV)
- RabAvert® (inactivated, purified chick embryo cell rabies vaccine), Novartis Vaccines and Diagnostics (manufacturer), Novartis Pharmaceuticals Canada Inc. (distributor). (PCECV)
RABIES IMMUNE GLOBULINS (Rablg)

- IMOGAM® Rabies Pasteurized (rabies immune globulin (human)), sanofi pasteur Ltd.
- HYPERRAB® S/D (rabies immune globulin (human)), GrifolsTherapeutics Inc.

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

EFFICACY, EFFECTIVENESS AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

HDCV or PCECV administered at the same time as Rablg (using a separate needle, syringe and injection site) and local treatment are highly effective in preventing rabies in exposed individuals. Failures of post-exposure management have occurred, although almost always after deviation from the recommended post-exposure prophylaxis protocol. No post-exposure prophylaxis failures have occurred in Canada or the US.

IMMUNOGENICITY

Pre-exposure immunogenicity

The immunogenicity of PCECV and HDCV for pre-exposure vaccination has been demonstrated in clinical trials. When PCECV was administered according to the recommended immunization schedule, 100% of subjects attained an adequate antibody titre by Day 28 or earlier. Persistence of adequate antibody titres for up to 2 years after immunization with PCECV has been demonstrated. After a three-dose primary series of HDCV, all vaccinees reached an adequate antibody titre. A 10-year follow-up study of subjects who received three doses of HDCV followed by a booster dose at 1 year has shown the maintenance of seroconversion up to 5 years in 96.2%. A seroconversion rate of 95.1% was demonstrated in travellers who received three ID injections of HDCV or PCECV with a booster after 12 months.

Post-exposure immunogenicity

Clinical studies in patients exposed to rabies virus have demonstrated that PCECV, when used in a five- or six-dose post-exposure schedule, provided protective antibody titres in 98% of patients within 14 days and in 100% of patients by Day 30. In a study of subjects who received HDCV in a five-dose post-exposure schedule as well as Rablg on day 0, all vaccinees reached a protective antibody titre by day 14 and remained at that level through day 90. One year later, protective antibody concentrations were maintained in 98.3% of subjects.

RECOMMENDATIONS FOR USE

PRE-EXPOSURE IMMUNIZATION

Pre-exposure rabies immunization with either HDCV or PCECV should be offered to people at high risk of close contact with rabid animals and/or the rabies virus, for example:

- Laboratory workers who handle the rabies virus.
- Veterinarians, veterinary staff, animal control and wildlife workers. Refer to Workers.
- Certain travellers. Refer to Travellers.
- Hunter and trappers in areas with confirmed rabies.
- Spelunkers (cavers).
POST-EXPOSURE MANAGEMENT

Risk assessment related to the exposure to the potentially rabid animal

Rabies prophylaxis must be considered in every incident in which human exposure to potentially rabid animals has occurred, unless rabies is known to be absent from the local animal population. In evaluating each case, local public health officials should be consulted. When considering the need for post-exposure management, the following should be reviewed:

- The species of animal, including the prevalence of rabies in that species and the prevalence of rabies in other species in the area.
- The type of exposure – bite, non-bite, or direct contact with a bat.
- The circumstances of the exposure – provoked, unprovoked.
- The vaccination status and behaviour of a domestic animal.
- The age of the exposed person.
- The location and severity of the bite (e.g., the size and number of bites).

In addition, the availability of the animal for observation or testing influences the management of the animal and the exposed person. Table 1 summarizes factors to be considered when assessing the risk related to the exposure to a potentially rabid animal.

Species of animal

The animals in Canada most often proven rabid are wild terrestrial carnivores (e.g. skunks, foxes and raccoons), bats, cattle and stray dogs and cats. As the distribution of animal rabies and the species involved vary considerably across Canada, it is important to consult local public health officials in cases of possible exposure. In North America, domestic dog and cat exposures may be managed differently than in other areas of the world where the prevalence of rabies in these animals is higher.

If the incident involved a dog or cat, determining if it is a stray or domestic animal assists with the risk assessment. Generally, rabies is less likely in domestic animals, particularly domestic dogs, compared to stray animals due to the following factors: domestic animals are more likely to be vaccinated; domestic animals may spend less time outdoors where exposure to a potentially rabid animal could occur; and an encounter with a potentially rabid animal is more likely to be recognized in a domestic animal.

Human exposures to livestock are usually confined to salivary contamination, with the exception of horses and swine, from which bites have been reported. The risk of infection after exposure to rabid cattle is low. Squirrels, hamsters, guinea-pigs, gerbils, chipmunks, rats, mice or other small rodents, as well as lagomorphs (such as rabbits and hares), are rarely found to be infected with rabies because it is believed that they are likely to be killed by the larger animal that could have potentially transmitted rabies to them. These small animals can, theoretically, become infected by bat strains of rabies; however, no cases of transmission of bat strains of rabies from these animals to humans have been documented. Because these small animals are not known to have caused human rabies in North America, post-exposure prophylaxis should be considered only if the animal’s behaviour was highly unusual. For example, a bite from a squirrel while feeding it would not be considered unusual behaviour and so does not warrant post-exposure prophylaxis based on this information alone. Rabies in larger rodents such as ground hogs/woodchucks and beavers is rare in Canada; exposure to these animals requires an assessment of the circumstances of the exposure to determine the need for post-exposure prophylaxis.

The manifestations of rabies and the incubation periods vary in different species. The length of time virus may be excreted in saliva before the development of symptoms has not been determined for the purpose of defining rabies exposure except in dogs, cats and ferrets. In dogs, cats and ferrets, rabies virus excretion does not generally precede symptom development beyond 10 days. It remains unclear as to whether asymptomatic carriage of rabies virus that can result in transmission from other animals is possible.
Type of exposure

Rabies is transmitted only when the virus is introduced into a bite wound, open cuts in skin, or onto mucous membranes such as the mouth or eyes. Transmission of rabies occurs most commonly through bites. Corneal transplants are the most common non-bite exposures leading to human rabies. In 2004, the US Centers for Disease Control and Prevention confirmed the first reported case of rabies following solid organ transplantation. Between 1956 and 1977, four cases of human rabies may have been acquired through aerosolized virus across mucous membranes. Two of these cases of rabies have been attributed to probable aerosol exposures in laboratories, and two cases have been attributed to possible airborne exposures in caves containing millions of bats; however, alternative infection routes cannot be discounted in several of these cases. Similar airborne incidents have not occurred in approximately 25 years, possibly because of elevated awareness of such risks resulting in increased use of appropriate preventive measures.

The contamination of open wounds, abrasions, scratches or mucous membranes with saliva or neural tissues are also considered forms of non-bite exposures. Only eight instances of human rabies from cutaneous or mucous membrane exposures were found in a review published in 2002 and these were not well documented, raising the possibility of other routes of exposure. The reports of scratches consist of a facial scratch from a bat in 1985 and a scratch from a rabid calf in the 1940s.

Types of exposures can be considered in three broad categories: bite exposures, non-bite exposures and bat exposures as follows:

- **Bite exposure**: A bite is defined as any penetration of the skin by teeth. Bites inflicted by most animals are readily apparent with the exception of bats. Bites inflicted by bats may not be felt and may leave no visible bite marks (refer to Bat Exposure).

- **Non-bite exposure**: Non-bite exposures, other than organ or tissue transplants, have almost never been proven to cause rabies, and post-exposure prophylaxis is not indicated unless the non-bite exposure involves saliva or neural tissue being introduced into fresh, open cuts or scratches in skin or onto mucous membranes. These exposures require a risk assessment that consider the likelihood of saliva contamination (e.g., did the animal lick the wound?), the prevalence of rabies in the area, the species involved (domestic or stray dog or cat, wild terrestrial animal, or bat) and the circumstances of the exposure (e.g., provoked or unprovoked; the behaviour of a domestic animal). Petting a rabid animal or handling its blood, urine or feces is not considered to be an exposure; however, such contact should be avoided. Being sprayed by a skunk is also not considered an exposure. These incidents do not warrant post-exposure prophylaxis.

Post-exposure prophylaxis or testing of a bat is generally recommended after direct contact with the bat (refer to Bat Exposure) because it is very difficult to ensure that a bite did not take place.

Post-exposure prophylaxis is recommended in rare instances, such as inhalation of aerosolized virus by spelunkers exploring caves inhabited by infected bats or by laboratory technicians homogenizing tissues infected with rabies virus without appropriate precautions; however, the efficacy of prophylaxis after such exposures is unknown.

Exposures occurring in the course of caring for humans with rabies could, theoretically, transmit the infection. No case of rabies acquired in this way has been documented, but post-exposure prophylaxis should be considered for individuals exposed to saliva or neural tissue from a person with rabies.

- **Bat exposure**: Post-exposure rabies prophylaxis following bat contact is recommended when both the following conditions apply:

  - There has been direct contact with a bat, AND
A bite, scratch, or saliva exposure into a wound or mucous membrane cannot be ruled out. Direct contact with a bat is defined as the bat touching or landing on a person. When there is no direct contact with a bat, the risk of rabies is extremely rare and rabies post-exposure prophylaxis is not recommended. In an adult, a bat landing on clothing would be considered reason for intervention only if a bite, scratch or saliva exposure into a wound or mucous membrane cannot be ruled out. In a child, a bat landing on clothing could be considered a reason for intervention, as a history to rule out a bite, scratch or mucous membrane exposure may not be reliable. When a bat is found in the room with a child or an adult who is unable to give a reliable history, assessment of direct contact may be difficult. Factors indicating that direct contact may have occurred include the individual waking up crying or upset while the bat was in the room or observation of an obvious bite or scratch mark.

From 1998 to 2009, NACI recommended that people who may not be aware of or able to report a bat bite (e.g., sleeping person, young child, cognitively impaired) be offered intervention if a bat was found in the room with them. This recommendation was revised (as described above) in 2009 based on the rarity of human rabies related to bats (one case in Canada reported approximately every 5 years). Research conducted in Canada estimated that a case of human rabies related to bedroom exposure to a bat (i.e., finding a bat in the room of a sleeping person with no recognized physical contact with the bat) is expected to occur in Canada once every 84 years. In addition, it has been determined that to prevent one case of rabies from bedroom exposure to a bat, using a conservative estimate, 314,000 people would need to be treated.

**Circumstance of the exposure**

An unprovoked attack is more likely to indicate that the animal is rabid; although, rabid animals may become uncharacteristically quiet. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. Untrained individuals should never handle wild or stray animals or any domestic animal that is behaving unusually and children should be taught this precaution.

**Vaccination status and behaviour of the animal**

Domestic pets with up-to-date rabies vaccination are unlikely to become infected with rabies. A veterinarian should be consulted to determine if the animal is up-to-date with its vaccinations. Any domestic dog, cat or ferret (regardless of vaccination history) that has bitten a human should be reported to public health officials for appropriate follow-up.

A history of abnormal or aggressive behaviour in a domestic animal, potential for exposure of a domestic animal to other animals that could transmit rabies to the domestic animal, and a previous encounter of a domestic animal with a wild animal should be considered when determining the likelihood that a domestic animal exposure carries a risk of rabies transmission. Generally, behaviour in wild animals cannot be accurately evaluated and should not be considered part of the risk assessment, however, some behaviours in bats may be considered abnormal and indicative of rabies, such as a bat attacking a person or hanging on tenaciously to a person.

**The age of the exposed person**

The history obtained from a child who has been potentially exposed to an animal can be difficult to interpret and potentially unreliable. This should be considered when determining the appropriate post-exposure management.

**The location and severity of the bite**

When the rabies virus is inoculated into a wound, it must be taken up at a nerve synapse to travel to the brain, where it causes fatal encephalitis. The virus may enter a nerve rapidly or it may remain at the site of the bite for an extended period before gaining access to the nervous system. Post-exposure prophylaxis is ineffective after the rabies virus invades the nervous system.
More severe bites may be more likely to suggest the animal is rabid and these bites may also provide more opportunity for transmission of the virus because of the extent of exposure to saliva.

A higher density of nerve endings in the region of the bite increases the risk of developing rabies encephalitis. Bites on the hands and face, because of the density of nerve endings, are considered higher-risk exposures.

Table 1 provides an outline of factors to consider in the risk assessment related to exposure to potentially rabid animals.
Table 1: Risk Assessment Related to the Exposure to the Potentially Rabid Animal
This table and accompanying text are guides for management and do not replace clinical judgment.

<table>
<thead>
<tr>
<th>Factors to Consider</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal</strong></td>
<td></td>
</tr>
<tr>
<td>How prevalent is rabies in the species of animal involved in the exposure?</td>
<td></td>
</tr>
<tr>
<td><em>In North America, rabies occurs mainly in bats, foxes, skunks, raccoons and stray dogs and cats.</em></td>
<td></td>
</tr>
<tr>
<td>Is the animal a domestic pet, wild animal or stray animal?</td>
<td></td>
</tr>
<tr>
<td><em>Domestic dogs and cats are less likely to be rabid than stray dogs or cats. Clinical signs of rabies in wild animals cannot be interpreted reliably.</em></td>
<td></td>
</tr>
<tr>
<td>Is the wild animal available for testing?</td>
<td></td>
</tr>
<tr>
<td><em>In the event of exposure to a fox, skunk, raccoon or bat in areas where rabies is known to occur in these animals, post-exposure prophylaxis should begin immediately unless the animal is available for rabies testing and rabies is not considered likely. Post-exposure prophylaxis should not be delayed beyond 48 hours while waiting for test results in wild animals.</em></td>
<td></td>
</tr>
<tr>
<td>Is the dog, cat or ferret available for observation?</td>
<td></td>
</tr>
<tr>
<td><em>If the dog, cat or ferret is healthy after a 10-day observation period, the animal would not have been shedding rabies virus in their saliva and would not have been infectious at the time of the exposure.</em></td>
<td></td>
</tr>
<tr>
<td>If the dog, cat or ferret is available, is it clinically healthy?</td>
<td></td>
</tr>
<tr>
<td><em>If the dog, cat or ferret has or develops signs of rabies, post-exposure prophylaxis should be initiated as soon as possible.</em></td>
<td></td>
</tr>
<tr>
<td>Was the animal behaving unusually?</td>
<td></td>
</tr>
<tr>
<td><em>Abnormal behaviour in a domestic pet may indicate that the animal is rabid. Generally, it is not possible to assess animal behaviour in wild animals.</em></td>
<td></td>
</tr>
<tr>
<td>If the animal is a domestic pet, what is the vaccination status of the animal?</td>
<td></td>
</tr>
<tr>
<td><em>Domestic pets with up-to-date rabies vaccination are unlikely to be infected with rabies.</em></td>
<td></td>
</tr>
<tr>
<td>If the animal is a domestic pet, has it been exposed to wild or outdoor animals?</td>
<td></td>
</tr>
<tr>
<td><em>Rabies may be transmitted to domestic pets during exposure to rabid wild or outdoor animals. Indoor animals have little opportunity to be exposed to rabid animals.</em></td>
<td></td>
</tr>
<tr>
<td><strong>Geographic</strong></td>
<td></td>
</tr>
<tr>
<td>In what geographic area did the exposure occur?*</td>
<td></td>
</tr>
<tr>
<td>How prevalent is rabies in the involved species in the geographic area?</td>
<td></td>
</tr>
<tr>
<td>How prevalent is rabies in other animal species in the geographic area?</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>What was the type of exposure: bite, non-bite or bat?</td>
<td></td>
</tr>
<tr>
<td><em>Transmission rarely occurs from non-bite exposures. Petting a rabid animal or handling its blood, urine or feces are not considered exposures.</em></td>
<td></td>
</tr>
<tr>
<td>Can a bite or saliva exposure into a scratch, wound or mucous membrane be ruled out?</td>
<td></td>
</tr>
<tr>
<td><em>Rabies transmission occurs most commonly through a bite. Aerosol transmission is rare as is transmission when scratches, wounds, or mucous membrane are contaminated from saliva or infected neural tissue.</em></td>
<td></td>
</tr>
<tr>
<td>What were the circumstances of the exposure (e.g., provoked or unprovoked attack)?</td>
<td></td>
</tr>
<tr>
<td><em>An unprovoked attack is more likely to indicate that the animal is rabid.</em></td>
<td></td>
</tr>
<tr>
<td><strong>Person</strong></td>
<td></td>
</tr>
<tr>
<td>What is the age of the exposed person? Is the exposed person able to provide a reliable history?</td>
<td></td>
</tr>
<tr>
<td><em>The history obtained from a child may be difficult to interpret and, potentially, unreliable. Assessment of the exposure may also be difficult in a cognitively impaired adult.</em></td>
<td></td>
</tr>
<tr>
<td>What is the location and severity of the wounds?</td>
<td></td>
</tr>
<tr>
<td><em>Bites on the face, neck or hand are considered higher-risk exposures due to the density of nerve endings in these areas. More severe bites may suggest the animal is rabid and also provide more opportunity for transmission.</em></td>
<td></td>
</tr>
</tbody>
</table>

Management of the potentially rabid animal

Any animal that has bitten a human or is suspected of being rabid should be reported to local public health officials. The CFIA veterinarian should be notified of any animal suspected of being rabid, regardless of whether it has been involved in a biting incident. CFIA veterinarians are familiar with the regulations concerning rabies and, if necessary, will collect and ship appropriate specimens to a federal laboratory for diagnosis.

Rabies testing of animals is done using a fluorescent antibody test, which is the gold standard recommended by the WHO. The test has a reported sensitivity of 98% to 100%. Further information and advice may be obtained from the CFIA district office, or the CFIA web site: Animal Health offices, (http://www.inspection.gc.ca/animals/terrestrial-animals/offices/eng/1300462382369/1300462438912)

Dogs, cats and ferrets

Exposures to dogs, cats and ferrets that could potentially result in rabies transmission (as described in Type of exposure) should be reported to local public health officials. Dogs, cats and ferrets that are apparently healthy should be confined and observed for 10 days after a bite regardless of the animal’s rabies vaccination status. Animals that are alive and healthy at the end of the 10-day period would not have transmitted rabies in their saliva at the time of the bite. If illness suggestive of rabies exists at the time of the bite or develops during the observation period, the animal should be humanely euthanized in a way that does as little damage to the brain as possible, and the head submitted for laboratory examination and rabies testing. Rabies virus is readily demonstrable in brains of animals with neurologic symptoms. The CFIA veterinarian should be contacted to assist with determining the need for testing, organizing the testing and following-up potential exposures to other domestic animals.

The confinement and observation of an apparently healthy dog, cat or ferret can take place at the owner’s home, an animal shelter, or a veterinarian’s office depending on circumstances including the reliability of the owner, the capacity to keep the animal away from people and other animals, and the suspicion of rabies in the animal. The person responsible for observation of the animal should be advised to notify public health officials if the animal becomes ill or escapes during the observation period. The animal should be observed by a public health official or veterinarian at the end of the 10-day observation period to ensure it is alive and healthy. Unvaccinated animals that remain healthy should be vaccinated at the end of the observation period.

Stray or unwanted dogs, cats or ferrets involved in an exposure that could potentially transmit rabies should be confined and observed as outlined above. If this is not possible, the animal should be humanely euthanized in a way that does as little damage to the brain as possible, and the head submitted for laboratory examination and rabies testing in consultation with the local CFIA veterinarian.

If the dog, cat or ferret has escaped, attempts should be made to find the animal and owner. If the dog, cat or ferret cannot be located, a decision should be made in consultation with public health officials regarding the need for post-exposure prophylaxis. Refer to Management of the person after exposure to a potentially rabid animal for additional information.

Wild terrestrial carnivores and exotic pets (other than ferrets)

The period of rabies virus shedding in a wild terrestrial carnivore (such as a skunk, fox or raccoon) or in an exotic pet (other than a ferret) is unknown. Therefore, when these animals are involved in an exposure that could potentially transmit rabies, a trained wildlife or animal control worker should be contacted to capture the animal. The worker should use extreme caution to ensure that there is no further exposure to the animal. The animal should be immediately humanely euthanized in a way that does as little damage to the brain as possible, and the head submitted for laboratory examination and rabies testing in consultation with the local CFIA veterinarian.
Bats

If there has been no direct contact with the bat, the bat should not be captured for testing and should be safely let out of the house. To remove a bat from the house, the area with the bat should be closed off from the rest of the house and people and pets kept out of the area. The doors or windows in the area with the bat should be opened to the exterior to let the bat escape.

If there has been direct contact with a bat (as defined in Bat exposure) a trained wildlife or animal control worker should be contacted to attempt to capture the bat. The worker should use extreme caution to ensure that there is no further exposure to the bat. They should wear thick leather gloves, avoid touching the bat, and place the intact bat in a closed secure container. Once the bat has been captured, local public health officials should be contacted. The public health department will contact the CFIA regarding rabies testing of the bat and the CFIA will follow-up any domestic animal that may have had exposure should the bat test positive. Bats should be submitted intact for rabies testing.

Management of the person after exposure to a potentially rabid animal

Table 2 outlines recommendations for the management of people after possible exposure to rabies. These recommendations are intended as a guide and may need to be modified in accordance with the specific circumstances of the exposure.

The objective of post-exposure management is to neutralize the rabies virus at the site of infection before the virus can enter the central nervous system. Immediate and thorough cleaning and flushing of the wound with soap and water is imperative and is probably the most effective procedure in the prevention of rabies. Care should be taken to clean the wound to its depth. Flushing for approximately 15 minutes is suggested. Some guidelines also suggest the application of a viricidal agent such as iodine-containing or alcohol solutions. Suturing the wound should be avoided if possible, and tetanus prophylaxis and antibiotics should be given as appropriate.

If exposure to rabies is considered highly likely, post-exposure prophylaxis should be started as soon as possible after the exposure. In other circumstances, if the initiation of post-exposure prophylaxis is delayed until test results from the involved animal are available, a maximum waiting period of 48 hours is recommended. In consultation with public health officials, the post-exposure vaccine series may be discontinued if appropriate laboratory testing of the involved animal is negative.

If indicated based on the risk assessment, post-exposure prophylaxis should be offered to exposed individuals regardless of the time interval after exposure.

Exposures to dogs, cats and ferrets

If the suspect animal is a dog, cat or ferret that is healthy and available for observation, post-exposure prophylaxis may be withheld pending the animal’s status after a 10-day observation period. However, if the animal has or develops signs suggestive of rabies, post-exposure prophylaxis of exposed persons should be initiated immediately. The animal should be humanely euthanized in a way that does as little damage to the brain as possible, and the head submitted for immediate laboratory examination and rabies testing. In consultation with public health officials, post-exposure prophylaxis may be discontinued if the animal tests negative for rabies.

If the dog, cat or ferret has escaped and cannot be located, a decision should be made in consultation with public health officials regarding the need for post-exposure prophylaxis. The decision should consider several factors including the frequency of rabies in the area, if it was a domestic or stray animal, the type of exposure, the circumstances of the exposure including whether it was a provoked or unprovoked exposure, and the severity and location of the wound.
Exposures to wild animals and exotic pets (other than ferrets)

Post-exposure prophylaxis should begin immediately following exposure to a wild terrestrial carnivore (such as a fox, skunk or raccoon) in enzootic areas unless the animal is available for rabies testing and rabies is not considered likely. The decision to start post-exposure prophylaxis while awaiting the laboratory test results should consider several factors including when the test results will be available, the species of animal, the frequency of rabies in that species and in other species in the area, the type of exposure, the circumstances of the exposure including whether it was a provoked or unprovoked exposure, and the severity and locations of the wounds. Initiation of post-exposure prophylaxis should not be delayed beyond 48 hours while waiting for laboratory tests if the exposure is from a terrestrial animal in an enzootic area. If post-exposure prophylaxis is started before the test results are available, in consultation with public health officials the rabies vaccine may be discontinued if the animal tests negative for rabies.

Exposure to small rodents (such as squirrels, chipmunks, rats, mice, hamsters, guinea pigs, gerbils) and lagomorphs (such as rabbits and hares) has not been known to transmit rabies; therefore, post-exposure prophylaxis is rarely indicated after exposure to these animals. Post-exposure prophylaxis should only be considered if the animal was behaving very unusually.

Larger rodents such as ground hogs/woodchucks and beavers can potentially carry rabies, although this is rare in Canada. The management of exposures to these animals requires a risk assessment which includes the frequency of rabies in these animals in the geographic area, the frequency of rabies in other animals, the type of exposure, and the circumstances of the bite including whether it was provoked or unprovoked.

Exposures to bats

When there is a known bat bite, scratch or saliva exposure into a wound or mucous membrane, rabies post-exposure prophylaxis should be initiated immediately because of the higher prevalence of rabies in bats. This is particularly important when the exposure involves the face, neck or hands, or when the behaviour of the bat is clearly abnormal, such as if the bat has attacked the person or hangs on tenaciously. If the bat is available for testing, post-exposure prophylaxis may be discontinued after consultation with public health officials if the bat tests negative for rabies.

If someone is touched by a bat (such as a bat in flight) and the bat is available for rabies testing, the health care provider may decide to delay post-exposure prophylaxis. Post-exposure prophylaxis should not be delayed more than 48 hours. If a bat tests positive for rabies, the need for post-exposure prophylaxis should depend on whether direct contact with the bat occurred and not the rabies status of the bat. If someone is touched by a bat, but the bat is not available for testing it should be considered a direct contact and post-exposure prophylaxis given.
Table 2: Summary of Post-exposure Prophylaxis for Persons Potentially Exposed to Rabies, by Animal Type *(Refer to text for details)*

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Condition of animal at time of exposure</th>
<th>Management of exposed persons not previously immunized against rabies</th>
<th>Management of exposed persons previously immunized against rabies</th>
</tr>
</thead>
</table>
| Dog, cat or ferret | Healthy and available for a 10-day observation period | 1. Local treatment of wound  
2. At first indication of rabies in the animal, give RabIg and begin four or five doses of HDCV or PCECV.  
3. At first indication of rabies in the animal, arrange to have the animal tested for rabies. | 1. Local treatment of wound  
2. At first indication of rabies in the animal, begin two doses of HDCV or PCECV.  
3. At first indication of rabies in the animal, arrange to have the animal tested for rabies. |
| Dog, cat or ferret | Unknown or escaped | 1. Local treatment of wound  
2. Consult public health officials for risk assessment | 1. Local treatment of wound  
2. Consult public health officials for risk assessment |
| Rabid or suspected to be rabid* | Rabid* | 1. Local treatment of wound  
2. RabIg and begin four or five doses of HDCV or PCECV.  
3. Arrange to have animal tested for rabies if available. | 1. Local treatment of wound  
2. Begin two doses of HDCV or PCECV.  
3. Arrange to have animal tested for rabies if available. |
| Skunk, bat, fox, coyote, raccoon and other carnivores. | Regard as rabid* unless geographic area is known to be rabies-free | 1. Local treatment of wound  
2. Post-exposure prophylaxis with RabIg and four or five doses of HDCV or PCECV should begin immediately. If animal is available for rabies testing, in some instances post-exposure prophylaxis may be delayed for no more than 48 hours while awaiting results.  
3. Arrange to have animal tested for rabies if available. | 1. Local treatment of wound  
2. Post-exposure prophylaxis with two doses of HDCV or PCECV should begin immediately. If animal is available for rabies testing, in some instances post-exposure prophylaxis may be delayed for no more than 48 hours while awaiting results.  
3. Arrange to have animal tested for rabies if available. |
| Livestock, rodents or lagomorphs (hares and rabbits) | Consider individually. Consult appropriate public health and CFIA officials. Bites of squirrels, chipmunks, rats, mice, hamsters, gerbils, guinea pigs, other small rodents, rabbits and hares would only warrant post-exposure rabies prophylaxis if the behaviour of the biting animal was highly unusual. Bites from larger rodents (e.g., ground hogs/woodchucks, beavers) require a risk assessment. | | |

RabIg = human rabies immune globulin, HDCV = human diploid cell vaccine, PCECV = purified chick embryo cell culture vaccine

*If possible, the animal should be humanely euthanized and the brain tested for rabies as soon as possible; holding for observation is not recommended. Discontinue vaccine if rabies testing of the involved animal is negative.
PREGNANCY AND BREASTFEEDING

Pregnancy and breastfeeding are not contraindications to post-exposure rabies prophylaxis, but it is prudent to delay pre-exposure immunization of pregnant women unless there is a substantial risk of exposure. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

Corticosteroids, other immunosuppressive agents, and immunosuppressive illnesses (e.g., congenital immunodeficiency, human immunodeficiency virus [HIV] infection, leukemia, lymphoma, generalized malignancy) may interfere with the antibody response to rabies vaccine. Because of suboptimal response, in general, immunocompromised persons should be counselled to avoid situations of rabies exposure. If possible, pre-exposure immunization should be delayed in immunocompromised individuals until the immunocompromised state has resolved. In situations where immunosuppression is planned (such as before organ transplant) and pre-exposure rabies vaccine is necessary, the vaccine series should be given only by the intramuscular route and should be completed at least 14 days prior to starting immunosuppression if possible. For hematopoietic stem cell transplant recipients, pre-exposure rabies vaccination can be started 6 to 12 months after transplant. Depending on the risk of exposure, it may be appropriate to consider temporarily discontinuing immunosuppressive medications, in consultation with the attending physician, or to vaccinate once the person is no longer considered immunocompromised. If pre-exposure vaccination of an immunocompromised person is considered necessary because animal exposure cannot be avoided and the immunocompromising condition cannot be corrected, the vaccination should be given only by the intramuscular route and serology should be checked 7 to 14 days post-vaccination in order to ensure an acceptable antibody response has developed.

When post-exposure prophylaxis is administered to an immunocompromised person, only a five-dose series (days 0, 3, 7, 14 and 28 days) should be used along with one dose of RabIg on day 0; serology should be checked 7 to 14 days after completion of the series to ensure that an acceptable antibody response has developed. If no acceptable antibody response is detected, the patient should be managed in consultation with their physician and appropriate public health officials to receive a second rabies vaccine series. RabIg should not be repeated at the initiation of this second course. Immunosuppressive agents should not be administered during post-exposure prophylaxis unless essential for the treatment of other conditions.

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

TRAVELLERS

Risk to travellers varies depending on itinerary, purpose and duration of the trip, as well as activities and access to medical care. Travellers to rabies endemic areas where there is poor access to adequate and safe post-exposure management, as well as frequent and long-term travellers to high risk areas should seriously consider receiving pre-travel rabies immunization. Children (especially those who are too young to understand either the need to avoid animals or to report a traumatic contact) are considered at greater risk of rabid animal exposure and should receive pre-exposure immunization when travelling to endemic areas. The WHO website includes a map of global areas where rabies transmission occurs: Rabies countries or areas at risk. [http://www.who.int/rabies/Global_Rabies_ITH_2008.png]

Public health officials should be consulted regarding travellers who have had an exposure to a potentially rabid animal in a developing country, even if the traveller received a complete course of post-exposure prophylaxis in that country. The prevalence of rabies in developing countries is generally higher than in Canada and there may be concerns about the potency of available vaccines in these countries. Options for consideration in the management of travellers exposed in developing countries include initiating or repeating all or part of the post-exposure management and/or obtaining post-vaccination serology. The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides additional information on assessing a traveller’s need for pre-travel vaccination or post-travel post-exposure prophylaxis, and identifies the rabies vaccines that meet the WHO’s safety, potency and efficacy requirements at: [http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/](http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/)
Refer to Immunization of Travellers in Part 3 for additional general information.

WORKERS
Pre-exposure rabies immunization should be offered to workers at high risk of occupational exposure to potentially rabid animals or the rabies virus. High risk individuals may include veterinarians, veterinary staff, animal control and wildlife workers, and laboratory workers exposed to the rabies virus. Refer to Immunization of Workers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
The IM dose is 1.0 mL; the ID dose is 0.1ml. Each 1.0 mL dose of HDCV or PCECV contains at least 2.5 international units (IU) of rabies antigen, which is the WHO recommended standard.

Pre-exposure immunization: route and schedule
Three doses of HDCV or PCECV are required and should be given on days 0, 7 and any time between days 21 to 28. The vaccine can be given as a 1.0 mL IM dose or a 0.1 mL ID dose. Rabies vaccine should never be administered in the gluteal muscle due to variable absorption.

While IM administration of pre-exposure rabies vaccine is the gold standard, the WHO considers the ID regimen an acceptable alternative as it uses less vaccine to produce a comparable degree of protection against rabies. The ID route should not be used in persons who are immunocompromised due to illness or medication, or are taking chloroquine as the immune response to the vaccine may not be protective. In these individuals, vaccine should be administered by the IM route only. This precaution is not known to apply to other antimalarial drugs. If a decision is made to give pre-exposure prophylaxis by the ID route to a person requiring chloroquine, chloroquine use must be delayed for at least one month after vaccination or only given if the person has been found to have an adequate titre post-vaccination.

Intradermal vaccines should only be administered by fully trained staff in settings in which there is a well-established cold chain. The proper syringe and needle are essential to ensure that the correct route and dose are used. Improper administration may result in a suboptimal dose of vaccine being administered or subcutaneous injection of the vaccine. Vaccine wastage should be minimized by immunizing a large group of individuals at the same time whenever possible.

When rabies vaccine is administered ID, post-immunization antibody titres should be determined at least 2 weeks after completion of the vaccine series to ensure that an acceptable level of protection has been achieved. If using the ID route for a booster dose, serology should be checked at least 2 weeks after the booster dose.

Post-exposure prophylaxis of previously unimmunized individuals
Post-exposure prophylaxis of previously unimmunized individuals should consist of both RabIg and rabies vaccine. The RabIg provides immediate passive protection until the exposed person mounts an immune response to the rabies vaccine.

**Rabies Immune Globulin (RabIg)**

The recommended dose of RabIg is 20 IU/kg body weight for all age groups, including children, given on the first day of initiation of therapy (day 0). Because of possible interference of RabIg with the immune response to the rabies vaccine, the dose of RabIg should not be exceeded. If possible, the full dose of RabIg should be thoroughly infiltrated into the wound and surrounding area. Any remaining volume of RabIg should be injected, using a separate needle, intramuscularly at a site distant from the site of vaccine administration. When more than one wound exists, each wound
should be locally infiltrated with a portion of the RabIg using a separate needle. In such instances, the RabIg can be diluted twofold to threefold in a solution of 0.9% sodium chloride in order to provide the full amount of RabIg required for thorough infiltration of all wounds. If the site of the wound is unknown, the entire dose should be administered intramuscularly at a separate site from where the rabies vaccine is administered. Rabies vaccine and RabIg should never be mixed in the same syringe. If RabIg is not administered as recommended at the initiation of the rabies vaccine series, RabIg can be administered up to day 7 after vaccine is initiated.

**Rabies vaccine**

The Advisory Committee on Immunization Practice (ACIP) in the US has recently recommended a shortened schedule for post-exposure rabies vaccine on days 0, 3, 7 and 14 for healthy individuals. This recommendation was based on the following:

- An understanding of rabies virus pathogenesis where protection is needed rapidly to prevent the virus from entering the central nervous system.
- Experimental animal models where vaccinated animals are monitored for serologic response and protection from rabies.
- Immunogenicity studies in humans where protective antibodies are detected by Day 14 post-initiation of vaccination in almost every individual.
- Epidemiologic studies that have not attributed any human rabies cases to failure to receive a fifth dose of vaccine.

ACIP continues to recommend five doses of rabies vaccine (on days 0, 3, 7, 14 and 28) for post-exposure prophylaxis in those taking corticosteroids, other immunosuppressive agents, antimalarials, and in those who have immunosuppressive illnesses.

Based on review of this information, NACI recommends:

- For post-exposure prophylaxis of immunocompetent persons previously unimmunized with rabies vaccine, four 1.0 mL doses of HDCV or PCECV should be administered IM. The first dose of the four-dose course should be administered as soon as possible after exposure (day 0) based on the considerations discussed in the Management of the person after exposure to a potentially rabid animal section. Additional doses should be administered on days 3, 7 and 14 after the first vaccination. Recommendations for the use of RabIg on day 0 remain unchanged.
- Previously unimmunized immunocompromised persons (including those taking corticosteroids or other immunosuppressive agents, and those who have immunosuppressive illnesses) and those taking chloroquine and other antimalarials (as per the ACIP recommendation), should continue to receive a five-dose vaccination regimen on days 0, 3, 7, 14 and 28 with one dose of RabIg on day 0.
- Recommendations for post-exposure prophylaxis of persons previously immunized remain unchanged.
- Recommendations for pre-exposure prophylaxis remain unchanged.

Vaccine should be administered IM into the deltoid muscle in older children and adults or into the vastus lateralis muscle (anterolateral thigh) in infants but never in the gluteal region as this may result in decreased response to the vaccine. The rabies vaccine and RabIg should be given at different anatomical sites on day 0 using a separate needle and syringe. For subsequent vaccine doses, the limb where the RabIg was administered can be used.

The vaccination schedule for post-exposure prophylaxis should be adhered to as closely as possible and it is essential that all recommended doses of vaccine be administered. Although there is little or no evidence, in keeping with routine immunization practice it is recommended that, if a dose of vaccine is given at less than the recommended interval, that dose should be ignored and the dose given at the appropriate interval from the previous dose. If a dose of vaccine is delayed, it...
should be given as soon as possible and the schedule resumed respecting the appropriate intervals from the latest dose. If the vaccination schedule has been altered such as there is doubt about an appropriate immune response, post-vaccination serology should be obtained 7 to 14 days after completing the vaccination series.

**Post-exposure prophylaxis of previously immunized individuals**

RabIg is not indicated and should not be given to someone who has been previously appropriately immunized as indicated below. In previously appropriately immunized individuals who require post-exposure prophylaxis, two doses of HDCV or PCECV, one administered immediately and the other 3 days later, are recommended. Appropriate rabies immunization consists of:

- Documentation of a complete course of pre-exposure or post-exposure prophylaxis with HDCV or PCECV, OR
- Documentation of complete immunization with other types of rabies vaccine or with HDCV or PCECV according to unapproved schedules with the demonstration of an acceptable concentration of neutralizing rabies antibody in serum. Refer to Serologic Testing for information regarding when serologic testing is recommended.

A complete course of HDCV or PCECV plus RabIg is recommended for those who may have received rabies vaccines in the past but do not fulfill the above criteria for appropriate vaccination. A serum sample may be collected before the initiation of post-exposure prophylaxis, and if an acceptable antibody concentration (0.5 IU/mL or greater) is demonstrated, the vaccine course may be discontinued, provided at least two doses of vaccine have been given. If in doubt, consultation with an infectious diseases or public health physician is recommended.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Some individuals with ongoing high risk of exposure to rabies such as certain veterinarians and veterinary staff, animal control or wildlife workers, those with ongoing bat exposures or those working with live rabies virus may require pre-exposure booster doses if their antibody titres fall below 0.5 IU/mL (refer to Serologic Testing for information regarding when serologic testing is recommended). People with ongoing high risk of exposure and inadequate titres should be given a booster dose of either rabies vaccine. Both HDCV and PCECV have been shown to be effective in boosting immunity in previously immunized individuals if given as a pre-exposure booster or for post-exposure management. A rapid anamnestic response is obtained regardless of whether the primary vaccine was HDCV or PCECV. Refer to Post-exposure prophylaxis of previously immunized individuals for information on the post-exposure management of these individuals.

Refer to Vaccine Administration Practices in Part 1 and Passive Immunizing Agents Part 5 for additional general information.

**SEROLOGICAL TESTING**

The Public Health Agency of Canada National Microbiology Laboratory (NML) is the Canadian rabies reference laboratory. ([https://www.nml-lnm.gc.ca/overview-apercu-eng.htm](https://www.nml-lnm.gc.ca/overview-apercu-eng.htm)) NML conducts testing on serum and cerebrospinal fluid samples from all provinces/territories in Canada with the exception of Ontario, where serological testing is performed by Public Health Ontario (PHO).

Following vaccination, neutralizing antibodies begin to develop within seven days and persist for at least two years. For testing vaccine response, NML uses a modified Fluorescent Antibody Virus Neutralization (FAVN) assay while PHO uses a modification of the Rapid Fluorescent-Focus Inhibition Test (RFFIT). Both institutions consider the antibody titre of at least 0.5 IU/mL as an acceptable correlate of protection. Protective antibodies are present immediately after passive vaccination with RabIg and have a half-life of approximately 21 days.
HEALTHY PEOPLE
Because of the excellent immune response to rabies vaccine, healthy people immunized with an appropriate regimen do not require routine antibody determinations after either pre-exposure or post-exposure rabies vaccination, unless one of the following applies:

- Pre-exposure vaccination was given by the ID route – check serology at least 2 weeks after completion of the vaccine series. If using the ID route for a booster dose, serology should be checked at least 2 weeks after the booster dose.
- The person is at ongoing high risk of exposure to rabies. Refer to People with ongoing high risk of exposure.
- There has been substantial deviation from the recommended post-exposure schedule – check serology 7 to 14 days after completing the series.
- The person has been immunized with a vaccine other than HDCV or PCECV – check serology at least 7 to 14 days after completing the series.

PEOPLE WITH ONGOING HIGH RISK OF EXPOSURE
People with ongoing high risk of exposure to the rabies virus or potentially rabid animals require periodic serology testing to ensure the persistence of circulating antibodies. If antibody levels fall below an acceptable concentration (less than 0.5 IU/mL), a booster dose of HDCV or PCECV is recommended. Serologic testing should occur at the following frequencies:

- Continuous risk (people who work with the rabies virus in a research or vaccine production laboratory) – obtain serology every 6 months.
- Frequent risk (rabies diagnostic laboratory workers; spelunkers; those who frequently handle bats; veterinarians, veterinary staff, animal control and wildlife workers in areas where rabies is enzootic) - obtain serology every 2 years.

Others who have less frequent risk of exposure to potentially rabid animals and/or whose risk is likely to be from a recognized source (such as veterinarians, veterinary staff, and animal control officers who work with terrestrial animals in areas where rabies is uncommon; veterinary students; and travellers to enzootic areas) do not require periodic serologic testing.

IMMUNOCOMPROMISED PEOPLE
If it is possible to avoid exposure, pre-exposure immunization should be deferred in immunocompromised people. If pre-exposure immunization must be given to immunocompromised individuals, antibody response should be determined. Determination of antibody response is also advisable if post-exposure vaccination is given to those whose immune response may be reduced by illness or medication. In these groups, antibody titres should be determined 7 to 14 days after completing the pre-exposure or post-exposure immunization series to ensure that an acceptable antibody concentration has been achieved. If an acceptable concentration is not obtained, revaccination with a second rabies vaccine series is recommended followed by serologic testing. Some immunocompromised people may never mount an appropriate immune response. Refer to Immunocompromised persons.

INTRAIDERMAL ADMINISTRATION
If vaccine is given by the ID route, post-immunization antibody titres should be determined at least 2 weeks after completion of the vaccine series and after booster doses to ensure that an acceptable level of protection has been achieved.
STORAGE REQUIREMENTS

HDCV (IMOVAX® Rabies): Store at +2°C to +8°C. Do not use if exposed to freezing. PCECV (RabAvert®): Store at +2°C to +8°C. Protect from light.

Once reconstituted, administer vaccine promptly.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information. Refer to Passive Immunizing Agents in Part 5 for information regarding RabIg storage requirements.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Data are not available regarding the concurrent administration of rabies vaccines with other vaccines. Other essential inactivated vaccines may be given concomitantly with rabies 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 IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

**HDCV**

Local injection site reactions such as pain, erythema, swelling, pruritus and induration at the injection site were reported in 60% to close to 90% of recipients. Mild systemic reactions such as headache, nausea, abdominal pain, muscle aches and dizziness were reported in about 6% to 55% of recipients.

**PCECV**

Local injection site reactions were reported in 11% to 57% of recipients, consisting of pain, tenderness, swelling, erythema and induration at the injection site lasting for 2 to 3 days. Systemic reactions are generally less common (i.e., 1% to 10% of recipients) and may consist of malaise, myalgia, arthralgia, headache and fever. Lymphadenopathy, nausea and rash have been reported occasionally.

**RabIg**

Local injection site pain, erythema and induration are commonly reported following administration of RabIg, as are systemic reactions such as headache and low-grade fever. The majority of reported events were mild.

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.

**HDCV**

Anaphylactic reactions have occurred in up to 1 in 10,000 vaccine recipients. Systemic allergic reactions characterized by generalized urticaria and accompanied in some cases by arthralgia, angioedema, fever, nausea and vomiting have been reported. These reactions are uncommon in people receiving primary immunization but have occurred in up to 7% of those receiving a booster dose, with onset after 1 to 21 days. Such reactions have been shown to follow the development of IgE antibodies to beta propiolactone-altered human serum albumin in the vaccine. Neurologic complications are rare, but three cases of neurologic illness resembling Guillain-Barré syndrome,
which resolved without sequelae within 12 weeks, were reported in the early 1980s but causal associations have not been established.

**PCECV**
Anaphylaxis following immunization with PCECV has been reported. Temporally associated neurologic events have also been very rarely reported but causal association with vaccination has not been established.

**RabIg**
Local pain, erythema and induration are common. Headache and low-grade fever may follow administration of RabIg. The majority of reported events were mild.

**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_guide/index-eng.php) and Vaccine Safety in Part 2 for additional information about AEFI reporting.

**CONTRAINDICATIONS AND PRECAUTIONS**
There are no contraindications to the use of rabies vaccine or RabIg after significant exposure to a proven rabid animal; however, care should be taken if post-exposure prophylaxis is to be administered to persons who are hypersensitive to the products or to any ingredient in the formulation or component of the container. Expert opinion should be sought in the management of these individuals.

Persons with a proven history of hypersensitivity to the vaccine or any component of the vaccine or its container should not be given the vaccine for pre-exposure immunization if possible. For specific advice, consult an allergy specialist. 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 rabies vaccines and rabies immune globulin, potential allergens include:

- **IMOVAX® Rabies**: neomycin, phenol red
- **RabAvert®**: amphotericin B, chick protein, chlortetracycline, neomycin, polygeline (gelatin)
- **IMOGAM® Rabies**: latex in vial stopper

Persons with egg allergies are not necessarily at increased risk of a hypersensitivity reaction to PCECV. However, for pre-exposure vaccination, an alternative vaccine, HDCV, should be given to persons with a history of hypersensitivity reactions to egg or egg products. If an alternative vaccine is not available, post-exposure prophylaxis using PCECV should be administered to a person with a hypersensitivity to egg with strict medical monitoring. Facilities for emergency treatment of anaphylactic reactions should be available. Refer to Anaphylactic Hypersensitivity to Egg and Egg Related Antigens in Part 2 for additional information.

Persons with specific IgA deficiency have increased potential for developing antibodies to IgA after receipt of blood products including rabies immune globulin and could have anaphylactic reactions to subsequent administration of blood products containing IgA, such as RabIg.

Infiltration of wounds with RabIg in some anatomical sites (finger tips) must be carried out with care in order to avoid increased pressure in the tissue compartment.

A history of a serious allergic or neuroparalytic reaction occurring during the administration of rabies vaccine poses a significant dilemma in the post-exposure situation. The risk of rabies developing must be carefully considered before a decision is made to discontinue immunization. The use of corticosteroids to attenuate the allergic response may inhibit the immune response to the vaccine. The existing titre of
rabies antibodies should be determined and expert opinion in the management of these individuals should be sought promptly.

Pregnancy is not a contraindication to post-exposure prophylaxis with rabies vaccine and RabIg, but it would be prudent to delay pre-exposure immunization of pregnant women unless there is a substantial risk of exposure.

Pre-exposure immunization with rabies vaccine should be postponed in persons with moderate or severe acute illness. Persons with minor acute illness (with or without fever) may be vaccinated. Post-exposure vaccination should not be postponed.

Refer to Contraindications, Precautions and Concerns in Part 2 and Passive Immunizing Agents in Part 5 for additional general information.

**DRUG INTERACTIONS**

Radiation therapy, chloroquine, corticosteroids, and other immunosuppressive agents may diminish the efficacy of rabies vaccine. There is no evidence that interference occurs with antimalarial drugs other than chloroquine.

**OTHER CONSIDERATIONS**

**INTERCHANGEABILITY OF VACCINES**

Wherever possible, an immunization series should be completed with the same product. However, if this is not feasible, PCECV and HDCV are considered interchangeable. People who require a booster dose of rabies vaccine can be given PCECV or HDCV regardless of the vaccine used for the initial vaccination series. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

**SELECTED REFERENCES**


PART 4

ROTAVIRUS VACCINE

- Epidemiology
- Preparations Available for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th>Rotavirus (RV) is the most common cause of severe gastroenteritis in infants and young children.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most children are infected by 5 years of age.</td>
</tr>
<tr>
<td></td>
<td>First infection usually does not lead to permanent immunity.</td>
</tr>
<tr>
<td></td>
<td>Responsible for more than 500,000 deaths in young children each year, worldwide.</td>
</tr>
<tr>
<td></td>
<td>RV vaccine efficacy against diarrhea of any severity in developed world settings is 74% to 87%; efficacy against severe diarrhea is 85% to 98%.</td>
</tr>
<tr>
<td></td>
<td>RV vaccine reduces physician and emergency room visits for diarrhea and hospital admissions for RV diarrhea.</td>
</tr>
<tr>
<td></td>
<td>RV vaccines are well tolerated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Recommended for infants (including healthy, non-hospitalized, premature infants) starting at 6 weeks of age.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Should not be given to known immunocompromised infants without consultation with a medical expert.</td>
</tr>
<tr>
<td></td>
<td>Not recommended for infants with a history of intussusception.</td>
</tr>
</tbody>
</table>

| How  | Administer first dose between 6 weeks and 14 weeks. To optimize protection, rotavirus vaccine should be initiated as soon after 6 weeks of age as feasible; |
|------|----------------------------------------------------------------------------------------------------------------|---|
|      | Rot-1 (Rotarix™) requires 2 doses (at least 4 weeks apart) and Rot-5 (RotaTeq™) requires 3 doses (4-10 weeks apart). |   |
|      | Rotavirus vaccines can be given with all the routine infant vaccines at 2 and 4 or 2, 4 and 6 months of age.    |   |

| Why  | RV is the most common cause of severe gastroenteritis in infants and young children.                           |
Since the publication of the 2006 Canadian Immunization Guide two rotavirus vaccines have become available for infants aged 6 weeks to 8 months.


EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Rotavirus (RV) is a non-enveloped virus belonging to the Reoviridae family. Serotype is defined by two structural proteins: the G protein and P protein. There are multiple variants of both G and P proteins, and since these two proteins can segregate independently there are numerous rotavirus serotypes. Although, the prevalence of rotavirus serotypes varies, G1P[8] is often the predominant strain in developed regions (e.g., North America, Europe and Australia).

Reservoir
Humans

Transmission
RV is transmitted through the fecal-oral route and there is some evidence that RV can also be transmitted through the respiratory route. The virus is stable in the environment; therefore, it can be transmitted through fomites and environmental surfaces. Household transmission of RV gastroenteritis is common, with at least one family member experiencing gastroenteritis in 47% of RV cases.

Rotavirus is highly infectious due to the small infective dose, high viral concentrations in stool, and prolonged viral shedding. Viral shedding can begin a few days prior to the onset of symptoms, and can continue until 21 days after the onset of illness. Asymptomatic shedding has been described. RV has an incubation period of 18 hours to 3 days.

Risk factors
Immunocompromised children are at an increased risk of severe, prolonged and even fatal gastroenteritis. In a study in the United States (US), risk factors associated with severe illness included: low birth weight (less than 2,500 grams), attendance at a child care facility, recipients of Medicaid or being without health insurance, another child less than 24 months of age in the household, maternal age less than 25 years, and a mother with less than a high school education. By contrast, a study of children in the Toronto area found that socioeconomic factors, parental and marital status, daycare attendance and ethnicity did not influence the rate of rotavirus hospitalizations. There is no evidence to suggest the risk for RV gastroenteritis and its outcomes varies by region within Canada.

Among adults in the US, RV infection causes gastroenteritis primarily in travellers returning from developing countries, parents and persons caring for children with RV gastroenteritis, immunocompromised persons, and older adults. Outbreaks of RV gastroenteritis, associated with considerable morbidity, have been reported in long term care facilities.

The impact of breastfeeding on the incidence and severity of RV is unclear. Several studies have shown breastfeeding as protective against symptomatic RV infection in the first 6 to 12 months of life; however, there was no protection when assessed over the first two years of life, suggesting that breastfeeding may postpone infection to a later age. In a Canadian study, 25% of children admitted to
In Canada and other temperate regions, the majority of RV cases occur in late winter and early spring.

Spectrum of clinical illness
RV infections can vary in presentation, including asymptomatic infection, mild disease, severe dehydration, and death. There is typically an acute onset of fever and vomiting. This is usually followed by diarrhea, which generally lasts five to seven days. Some children may only experience vomiting. In general, few clinical or epidemiologic features distinguish the child with RV diarrhea from those with diarrhea due to other causes; although the presence of all three symptoms of fever, vomiting and diarrhea is reported more commonly with RV that with other gastrointestinal viruses.

In the first three months of life, illness is generally mild as a result of passively transferred maternal RV antibodies. In infants and children three months to five years of age, there is a spectrum of disease from mild gastroenteritis to dehydration with shock, electrolyte imbalance and, very rarely in Canada, death. Disease is often most severe in children aged 3 months to 24 months, the majority of hospitalizations for RV (63%) occur in children less than 2 years of age. Although RV gastroenteritis is typically self-limited, it is associated with considerably more health care resource utilization than gastroenteritis due to other causes.

Children can be re-infected because immunity to RV is incomplete following infection; however, subsequent courses of RV gastroenteritis are typically milder than initial infection.

DISEASE DISTRIBUTION

Incidence/prevalence

Global
RV infections are extremely common worldwide. By five years of age most children will have experienced at least one RV infection. This is true in both developed and developing countries, suggesting that improved sanitation does not decrease RV transmission. However, mortality due to RV infection is much higher in developing countries. The World Health Organization (WHO) estimates that 453,000 children aged less than 5 years died in 2008 from vaccine-preventable RV infections; most of these children live in low-income countries. Globally, these 453,000 child RV deaths account for approximately 5% of all child deaths.

National
In Canada, RV is a common cause of gastroenteritis in children, accounting for 10% to 40% of all childhood gastroenteritis. Based upon Canadian data, it is estimated that RV is associated with considerable health care resource utilization. Approximately 36% of children with RV gastroenteritis see a physician, 15% visit an emergency department, and 7% require hospitalization. RV causes the majority of childhood gastroenteritis requiring hospitalization; between 1 in 62 to 1 in 312 children less than 5 years of age will require hospitalization for RV. Parents of children with RV gastroenteritis are more likely than parents of children with non-RV gastroenteritis to miss work and out-of-pocket costs are considerable for families of affected children, even for cases of low severity. One Canadian study estimated a total societal cost of $674.80 for each case of RV requiring a visit to the emergency room.
PREPARATIONS AVAILABLE FOR USE CANADA

ROTAVIRUS VACCINES

- RotaTeq® (live, oral, pentavalent rotavirus vaccine), Merck Canada Inc. (Rot-5)
- ROTARIX™ (live, oral, monovalent, attenuated human rotavirus vaccine), GlaxoSmithKline Inc. (Rot-1)

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

RV vaccine efficacy against diarrhea of any severity in developed world settings is 74% to 87% and efficacy against severe diarrhea is 85% to 98%. Data on the efficacy of an incomplete vaccine series is limited but does suggest that infants vaccinated during the RV season may derive substantial early protection against severe RV disease despite not having completed a full series of immunization.

As of June 2011, rotavirus vaccine had been introduced into the national childhood immunization programs of 14 (44%) of 32 countries in Latin America; numerous other countries have adopted programs as well. Countries with routine rotavirus immunization programs, such as the United States, Australia, Brazil and Mexico have seen reductions in the number of infants and children needing hospitalization or emergency department care for RV disease by about 85%.

IMMUNOGENICITY

Correlation between antibody responses and protection from RV disease has not been established. In clinical trials, seroconversion rates were significantly higher in vaccine recipients than placebo groups. Most infants developed antibodies to the vaccine after completing a vaccine series.

RECOMMENDATIONS FOR USE

HEALTHY INFANTS

Rotavirus vaccines are recommended for infants starting at 6 weeks - 14 weeks of age. The vaccination series should be completed before 8 months of age. RotaTeq™ requires 3 doses (4-10 weeks apart); Rotarix™ requires 2 doses (at least 4 weeks apart). To optimize protection, rotavirus vaccine should be initiated as soon after 6 weeks of age as feasible. Rotavirus vaccines can be given with the routine vaccines at 2 and 4 or 2, 4 and 6 months of age. If catch-up is needed, the first dose of Rotarix™ may be given up to 20 weeks of age.

Infants with a history of intussusception

Refer to Contraindications and Precautions.

Infants with a history of previous rotavirus infection

Infants who have had RV gastroenteritis before receiving the full course of RV vaccinations should still initiate or complete the 2 or 3 dose vaccine series, because the initial infection frequently provides only partial immunity.
PREGNANCY AND BREASTFEEDING

Infants living in households with pregnant women can be vaccinated. The risk of infection and disease from vaccine virus is low because most women of childbearing age have pre-existing immunity to RV through natural exposure and RV infection during pregnancy is not known to pose a risk to the fetus.

The efficacy of RV vaccines is similar among infants who are breastfed and those who are not; therefore, breastfed infants can receive RV vaccine.

Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised patient, approval from the infant’s attending physician should be obtained and referral to a consultant with expertise in immunization and/or immunodeficiency is advised. Severe cases of RV gastroenteritis have been reported after vaccination of infants with Severe Combined Immunodeficiency so RV vaccine is contraindicated in these infants.

Household contacts

Following administration of RV vaccine, viral antigen shedding in the stool may be detected in some vaccinees. Data on the potential for transmission of vaccine virus from vaccinees to household contacts has not been published; however, many experts believe that the benefit of protecting immunocompromised household contacts from naturally occurring RV by immunizing infants outweighs the theoretical risk of transmitting vaccine virus. Thus, infants living in households with persons who have or are suspected to have immunosuppressive conditions or who are receiving immunosuppressive medications can be vaccinated. To minimize the risk of transmission of RV vaccine virus, careful hand washing should be used after contact with the vaccinated infant, especially after handling feces (e.g., after changing a diaper), and before food preparation or direct contact with the immunocompromised person.

Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

TRAVELLERS

Infants who are travelling (particularly to developing countries) should receive RV vaccine as appropriate for age. Refer to Immunization of Travellers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose of Rot-5 vaccine is 2.0 mL. Each dose of Rot-1 vaccine is 1.5 mL.

Route of administration

RV vaccines are for oral administration only and must not be injected. All doses should be given in a clinic/office setting under the direction of a health care provider.
Schedule

Healthy infants
Vaccination may be provided with either RV vaccine:

- Rot-5 vaccine is given as 3 separate 2.0 mL oral doses
- Rot-1 vaccine is given as 2 separate 1.5 mL oral doses

The first dose of RV vaccine should be given between 6 weeks and 14 weeks of age. Vaccination should not be initiated in infants aged 15 weeks or older as the safety of providing the first dose of RV vaccine in older infants is not known. The minimum interval between doses of RV vaccine is 4 weeks. All doses of RV vaccine should be administered by age 8 months.

For infants in whom the first dose of RV vaccine is inadvertently administered at age 15 weeks or older, the rest of the RV vaccine vaccination series should be completed with a minimum of 4 weeks between each dose and all doses should be administered by age 8 months plus 0 days. If an incomplete dose is administered for any reason (e.g., infant spits or regurgitates the vaccine) a replacement dose should NOT be administered.

SEEROLOGICAL TESTING

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

STORAGE REQUIREMENTS

Store and transport RV vaccine at +2°C to +8°C and do not freeze. Protect from light. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

RV vaccine may be administered concomitantly with routine infant vaccines. The impact of concomitant administration of Rot-1 vaccine with diphtheria/tetanus/acellular pertussis/hepatitis B/inactivated poliomyelitis/Haemophilus influenzae type b (DTaP-HB-IPV-Hib), DTaP, DTaP-IPV, Hib, DTP(whole cell)-HB, HB, pneumococcal conjugate, meningococcal serogroup C conjugate, and IPV vaccines have been evaluated and the immune responses and safety profile have been shown to be unaffected by concomitant administration. Concomitant administration of Rot-1 vaccine and oral poliomyelitis vaccine (OPV) may result in reduced immune response to Rot-1 vaccine; therefore, Rot-1 vaccine and OPV should be given at least 2 weeks apart. OPV is not available in Canada.

Live oral vaccines, like RV vaccine, may be given concomitantly with, or at any time before or after, live parenteral vaccines. This is an exception to the general rule to give live parenteral vaccines either simultaneously or at least four weeks apart. 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 large clinical trials, RV vaccines did not exhibit many differences in adverse events compared to placebo. In one large study, infants who received Rot-5 vaccine had a small, but statistically significant
increased rate of diarrhea in the 7-day period after vaccination (10% to 18% versus 6% to 15%). Vaccinees also had a small, but statistically significant, greater rate of vomiting (12% versus 10%).

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. Serious adverse events were not found to be different between RV vaccine and placebo in clinical trials. Among infants given Rot-5 vaccine or placebo in clinical trials, the incidence of serious adverse events was 2.4% in vaccinees and 2.6% in placebo recipients, which was not significantly different. In a study of Rot-1 vaccine or placebo recipients, at least 1 serious adverse event was reported in 1.7% of vaccinees and 1.9% of placebo recipients.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Intussusception

Intussusception in infancy is rare, peaking in the first year of life and occurring at a background rate of about 34 infants per 100,000 per year. In 1998, a RV vaccine (RotaShield®, Wyeth-Ayerst) was recommended for routine vaccination of US infants. In the first 9 months after introduction of the vaccine into routine programs, more than 600,000 children were immunized and 15 of these children developed intussusceptions in the 2-week period immediately following vaccine administration. Subsequent epidemiologic investigations confirmed the increased incidence following vaccination, especially in infants receiving their first dose at age greater than 3 months. As a result, the vaccine was withdrawn from the US market. When the next generation of RV vaccines was developed, very large safety trials were conducted and administration of the first dose of vaccine was limited to infants less than 90 days of age, before the period when intussusception is most common, to ensure greater safety than with the previous vaccine.

The risk of intussusception was evaluated in large safety and efficacy trials of Rot-1 and Rot-5 vaccines, and no evidence of clustering of cases of intussusception was observed within a 7-day or 14-day window after vaccination for any dose. Of 71,725 infants enrolled in Rot-5 vaccine trials, six cases of intussusception were observed in the Rot-5 vaccine group versus five cases in the placebo group within 42 days of any vaccine dose. Of 63,225 infants enrolled in Rot-1 vaccine trials, six cases of intussusception occurred within 31 days of either dose of vaccine in the Rot-1 vaccine group and 7 cases in the placebo group. Across all clinical trials, the reported frequency of intussusception was 0.047% for Rot-1 vaccine recipients and 0.05% for placebo recipients. None of these differences were statistically significant.

There is new evidence from post-marketing surveillance for intussusception following the introduction of routine infant RV immunization programs in Mexico, Brazil, and Australia suggesting a small increased risk of IS in infants following RV vaccine. In Mexico, receipt of Rot-1 was associated with a small excess risk of IS in the 7 days following dose 1 of approximately 1:51,000 vaccinated infants. A small but less consistent increased risk was observed following dose 2. Surveillance in Brazil, where OPV is used, did not demonstrate an increased risk of IS in the 7 days following the first dose of Rot-1 but did demonstrate a small excess risk of IS in the 7 days following dose 2 of 1:68,000 vaccinated infants. In Australia, post-marketing surveillance has demonstrated a small excess risk of IS following the first dose of either Rot-1 or Rot-5 of 2: 100,000 (or 1:50,000) vaccinated infants. The small excess risk of IS observed in Brazil, Mexico and Australia has not been demonstrated in the US. Analysis conducted by the Vaccine Safety Data Link in the US following administration of over 300,000 first doses and 750,000 total doses of Rot-5 identified 56 cases of IS, 30 in vaccinated infants and 26 in infants who had not received Rot-5. After adjustment for age, no increased risk of IS was demonstrated in either the first 7 or 30 days following dose 1 in the US. The Global Advisory Committee on Vaccine Safety (GACVS) has reviewed the data and indicated that the benefits of rotavirus vaccine outweigh the potential risks.

Parents should be informed of the small risk of IS following RV vaccine observed in some countries.
and counseled regarding the signs and symptoms of IS and the importance of seeking medical care should symptoms develop. Providers should report any observed case of IS.

Hematochezia
In infants, hematochezia (bloody stools) in conjunction with abdominal pain is associated with intussusception. No significant increase in the frequency of bloody stools has been found following use of either RV vaccine.

Kawasaki disease
During a large clinical trial of more than 30,000 children, there were 5 cases of Kawasaki disease in the vaccinated group. The GACVS reviewed all available data from the US (where Rot-5 vaccine is used) and the European Union (where Rot-1 vaccine is used), to determine if there was any association between Kawasaki disease and RV vaccines, and concluded there was no evidence for a causal association between RV vaccines and Kawasaki disease.

Seizures
In a study of 63,225 infants, 16 infants in the group receiving Rot-1 vaccine had adverse events coded as convulsions compared to 6 subjects in the group receiving placebo. Although this difference was statistically significant, no difference between vaccine and placebo recipients was noted when all convulsion-like events were combined. In studies of Rot-5 vaccine there was no difference in the frequency of seizures in vaccine and placebo recipients.

Porcine circovirus (PCV)
Components of porcine circovirus-1 (PCV-1) were found to be present in Rot-1 vaccine when an independent US academic research team applied a new technology for detecting viral genetic material. Subsequently, components of PCV-1 and porcine circovirus-2 (PCV-2) were also found in Rot-5 vaccine. Health Canada is reviewing information regarding the presence of PCV-1 and PCV-2 DNA in both Rot-1 and Rot-5 vaccines. Porcine circovirus does not cause illness in humans. There is no evidence that the presence of PCV-1 or PCV-2 in RV vaccines poses a safety risk to vaccinees, and the WHO and the US Food and Drug Administration have recommended that the vaccines continue to be used.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)
Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Intussusception in the first 7 to 14 days following any dose of RV vaccine
- 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.


CONTRAINDICATIONS AND PRECAUTIONS
RV vaccines are contraindicated in infants with Severe Combined Immunodeficiency Disease (SCID), a history of anaphylaxis after previous administration of the vaccine and in infants with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer to Table 1 in Components of Immunizing Agents Available in Canada in Part 1 for lists of all vaccines available for use in Canada and their contents. There is no longer latex in the stopper of Rotarix vaccine.

Previous history of intussusception
Infants with a history of intussusception should not be given RV vaccines; however, there is no evidence that children who have a history of intussusception are at a higher risk of another
intussusception after receiving RV vaccine. The recommendation to not administer RV vaccine to children who have previously had intussusception is based on expert opinion, considering the following evidence: about 4% of infants with intussusception will have another episode in the following year; an earlier generation RV vaccine was associated with increased rates of intussusception and there is an incomplete understanding of the pathogenic mechanisms underlying that increased risk; and there is no data on use of the vaccine in infants who have had intussusception as children with a history of intussusception were excluded from immunogenicity and efficacy trials.

Immunodeficiency

Infants known or suspected to be immunocompromised should not receive RV vaccine without consultation with a physician with expertise in immunization and/or immunodeficiency.

Individuals with Severe Combined Immunodeficiency Disease (SCID) should not receive either RV vaccine. Cases of gastroenteritis associated with RV vaccine virus have been reported in infants with SCID.

Infants with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive RV vaccine unless their immune competence has been established.

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

Other medical conditions

RV vaccines can be administered to infants with minor acute illness, with or without fever.

In infants with moderate-to-severe gastroenteritis, RV vaccine should be deferred until the condition improves unless deferral will result in scheduling of the first dose after 14 weeks plus 6 days of age. Infants with mild gastroenteritis can be vaccinated. The immunogenicity and efficacy of the RV vaccines has not been studied in infants with concurrent gastroenteritis; however, immunogenicity and effectiveness of the vaccine may theoretically be reduced.

The safety and efficacy of RV vaccines has not been established in children with pre-existing chronic gastrointestinal conditions. However, infants with chronic gastrointestinal disease who are not considered immunocompromised are likely to benefit from RV vaccine and can be vaccinated.

Infants with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception should not receive RV vaccine.

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

DRUG INTERACTIONS

There are no restrictions on the infant’s consumption of food or liquid, including breast milk, either before or after vaccination with RV vaccine.

No safety or efficacy data are available for the administration of RV vaccines to infants who have recently received immune globulins or other blood products. In theory, such infants might have a reduced immunologic response to a dose of RV vaccine. However, 2 or 3 doses of vaccine (depending on the product) are administered in the full RV vaccine series, and no increased risk for adverse events is expected. Therefore, RV vaccine may be administered at any time before, concurrent with, or after administration of immune globulins or other blood products.
OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

There are no data on safety, immunogenicity, or efficacy when Rot-1 vaccine is administered as the first dose and Rot-5 vaccine is used as the second dose or vice versa. Given that the two vaccines differ in composition and schedule, the vaccine series should be completed with the same product whenever possible. However, in the event that the product used for a previous dose(s) is unknown, the series should be completed with the available product. If any dose in the series was Rot-5 vaccine, a total of 3 doses of vaccine should be administered.

SELECTED REFERENCES


PART 4

RUBELLA VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Up to 50% of rubella infections are subclinical; if a woman develops rubella during pregnancy, it can result in Congenital Rubella Syndrome (CRS) in the infant. Rubella vaccine is available as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine. Over 97% of individuals develop immunity after one dose of rubella vaccine. Reactions to MMR and MMRV vaccine are generally mild and transient and include pain and redness at the injection site, low-grade fever and rash. |
| Who | Rubella-containing vaccine is recommended for routine immunization of healthy children and for immunization of children and adolescents who missed rubella immunization on the routine schedule. Rubella-containing vaccine is recommended for all susceptible adults. Priority groups for rubella immunization include: Non-pregnant women of childbearing age - especially foreign-born, and staff and students in educational settings People who work with children (e.g., child care workers, teachers) Health care workers Travellers to rubella-endemic areas |
| How | **Routine childhood immunization:** administer one dose of rubella-containing vaccine at 12 to 15 months of age. MMRV vaccine may be used in healthy children aged 12 months to 12 years. **Susceptible children, adolescents and adults:** administer one dose of MMR vaccine |
| Why | Rubella occurs worldwide and is highly communicable. Rubella during pregnancy can result in CRS in the infant. MMR and MMRV vaccines are safe and effective. |
Since the publication of the 2006 Canadian Immunization Guide a new combined multivalent vaccine (measles-mumps-rubella-varicella vaccine [MMRV]) has become available for children aged 12 months to 12 years.


EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Rubella (German measles) is caused by rubella virus, a ribonucleic acid (RNA) virus of the Togaviridae family.

Reservoir
Humans

Transmission
Rubella virus is highly communicable and is transmitted by droplet spread or direct contact with nasopharyngeal secretions of infected people. Transplacental transmission from an infected mother to her fetus during pregnancy may result in Congenital Rubella Syndrome (CRS) in the infant. Infants with CRS may shed the virus in their urine and nasopharyngeal secretions for 1 year or more. The incubation period for rubella is from 14 to 17 days (range, 14 to 21 days). The period of communicability extends from 1 week before to at least 4 days after the onset of rash. People who recover from rubella have lifetime immunity.

Risk factors
People of any age who have not been successfully vaccinated or have not had rubella disease are at risk of being infected. In Canada, routine infant immunization programs have resulted in sustained high rates of immunity in the general population, but the risk of limited transmission resulting from importation still exists.

Seasonal/temporal pattern
Historically, the incidence of rubella peaked in the spring and winter months in temperate zones; rubella is now limited to sporadic cases and outbreaks.

Spectrum of clinical illness
Rubella results in a transient erythematous rash, post-auricular and suboccipital lymphadenopathy, arthralgia and low-grade fever. As symptoms are non-specific, it may be mistaken for infection due to other viruses. Adult infection is frequently accompanied by transient polyarthralgia or polyarthritis. Serious complications are rare, and up to 50% of infections are subclinical.

Rubella infection in pregnancy may give rise to CRS, which can result in miscarriage, stillbirth and fetal malformations, including congenital heart disease, cataracts, deafness and mental retardation. Fetal infection can occur at any stage of pregnancy, but the risk of fetal damage following maternal infection is particularly high in the earliest months after conception (85% in the first trimester) with progressive diminution of risk thereafter, and it is very uncommon after the 20th week of pregnancy. Infected infants who appear normal at birth may later show eye, ear or brain damage.
DISEASE DISTRIBUTION

Incidence/prevalence

Global
Rubella occurs worldwide; however, during the last decade, rubella vaccination programs have greatly reduced incidence rates of rubella in most industrialized countries. By 2008, 66% of World Health Organization (WHO) member countries had included rubella in their childhood immunization schedule. In 2003, the Pan American Health Organization established a goal to eliminate indigenous rubella and CRS from the WHO region of the Americas by 2010. By October 2008, all 38 countries and territories in the Americas, with the exception of Haiti, had introduced MMR vaccine into routine immunization schedules. Beginning in 2009, Haiti planned to introduce measles-rubella (MR) vaccine into its routine immunization program after completion of a one-time MR mass vaccination campaign. In the region of the Americas, the average annual number of cases for the period of 2003 to 2008 dropped 92% compared with the annual number of cases for the period of 1997 to 2002.

National
In Canada, the MMR immunization program for infants was introduced in April 1983 and has resulted in sustained high rates of immunity in the general population. In addition, measles elimination strategies employed since the mid-1990s have indirectly resulted in a reduction in the proportion of the population that is rubella-susceptible because of the use of rubella-containing vaccines for the two dose routine immunization program and measles elimination catch-up campaigns.

The average annual number of rubella cases reported in Canada decreased from approximately 5,300 (1971-1982), to about 1,800 (1983-1997), to less than 30 (1998-2004). From 2006 to 2010, on average fewer than 5 cases were reported annually.

In 2005, the incidence rate of rubella in Canada increased to about 10 per 1,000,000 with the majority of cases occurring in a large outbreak in southwestern Ontario (refer to Recent outbreaks). The average annual incidence rate of rubella has decreased from 2.1 per 1,000,000 in 1998 to 0.29 per 1,000,000 in 2010.

From 1996 to 2010, fewer than 3 cases of CRS were reported each year in Canada and most of these infants were born to foreign-born women. There have been no CRS cases due to exposure to rubella in Canada since 2000. Since that time, the six CRS cases reported were imported from other countries.

RECENT OUTBREAKS
In the two decades following the 1983 introduction of routine infant rubella immunization, epidemics of rubella continued to occur every 3 to 10 years. Many of these outbreaks, including one involving over 3,900 cases in Manitoba in 1997, differentially affected males aged 15 to 24 years of age who were not immunized because of pre-1983 selective rubella immunization programs of girls only in some jurisdictions. Since the late 1990s, outbreaks have largely been restricted to isolated clusters of unimmunized people, including those who decline immunization for religious or philosophical reasons.

In 2005, there was a rubella outbreak involving 309 laboratory confirmed cases in an unimmunized southwestern Ontario community. The outbreak was attributed to under-vaccination of persons in a community that is philosophically opposed to immunization. Over 60% of the cases were in unimmunized children aged 5 to 14 years. Ten cases involved pregnant women, but no cases of CRS were reported. As a result of high immunization rates in the general population, spread of the outbreak to the surrounding community was limited.
Figure 1: Reported number of cases and incidence rates of rubella in Canada, 1979 to 2010

PREPARATIONS AVAILABLE FOR USE IN CANADA

RUBELLA-CONTAINING VACCINES

- **M-M-R® II** (live, attenuated combined measles, mumps and rubella vaccine), Merck Canada Inc. (MMR)
- **PRIORIX®** (live, attenuated, combined measles, mumps and rubella vaccine), GlaxoSmithKline Inc. (MMR)
- **PRIORIX-TETRA®** (live, attenuated combined measles, mumps, rubella and varicella vaccine), GlaxoSmithKline Inc. (MMRV)

In Canada, rubella vaccine is only available in combination with measles and mumps vaccine (MMR) or measles, mumps and varicella vaccine (MMRV). In many countries outside of Canada, measles vaccine alone is given and rubella vaccination is not offered.

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

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

The duration of protection following immunization with rubella-containing vaccine is not known, but studies indicate that the duration of both cellular and humoral immunity exceeds 20 years. Asymptomatic rubella re-infection, manifest by a rise in antibody, has been observed in some vaccinees. Asymptomatic re-infection has also been observed in women with naturally acquired immunity associated with very low antibody titres. There are no data regarding the efficacy of MMRV vaccine.
IMMUNOGENICITY
In clinical trials, 95% or more of vaccinees aged 12 months and older developed serologic evidence of rubella immunity after a single dose of rubella-containing vaccine. Antibody titres are generally lower than those observed in natural rubella infection. Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies following MMRV vaccinations are under evaluation.

RECOMMENDATIONS FOR USE

CHILDREN (12 months to 17 years of age)
One dose of rubella-containing vaccine should be given for routine immunization of children and for immunization of children and adolescents who missed rubella immunization on the routine schedule. MMRV vaccine may be used in children aged 12 months to 12 years.

ADULTS (18 years of age and older)
Adults who do not have documented evidence of receiving rubella-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed rubella infection should be immunized with one dose of MMR vaccine.

Rubella immunization recommendations differ from measles and mumps recommendations. Because the available preparations all contain measles, mumps and rubella, extra rubella vaccinations may be administered when following the recommendations for measles and mumps vaccination.

Susceptibility and immunity
Individuals who have one or more of the following are considered immune to rubella. Individuals who do not have ANY of the following are considered susceptible to rubella:

- Documented evidence of immunization with a rubella-containing vaccine on or after the first birthday
- A history of laboratory confirmed rubella infection
- Laboratory evidence of immunity

PRIORITY GROUPS
The following groups are priorities for rubella immunization:

- **Susceptible women of childbearing age** should be vaccinated before pregnancy or post-partum. Refer to [Pregnancy and breastfeeding](#).
- **Susceptible non-pregnant, foreign-born women of childbearing age** from countries where rubella vaccine is not in use should be immunized with MMR vaccine as soon as possible after entry to Canada. Refer to [Persons new to Canada](#).
- **Susceptible non-pregnant women of childbearing age in educational settings** (e.g., schools, colleges, and universities) should be immunized with MMR vaccine because of their relatively high risk of exposure.
- **Susceptible people who work with children** (e.g., child care workers, teachers) should be immunized with MMR vaccine because of their relatively high risk of exposure.
- **Susceptible health care workers** should receive one dose of MMR vaccine. Refer to [Workers](#).
- **Susceptible travellers** to rubella-endemic areas should receive one dose of rubella-containing vaccine. Refer to [Travellers](#).
SECOND DOSE OF VACCINE
A second dose of MMR or MMRV vaccine (as appropriate for age and risk factors) may be recommended for measles and mumps protection (MMR and MMRV) and varicella protection (MMRV) in certain people. Although a second dose of the rubella component is not considered necessary for elimination of CRS, it is not harmful and may benefit the 1% to 5% of people who do not respond to primary immunization. Refer to Measles Vaccine, Mumps Vaccine and Varicella (Chickenpox) Vaccine in Part 4 for additional information and to Schedule.

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, unless known to be immune based on laboratory testing. MMR or MMRV vaccine as appropriate may be given regardless of possible previous receipt of the vaccine because additional adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING
Immunity to measles, mumps and rubella should be reviewed in women of reproductive age, and vaccination should be recommended to non-pregnant susceptible women. Ideally, the immunization status of women intending to become pregnant should be reviewed and vaccines updated as necessary prior to conception. Women should delay pregnancy by at least 28 days following vaccination with a live vaccine.

MMR and MMRV vaccines should generally not be given during pregnancy because of the theoretical risk of disease transmission to the fetus; however, there is no evidence demonstrating a teratogenic or other risk from such vaccines. In one study, there was no evidence of CRS in any of the offspring of 226 women inadvertently vaccinated during pregnancy. Inadvertent immunization with MMR vaccine is not a reason for pregnancy termination. In some situations, potential benefits of MMR vaccination may outweigh risks such as during measles or rubella outbreaks, in which case vaccination may be considered.

Women who are breastfeeding can be vaccinated with MMR vaccine.

Refer to Contraindications and Precautions. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

PERSONS/RESIDENTS IN HEALTH CARE INSTITUTIONS
Susceptible residents of long-term care facilities should receive measles, mumps and rubella-containing vaccine as well as all routine immunizations appropriate for their age and risk factors. Refer to Immunization of Persons/Residents in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS
In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised person with a live vaccine, approval from the individual’s attending physician should be obtained before vaccination. For complex cases, referral to a physician with expertise in immunization or immunodeficiency or both is advised. Refer to Immunocompromised persons in Measles Vaccine in Part 4 for additional information.

Household contacts
Susceptible household contacts of immunocompromised people should receive a rubella-containing vaccine as appropriate for age and risk factors.
Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional information.

PERSONS WITH CHRONIC DISEASES

Neurologic disorders
People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including MMR or MMRV vaccine. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional general information.

TRAVELLERS
Protection against rubella is important for people planning travel to rubella-endemic areas. Susceptible travellers should receive one dose of rubella-containing vaccine.

Refer to rubella incidence rates in WHO member countries for additional information. (http://www.who.int/immunization/monitoring_surveillance/en/)

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. In many countries outside of Canada, mumps and rubella vaccines are in limited use and measles vaccine alone is given. A Canadian study showed that more than one-third of new immigrants and refugees, particularly women, were susceptible to measles, mumps, or rubella.

Unless known to be immune to rubella because of prior serology or documentation of a dose of rubella-containing vaccine, rubella-containing vaccine should be given to persons new to Canada; pre-immunization serology is not needed. Unless there is a contraindication to use, rubella-susceptible people should be immunized with one dose of a measles-mumps-rubella-containing vaccine as soon as possible after entry to Canada. Foreign-born women of childbearing age from countries where rubella-containing vaccine is not in use should be a priority. Susceptible women who are pregnant should receive MMR vaccine after delivery. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS
It is recommended that all health care workers be immune to rubella. Health care workers who do not have documented evidence of receiving one dose of rubella-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed rubella disease should receive one dose of MMR vaccine. Non-immune people who work with children (e.g., child care workers, teachers) and non-immune, non-pregnant female workers of childbearing age in educational settings are priorities for rubella immunization. Refer to Immunization of Workers in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION
Post-exposure MMR vaccination does not prevent or alter the clinical severity of rubella after exposure; however, if exposure to rubella does not cause infection, post-exposure vaccination with MMR vaccine should induce protection against subsequent infection. There is no evidence of increased risk of adverse reactions from immunization with MMR vaccine if an individual is already immune to one or more components of the vaccine or infected by rubella virus.

Passive immunization with human immune globulin (Ig) is not effective in preventing rubella. Ig given soon after exposure to rubella may modify or suppress symptoms but may not prevent infection, including
congenital infection. Therefore, the routine use of Ig in susceptible women exposed to rubella early in pregnancy is not recommended.

**OUTBREAK CONTROL**
During rubella outbreaks, susceptible people should be given MMR vaccine promptly without prior serologic testing. In consultation with public health officials, it may be appropriate to vaccinate pregnant women.

**VACCINE ADMINISTRATION**

**DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE**

**Dose**
Each dose is 0.5 mL.

**Route of administration**
MMR vaccine should be administered subcutaneously; MMRV can be administered subcutaneously or intramuscularly. Refer to [Vaccine Administration Practices](#) in Part 1 for additional information.

**Schedule**

*Children* (12 months to 12 years of age)
For routine immunization of children aged 12 months to 12 years, one dose of rubella-containing vaccine (MMR or MMRV) should be administered at 12 to 15 months of age.

*Adolescents* (13 to 17 years of age)
Rubella-susceptible adolescents should receive one dose of MMR vaccine.

*Adults* (18 years of age and older)
Rubella-susceptible adults should receive one dose of MMR vaccine.

**BOOSTER DOSES AND RE-IMMUNIZATION**
Re-immunization with rubella-containing vaccine after documented receipt of one dose of rubella-containing vaccine is not necessary. However, if a booster dose is given, it is not harmful and may benefit individuals who do not respond to primary immunization.

**SEROLOGICAL TESTING**
Serologic testing is not routinely recommended before or after receiving rubella-containing vaccine.

Pregnant women without documented evidence of prior immunization with a rubella-containing vaccine should be serologically screened for rubella antibodies, unless there is documented evidence of receipt of a rubella-containing vaccine. Those found to be non-immune serologically should be vaccinated with one dose of MMR vaccine in the immediate post-partum period, before discharge from hospital (unless they have received Rh immune globulin [RhIg] – refer to [Rh immune globulin and MMR vaccine in Immunization in Pregnancy and Breastfeeding](#) in Part 3). Women who have been appropriately immunized post-partum do not need to be serologically screened for rubella antibodies either post-immunization or in subsequent pregnancies. Women who have been found to be serologically positive in one pregnancy do not need to be screened again in subsequent pregnancies.
STORAGE REQUIREMENTS

M-M-R® II: Maintain vaccine at +10°C or colder during shipment. Freezing during shipment will not affect potency of the vaccine. Protect the vaccine from light. Before reconstitution, store the vial of vaccine at +2°C to +8°C or colder. The diluent may be stored in the refrigerator or at room temperature and must not be frozen.

PRIORIX®: Store in a refrigerator at +2°C to +8°C. The diluent may be stored separately at room temperature. Protect from light.

PRIORIX-TETRA®: Store the vaccine and diluent in a refrigerator at +2°C to +8°C and do not freeze. Protect the vaccine from light.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Live vaccines given by the parenteral route may be administered concomitantly with all other vaccines during the same visit using different injection sites and separate needles and syringes. In general, if two live parenteral vaccines are not administered concomitantly, there should be a period of at least 4 weeks before the second live parenteral vaccine is given. Exceptions are varicella-containing vaccines, such as MMRV vaccine:

- Administer doses of varicella-containing vaccine at least 3 months apart for children 1 to 12 years of age. If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between 2 doses may be used for children 1 to 12 years of age.
- Do not concomitantly administer varicella-containing vaccines with smallpox vaccine; administer varicella-containing vaccine and smallpox vaccine at least 4 weeks apart.

Oral and intranasal vaccines can be given at the same time as, or any time before or after any other live vaccine, regardless of the route of administration of the other live 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

**MMR vaccine**

Adverse events following MMR immunization occur less frequently and are less severe than those associated with natural disease. Adverse reactions are less frequent after the second dose of vaccine and tend to occur only in those not protected by the first dose. Six to 23 days after MMR immunization, approximately 5% of immunized children experience malaise and fever (with or without rash) lasting up to 3 days. Parotitis, rash, lymphadenophy, and joint symptoms also occur occasionally after MMR immunization.

**MMRV vaccine**

Pain and redness at the injection site or low-grade fever or both occur in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C) occur in 1% to less than 10% of vaccinees. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus,
health care providers should obtain specimens using viral transport media from a lesion of the vaccinée to ensure varicella disease is not confused with a reaction to vaccination.

Rubella-containing vaccines
Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with rubella-containing vaccine, lasts for about 1 to 3 weeks, and rarely recurs. This is more common in post-pubertal females, among whom arthralgia develops in 25% and arthritis in 10% after immunization with rubella-containing vaccine. There is no evidence of increased risk of new onset, chronic arthropathies or neurologic conditions.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

MMR and MMRV vaccines
Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. As with other vaccines, anaphylaxis following vaccination with MMR or MMRV vaccine may occur but is very rare.

**Immune Thrombocytopenic Purpura (ITP)**
Rarely, ITP occurs within 6 weeks after immunization with MMR or MMRV vaccine. In most children, post-immunization thrombocytopenia resolves within three months without serious complications. In individuals who experienced ITP with the first dose of MMR or MMRV vaccine, serologic status may be evaluated to determine whether an additional dose of vaccine is needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases.

**Encephalitis**
Encephalitis has been reported in association with administration of measles vaccine in approximately 1 per million doses distributed in North America which is much lower than that observed with natural measles disease (1 per 1,000 cases).

**Febrile seizures**
Recent studies have found a higher risk of febrile seizures with the first dose of a MMRV vaccine (ProQuad®, not authorized for use in Canada) when compared to the concomitant administration of MMR and univalent varicella vaccine. Data from the United States (US) estimated that the risk of febrile seizures in the 5 to 12 days following the first dose of this MMRV vaccine is 1 for every 2,600 vaccinated children aged 12 to 23 months. Experience with the MMRV vaccine available in Canada is more limited; however, one study showed an additional risk of febrile seizures with MMRV vaccine compared to MMR and univalent varicella vaccines given as two separate products administered concomitantly. The risk with the Canadian vaccine was smaller than the risk found with the US product. Close surveillance and further investigation are underway.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS
In the mid to late 1990s, researchers from the United Kingdom reported an association between MMR vaccine and inflammatory bowel disease, and MMR vaccine and autism. Rigorous scientific studies and reviews of the evidence have been done worldwide, and there is now considerable evidence to refute those claims. In 2010, the original study suggesting a link between the MMR vaccine and autism was retracted.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)
Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with MMR or MMRV vaccine.
- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with MMRV vaccine.
- 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 and Vaccine Safety in Part 2 for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

MMR and MMRV 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 (with the exception of egg allergy [refer below]) or its container. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of vaccines available for use in Canada and their contents. For rubella-containing vaccines, potential allergens include:

- M-M-R® II: neomycin, phenol red, porcine gelatin, residual components of chick embryo cell cultures
- PRIORIX®, egg protein, neomycin
- PRIORIX-TETRA® egg protein, neomycin

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.

The measles and mumps components of MMR and MMRV vaccines are produced in chick embryo cell culture and may contain traces of residual egg and chicken protein. The trace amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is not recommended prior to vaccination as it does not predict reaction to the vaccine. MMR or MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens’ eggs. Prior egg ingestion is not a prerequisite for immunization with egg protein-containing vaccine. For all vaccines, immunization should always be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.

Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Refer to Immunocompromised persons.

MMR and MMRV vaccines are contraindicated during pregnancy. Refer to Pregnancy and breastfeeding.

MMR vaccine is contraindicated in individuals with active, untreated tuberculosis. While tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles, such as MMR or MMRV, vaccine has such an effect.

A history of febrile seizures or a family history of convulsions is not a contraindication for the use of MMRV vaccine.

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

It is recommended to avoid the use of salicylates (e.g., acetylsalicylic acid [ASA]) for 6 weeks after
immunization with MMRV vaccine because of an association between wild-type varicella, salicylate therapy and Reye’s syndrome.

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

**DRUG INTERACTIONS**

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine such as MMRV. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible from at least 24 hours before administration of MMRV vaccine and should not restart antiviral therapy until 14 days after.

The measles component in measles-containing vaccines can temporarily suppress tuberculin reactivity, resulting in false-negative results. If tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) test is required, it should be done on the same day as immunization or delayed for at least 4 weeks after measles vaccination. Vaccination with measles-containing vaccine may take place at any time after tuberculin skin testing has been performed and/or read.

Passive immunization with human immune globulin (Ig) or receipt of most blood products can interfere with the immune response to MMR and MMRV vaccines. These vaccines should be given at least 14 days prior to administration of an Ig preparation or blood product, or delayed until the antibodies in the Ig preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an Ig preparation or blood product is less than 14 days or before the antibody has degraded, repeat the vaccine dose after the recommended interval. The recommended interval between administration of an Ig preparation or blood product and subsequent immunization varies, depending on the Ig preparation or blood product. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to MMR or MMRV vaccines. Refer to Blood Products, Human Immune Globulin and Timing of Immunization in Part 1 for additional general information.

**OTHER CONSIDERATIONS**

**INTERCHANGEABILITY OF VACCINES**

On the basis of expert opinion, the MMR vaccines authorized in Canada may be used interchangeably. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

**SELECTED REFERENCES**


Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices Provisional Recommendations for Measles-Mumps-Rubella (MMR) ‘Evidence of Immunity’ Requirements for


PART 4

SMALLPOX VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Immune Globulin Safety and Adverse Events
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox is a systemic viral illness with a characteristic rash that can have a 15% to 45% or higher mortality rate in an unimmunized population.</td>
</tr>
<tr>
<td>Naturally occurring smallpox disease was eradicated by 1977 through a worldwide vaccination program.</td>
</tr>
<tr>
<td>Smallpox vaccine provides cross-protection against all orthopox viruses and is used to protect laboratory workers against these viruses.</td>
</tr>
<tr>
<td>Remaining variola (smallpox) virus stocks are kept in two World Health Organization (WHO) reference laboratories. There is a lingering concern that variola virus stocks may be held outside of the two official laboratories which could result in an accidental release or use for terrorist purposes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine immunization of the general Canadian population with smallpox (vaccinia virus) vaccine is not recommended.</td>
</tr>
<tr>
<td>Vaccination is recommended for laboratory workers who handle vaccinia or other orthopox viruses (including recombinant vaccinia products) in specialized reference or research facilities.</td>
</tr>
<tr>
<td>In the event of a suspect case of smallpox, vaccination of public health and health care personnel involved in the case investigation and clinical management is indicated.</td>
</tr>
<tr>
<td>Once a case is confirmed, vaccination of contacts of cases and those living in the immediate vicinity (ring vaccination) is indicated. Vaccination of public health staff and health care workers, as well as first responders, such as police officers, firefighters, ambulance attendants, the military and others may also be indicated.</td>
</tr>
<tr>
<td>Because of the relatively long incubation period for smallpox, historical data collected during the smallpox eradication program using the first generation vaccine showed that vaccination within 2 to 3 days of exposure may protect against clinical disease, and if given within 4 to 5 days, may decrease the risk of death.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should a smallpox case be suspected, immediate telephone communication with local or provincial/territorial public health officials is required; the Public Health Agency of Canada (PHAC) should then be notified.</td>
</tr>
<tr>
<td>Smallpox vaccine can be obtained by contacting PHAC’s Centre for Emergency Preparedness and Response</td>
</tr>
</tbody>
</table>
Why

- To protect laboratory workers from orthopox virus infections (e.g., smallpox [variola virus])
- To prevent the re-emergence of smallpox, a severe and frequently fatal disease that has been eradicated by vaccination.
- A case of smallpox anywhere in the world constitutes a global health emergency.
- Under the International Health Regulations, it is the responsibility of PHAC to notify the WHO if a case of smallpox is suspected.

Since the publication of the 2006 Canadian Immunization Guide:

- Recommendations for smallpox vaccination of laboratory personnel who handle vaccinia or other orthopox viruses have been updated.
- A new recommendation has been made about the reporting of secondary or tertiary cases of vaccinia from smallpox vaccine.
- Frozen, liquid smallpox vaccine has been stockpiled in addition to the licensed lyophilized vaccine.

The Canadian Smallpox Contingency Plan provides recommendations for actions to be taken if smallpox occurs in Canada or elsewhere in the world. For additional information, refer to the National Advisory Committee on Immunization (NACI) Statement on smallpox vaccination.


EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Smallpox is a systemic viral disease caused by the variola virus, a species of the Orthopoxvirus.

Reservoir
Humans. There are no animal reservoirs of variola virus and the last human case occurred in 1978. Currently the virus is maintained in two designated laboratories.

Transmission
Smallpox is spread by droplets from the respiratory tract or by direct or indirect contact with the virus shed from skin lesions. Airborne spread is thought to be less frequent, but transmission over significant distances has been documented, including transmission through a hospital stairwell. In addition, the virus is stable in dried form for months and has been transmitted by fomites such as bed linen.

The incubation period is from 7 to 19 days, typically 10 to 14 days to the onset of illness and 2 to 4 more days to the onset of the rash. Infectivity can occur at any time from the development of the rash to the disappearance of all scabs – approximately 3 weeks. Infectivity is highest early in the clinical disease.

Risk factors
Canadians born in 1972 or later have not been routinely immunized against smallpox (unless immunized for travel to other countries); therefore, most are fully susceptible. Discontinuation of vaccination for travel was recommended by the WHO in 1980 and was no longer required by any country by 1982. Individuals who have been vaccinated in the past may have partial immunity.

Spectrum of clinical illness
Early symptoms of smallpox are initially similar to influenza: sudden onset of high fever, malaise, headache, fatigue and occasional abdominal pain and vomiting. After 2 to 4 days the fever subsides
and there is a characteristic “centrifugal rash” first appearing on the face and extremities, including the palms and soles, and subsequently on the trunk. The rash progresses through all the phases of macules, papules, vesicles, pustules and then crusted scabs that fall off 3 to 4 weeks after the appearance of the rash. There are two strains of the smallpox virus, each with a different clinical course. Variola minor has a case fatality rate of less than 1%; Variola major has a case fatality rate among unvaccinated populations ranging from 15% to 45% or higher. Rates may vary depending up the virulence of the specific variola virus strain that circulates, and the vulnerability of the population it attacks. The case fatality rate is higher in pregnant women and in young children.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

The last known case of naturally occurring smallpox occurred in Somalia in 1977; two cases of smallpox occurred in England in 1978 as a result of a laboratory accident. In December 1979, the WHO officially declared that smallpox had been eradicated globally and in 1980 the World Health Assembly recommended all countries cease routine smallpox immunization programs. Remaining variola virus stocks are kept in two WHO reference laboratories in the United States (US) and Russia for research purposes.

With the breakup of the Soviet Union and the subsequent loss of safety and security controls over their biological weapon stockpiles, there has been a concern that there could be an accidental release of variola virus. Weapon-grade variola virus could also have been sold covertly by former Soviet laboratory personnel to other governments or terrorist groups. In the US, a smallpox vaccination program was initiated in the military in December 2002. Subsequent smallpox vaccination programs were conducted in some health care workers in the US and the United Kingdom.

Due to its current eradication yet potential use as a biological weapon, the occurrence of a single case of smallpox anywhere in the world constitutes a global health emergency.

National

Concerted vaccination campaigns were successful in eliminating endemic smallpox from Canada by 1946. Nova Scotia had a suspected case in 1949; with rigid quarantine the disease did not spread. The final laboratory-confirmed case in Canada in 1962 involved an adolescent who returned to Toronto from Brazil.

PREPARATIONS AVAILABLE FOR USE IN CANADA

PHAC has a stock of two types of smallpox (vaccinia virus) vaccine (Sma):

- lyophilized (freeze-dried) vaccine - Smallpox Vaccine (Dried) (sanofi pasteur Ltd.)
- frozen liquid formulation vaccine - Smallpox Vaccine (Frozen-Liquid) (sanofi pasteur Ltd).

The lyophilized vaccine is an authorized product and is currently used to vaccinate laboratory workers working with orthopox viruses. The frozen liquid vaccine would be released in emergency situations (e.g., in response to a smallpox case) through Health Canada’s Special Access Programme. Both vaccines are prepared from live, vaccinia virus. Vaccinia virus is a member of the Orthopoxvirus family and confers immunity against variola (smallpox) and other orthopox viruses through cross-reactivity. A third generation vaccine is currently under development.

PHAC provides smallpox vaccine to laboratory staff working with vaccinia virus or other orthopox viruses and would also provide vaccine to provinces/territories in the event of a smallpox case. For non-emergency situations, contact the Centre of Emergency Preparedness and Response, PHAC by telephone: (613) 960-1830 or email: vaccine.info@phac-aspc.gc.ca to obtain additional information.
For emergency situations (suspected or confirmed smallpox case), contact the PHAC Operations Centre by telephone: 1-800-545-7661 or 613-952-7940 or e-mail: hpoc_cops@phac-aspc.gc.ca

VACCINIA IMMUNE GLOBULIN
Vaccinia Immune Globulin Intravenous (Human) (VIG) is a solution of gamma globulin from the serum of individuals recently immunized with smallpox vaccine. It is used to treat severe smallpox vaccine-associated adverse events. The Canadian Smallpox Contingency Plan indicates that VIG would be sent to the provinces/territories at the same time as smallpox vaccine and related supplies if smallpox occurs in Canada.

EFFECTICITY, EFFECTIVENESS, AND IMMUNOGENICITY
In the early 1970s before smallpox was eradicated, a retrospective study conducted in West Pakistan showed a mortality rate of 52% among those who had never been vaccinated, 1.7% among those who had been vaccinated within 10 years, and 11% among those who had been vaccinated 20 or more years earlier.

The specific mechanisms that result in immunity to smallpox following vaccination have not been well characterized. Studies conducted in the 1970s suggest that both antibody and cell-mediated immunity are stimulated by smallpox vaccination. A more recent study showed that more than 95% of primary vaccinees had detectable neutralizing antibody within 1 to 2 weeks after immunization and strong increases in vaccinia-specific CD8+ cytotoxic T lymphocytes and interferon-gamma-producing T cells.

RECOMMENDATIONS FOR USE
Given that naturally occurring smallpox has been eradicated worldwide and smallpox vaccination is associated with the risk of significant morbidity and even mortality, the overall risk benefit analysis supports the recommendation to not routinely immunize the general Canadian population against smallpox. As a result, smallpox vaccination is highly restricted.

WORKERS
Smallpox vaccine may be indicated for certain workers at high risk of exposure, such as laboratory workers who handle vaccinia or other orthopox viruses (including recombinant vaccinia vaccine products) in specialized reference or research facilities.

In the event of a suspect case of smallpox, vaccination of public health and health care personnel involved in the case investigation and clinical management is indicated. Once a case is confirmed, vaccination of public health staff and health care workers, as well as first responders such as police officers, firefighters, ambulance attendants, the military and others may also be indicated.

Laboratory workers may be hesitant to receive smallpox vaccine. Vaccine providers should explain that the lyophilized smallpox vaccine is authorized by Health Canada and that vaccination is important in light of the highly contagious nature of orthopox viruses and the implications of even a single case.

OUTBREAK CONTROL
The Canadian Smallpox Contingency Plan includes actions to be taken if a case of smallpox occurs in Canada or elsewhere. A single case of smallpox is considered an outbreak. In general terms, cases should be isolated immediately, preferably at home. If hospitalisation is required, cases should be admitted to rooms under negative pressure equipped with high efficiency particulate air-filtration (HEPA) filters (airborne infection isolation rooms). Contacts and those living in the immediate vicinity of the identified case should be immunized immediately (ring vaccination) and placed under observation in quarantine. Vaccination is indicated for face-to-face contacts (less than 6.5 feet or 2 meters), household contacts, personnel involved in the medical care, public health evaluation or transportation of confirmed or suspected smallpox cases, laboratory personnel involved in the collection or processing of clinical
specimens from confirmed or suspected smallpox cases, and persons who have a high likelihood of exposure to infectious materials (e.g., those responsible for medical waste disposal, linen disposal or disinfection) of smallpox cases.

Vaccine can be given after exposure with beneficial effect as smallpox has a relatively long incubation period. Historical data collected during the smallpox eradication program using first generation vaccine showed that vaccination within 2 to 3 days of exposure may protect against clinical disease, and if given within 4 to 5 days, may decrease the risk of death.

**VACCINIA IMMUNE GLOBULIN**

PHAC's Centre for Emergency Preparedness and Response has a supply of VIG based on a requirement of 1 dose of VIG for every 10,000 doses of smallpox vaccine. VIG is indicated to treat severe smallpox vaccine-associated adverse events: eczema vaccinatum, progressive vaccinia, severe or recurrent generalized vaccinia, and extensive lesions resulting from accidental implantation (transfer of vaccinia virus from the primary vaccination site to other parts of the body). VIG is ineffective in the treatment of post-vaccinial encephalitis and has no role in the treatment or prevention of smallpox.

**VACCINE ADMINISTRATION**

**DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE**

Smallpox vaccine is administered by scarification into the epidermis, usually in the deltoid area of the non-dominant arm, by using the multiple-puncture technique with a bifurcated needle, packaged with the vaccine and diluent. According to the product labelling, 15 punctures are recommended for vaccination. A trace of blood should appear at the vaccination site after 15 to 20 seconds; if no trace of blood is visible, additional insertions should be made by using the same bifurcated needle without reinserting the needle into the vaccine vial. If alcohol is used to cleanse the skin before immunization, the skin must be allowed to dry thoroughly before the vaccine is administered, to prevent inactivation of the vaccine by alcohol.

Other methods of administration, such as multiple pressure method are possible in case bifurcated needles are not readily available. Refer to the product label for detailed instructions.

When vaccinia virus is inoculated into the epidermis the virus induces an immune reaction that is termed “a take”. There is often no visible reaction for the first few days. On day 3 to 4 a papule appears and progresses to a vesicle with surrounding erythema. Typically, one week or so after vaccination, the centre of the vesicle umbilicates and pustulates. After about 2 weeks, the pustule crusts and a dark brown or black scab forms. After 3 weeks, the scab detaches leaving a scar. The vaccination site should be inspected 6 to 8 days after vaccination to ensure that a take has occurred. If there is no evidence of papules or vesicles and erythema, the person should be vaccinated again.

Optimal infection-control practices and appropriate vaccination site care should be used. Gloves should be worn by the vaccine provider when administering smallpox vaccine due to the increased risk of autoinoculation from the use of a bifurcated needle. Each vaccinee and anyone caring for the vaccination site should wash their hands thoroughly after touching the site or handling bandages used to cover the site. Contaminated bandages and scabs should be placed in sealed plastic bags before disposal in the garbage. The vaccinee should avoid rubbing or scratching the site.

A sterile piece of porous bandage (e.g., gauze) should be used to loosely cover the vaccination site until the scab falls off in order to deter the vaccinee from touching the scab, to prevent inadvertent self-inoculation or inoculation of others, and to contain the scab so it is not lost. Preferably, a semi-permeable dressing should be placed over the gauze and not directly on the site; occlusive dressings should not be used. Dressings used to cover the site should be changed frequently to prevent accumulation of exudates and consequent maceration. Frequent dressing changes are particularly important for vaccinees who have close contact with children or people at high risk for vaccinia complications.
Health care workers providing direct patient care should keep their vaccination sites covered with gauze in combination with a semipermeable membrane dressing to absorb exudates and to provide a barrier for containment of vaccinia virus to minimize the risk of transmission; the dressing should also be covered by a layer of clothing. Similar precautions should be used for vaccinated persons in close contact with children or other persons at high risk of serious complications of vaccinia.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Booster doses should be given every 10 years for laboratory workers with ongoing risk of exposure.

**VACCINIA IMMUNE GLOBULIN**

VIG should be given intravenously through a dedicated infusion line at a rate of 2 mL/min; VIG is compatible with sodium chloride 0.9%. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration; it should not be used if the solution is turbid. The vial should not be shaken as it may cause foaming.

VIG should be administered at a dose of 6,000 units/kg as soon as symptoms appear and are judged to be due to a severe vaccinia-related complication. Two exceptions to this are vaccinia keratitis and encephalitis. VIG should not be given for vaccinia keratitis due to the potential of increased corneal scarring, and should not be given for encephalitis due to lack of efficacy. For other VIG-treated complications, consideration may be given to repeat dosing, depending on the severity of the symptoms and response to treatment; however, clinical data on repeat doses are lacking. The administration of an additional dose of 9,000 units/kg may be considered in the event that the person does not respond to the initial 6,000 units/kg dose.

**SEROLOGICAL TESTING**

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

**STORAGE REQUIREMENTS**

Lyophilized smallpox vaccine should be stored in a refrigerator at +2°C to +8°C and reconstituted before use. The frozen liquid smallpox vaccine is frozen for long-term storage and thawed for shipping; the thawed vaccine should be maintained between +2°C and +8°C. Open vaccine vials should be used within 24 hours.

Refer to [Storage and Handling of Immunizing Agents](#) in Part 1 for additional general information.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**

In non-emergency situations (i.e., non-outbreaks), smallpox vaccine can be administered simultaneously with any inactivated vaccine. To avoid confusion in ascertaining which vaccine might have caused post-vaccination skin lesions or other adverse events, varicella (chickenpox) vaccine or herpes zoster (shingles) vaccine should not be administered concomitantly with smallpox vaccine; there must be an interval of at least 4 weeks between administration of varicella or herpes zoster vaccines and smallpox vaccine. Smallpox vaccine can be administered simultaneously with other live parenteral vaccines; if not administered simultaneously, there must be an interval of at least 4 weeks between smallpox vaccine and other live parenteral vaccines.

**VACCINE AND IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS**

Refer to [Vaccine Safety](#) Part 2 for additional general information.
COMMON AND LOCAL ADVERSE EVENTS
In a study of 200 health care workers, 142 (71%) of vaccinees reported pain at the injection site, of which 25% considered it to be moderate or severe; 32 vaccinees (16%) recorded a temperature of greater than 37.7°C, two of which exceeded 39°C. Other, mainly minor, adverse events were common; local itching was reported in 72%, erythema at the injection site in 27%, axillary pain or lymphadenopathy in 38%, malaise or influenza-like symptoms in 40% and headache in 23%. The incidences of minor adverse events were lower in re-vaccinees, compared with primary vaccine recipients.

Bacterial infection of the vaccination site can occur.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Inadvertent inoculation
Inadvertent inoculation is the transfer of the virus from the site of immunization to other body sites or other persons resulting in vaccinia lesions. The most susceptible areas are the eye, mouth, nose, face and genitalia. Children are most susceptible to inadvertent inoculation. Inadvertent inoculation is the most common (significant) adverse reaction, with rates approaching 600 cases per million doses administered. Most ensuing lesions heal spontaneously. There are recent case reports of secondary and tertiary vaccinia arising in sexual contacts of a person recently vaccinated; these cases were severe enough to require VIG to manage vaccinia-related complications. When a secondary case of vaccinia is diagnosed, contract tracing is indicated to ascertain whether there are additional secondary or tertiary cases.

Generalized vaccinia
Generalized vaccinia may occur within a week after vaccination. Lesions appear on unimmunized skin and are thought to arise from viremia. Lesions are similar to those associated with the vaccination site but are usually smaller and evolve to scarring more rapidly, often within a week. In healthy individuals this is a benign complication of primary vaccination that needs to be differentiated from progressive vaccinia. Individuals with underlying and unsuspected immunosuppressive illnesses may develop a serious reaction.

Progressive vaccinia (Vaccinia Necrosum)
Progressive vaccinia is a severe complication of smallpox vaccination. It often occurs because of an immune defect, especially T cell deficiencies. It is characterized by progressive necrosis at the site on immunization and, in the presence of viremia, leads to implants in distant skin sites and multiple organs. Progression is slow, persistent and resistant to treatment. In those with profound T cell defects, it is nearly always fatal.

Eczema vaccinatum
Eczema vaccinatum occurs in vaccinees or their unvaccinated contacts with active or healed eczema lesions or other exfoliative skin conditions. Vaccinial skin lesions appear on skin that is currently or was previously affected by eczema. Usually the illness is mild and self-limited, but it can be severe and fatal.

Vaccinia keratitis
Vaccinia keratitis can threaten eyesight through corneal abrasions, ulcerations and subsequent corneal clouding. If this occurs, consultation with an ophthalmologist is strongly recommended. VIG is contraindicated because of the potential of increased corneal scarring.

Post-vaccinial encephalitis
Post-vaccinial encephalitis is a rare but serious complication that can develop 7 to 14 days after vaccination. There are no known predictors of susceptibility, but the incidence is somewhat higher among infants less than 1 year of age. Approximately, 25% of cases with encephalitis develop
permanent sequelae (both motor and/or intellectual impairment) and up to 35% die. VIG is not recommended due to lack of efficacy.

**Acute myopericarditis**

During a smallpox vaccination program for US military personnel which started in 2002, a previously unreported adverse event, acute myopericarditis, was recognized. Most of the affected vaccinees experienced chest pain and returned to normal activities within 7 to 10 days; all recovered. It is unclear whether these events were adverse outcomes of smallpox vaccination.

VIG is available to treat certain smallpox vaccine-associated adverse events. Refer to [Vaccinia Immune Globulin](#) for additional information.

**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 thought to be temporally related to smallpox vaccination, including any case of secondary or tertiary vaccinia. 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 [Table 1 in Vaccine Safety](#) in Part 2 and the [User Guide to completion and submission of the AEFI](http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php) for additional information about AEFI reporting. ([Brighton case definitions](#)) are also available.

**CONTRAINDICATIONS AND PRECAUTIONS**

**Smallpox vaccine**

Contraindications to smallpox vaccine are only applicable if the variola (smallpox) virus has not been introduced into the environment. In an outbreak situation, if smallpox cases are occurring and a risk of infection exists for an individual, there are no absolute contraindications to immunization.

The product leaflet lists the following contraindications in a non-emergency setting. For people at higher risk of vaccinia complications, potential risks and benefits must be weighed, including VIG availability.

*Persons less than 18 years of age*

Smallpox vaccination is contraindicated for children and adolescents because they are more likely to suffer from adverse reactions and cause inadvertent self-reinoculation and inoculation of others.

*Hypersensitivity or anaphylaxis*

Smallpox vaccines are contraindicated in people 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 [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 smallpox vaccines, potential allergens include: streptomycin, neomycin and latex in the stopper of vial.

*Immunodeficiency and immunosuppression*

Smallpox vaccination is contraindicated for people who are immunosuppressed such as those with leukemia, lymphoma, or a systemic malignancy; persons on immunosuppressive therapies; persons with some hereditary immune deficiency disorders; and persons with HIV/AIDS. It is generally contraindicated pre/post solid organ transplant and hematopoietic stem cell transplant (HCST). Refer to [Immunization of Immunocompromised Persons](#) in Part 3 for additional information.
**Atopic dermatitis and other widespread skin disorders**
Diffuse vaccinia virus infection can occur in the presence of acute atopic dermatitis and other widespread exfoliative skin disorders.

**Pregnancy and breastfeeding**
Smallpox vaccine is generally contraindicated in pregnant women in non-emergency situations although it is not known to cause congenital malformations. It can very rarely lead to fetal vaccinia after primary immunization during pregnancy, resulting in stillbirth or neonatal death. Women of childbearing age should be asked before vaccination if they are pregnant or intend to become pregnant during the next 4 weeks. If a woman becomes pregnant within 4 weeks after smallpox vaccination she should be counselled regarding concern for the fetus.

Breastfeeding mothers should not receive the smallpox vaccine in non-emergency situations. The close physical contact that occurs during breastfeeding increases the chance of inadvertent inoculation of the baby. It is not known whether vaccine virus or antibodies are excreted in human milk. A breastfeeding woman should only be immunized if she has been exposed to smallpox; in that case breastfeeding and other close contact should be delayed until after the vaccination scab has separated from the vaccination site.

**Heart disease and cardiac risk factors**
Smallpox vaccine is contraindicated in people with known underlying heart disease (with or without symptoms), or who have three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking). A risk assessment needs to be done in an emergency situation such as exposure to a case of smallpox.

The product monograph lists the following precautions:

**Ocular or periorbital disease**
Persons with inflammatory eye disease may be at increased risk for inadvertent inoculation as a result of touching or rubbing the eye. Therefore, deferring vaccination is prudent for persons with inflammatory eye diseases requiring steroid treatment until the condition resolves and the course of therapy is complete.

**Close contacts**
Generally, smallpox vaccine should not be administered to household contacts of an immunocompromised person in a non-emergency situation. If vaccination is required in an outbreak situation, precautions should be taken for unvaccinated household and other close contacts. Vaccinees with household and other close contacts with active eczema or a history of eczema or other exfoliative skin conditions, immunosuppressive disorders, or with close contact with infants or pregnant women, should take special precautions in order to prevent viral transfer to these contacts. Such precaution can include isolation of the vaccinee from their higher risk household contacts until the vaccine scab falls off.

**Vaccinia immune globulin**
The most common adverse events related to VIG are headache, nausea, rigors and dizziness.

Relative contraindications to VIG include:

- a history of systemic allergic reactions to human immune globulin products
- isolated vaccinia keratitis due to the potential of increased corneal scarring
- selective immunoglobulin A deficiency with antibodies against IgA and a history of IgA hypersensitivity (because VIG contains trace amounts of IgA)
It is not known whether VIG can cause fetal harm or affect reproductive capacity when given to pregnant women. Counselling based on an individual risk benefit assessment is indicated. VIG should not be withheld if a pregnant woman experiences a condition for which VIG is needed.

**DRUG INTERACTIONS**

There is some evidence for tuberculin skin test (TST) suppression following the administration of live, attenuated virus vaccines; a TST can be done on the same day as immunization or delayed until 4 weeks after smallpox vaccination.

**SELECTED REFERENCES**


Grabenstein JD, Winkenwerder W. *US military smallpox vaccination program experience.* JAMA 2003;289:3278-82.


PART 4
TETANUS TOXOID

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
  - Post-exposure prophylaxis
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Immune Globulin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Tetanus (lockjaw) occurs worldwide but is rare in Canada. |
|      | Tetanus toxoid is only available as a combination vaccine. |
|      | A primary series and boosters, including post-exposure boosters, are recommended to develop and maintain high circulating concentrations of tetanus antibody in the event of exposure to Clostridium tetani spores and subsequent toxin production. In unvaccinated or inadequately vaccinated individuals, tetanus immune globulin is recommended post-exposure in certain situations. |
|      | After a complete primary series (at least 3 doses), more than 99% of vaccinees develop antibody concentrations that are protective against tetanus, but there is declining immunity over time. |
|      | Redness, swelling and pain at the injection site are the most common adverse reactions to tetanus toxoid-containing vaccines. |

| Who | Tetanus toxoid-containing vaccine is recommended for: |
|     | o routine immunization of infants and children |
|     | o immunization of children who missed tetanus immunization on the routine schedule |
|     | o immunization of previously unvaccinated or incompletely vaccinated adults |
|     | o routine booster immunization of adolescents and adults |
|     | o post-exposure prophylaxis in some wound management situations |
**How**

- **Routine tetanus 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 tetanus 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.
- **Post exposure/wound management**: the need for tetanus toxoid-containing vaccine in wound management, with or without tetanus immune globulin depends on both the nature of the wound and the vaccination history.
- Tetanus toxoid-containing vaccines may be administered concomitantly with routine vaccines at different injection sites using separate needles and syringes.

**Why**

- Tetanus occurs worldwide.
- Many Canadians, especially those who are older or born outside of Canada, do not have protective concentrations of tetanus antitoxin.
- The case fatality rate in the unvaccinated varies from 10% to over 80% and is highest in infants and the elderly.

* Refer to [Tetanus 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 vaccines (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.


**Epidemiology**

**Disease Description**

**Infectious agent**

Tetanus (lockjaw) is caused by a neurotoxin produced by the bacterium *Clostridium tetani*.

**Reservoir**

*C. tetani* spores are widely distributed in soil worldwide and have also been detected in the intestines of animals and humans.
Transmission

*C. tetani* spores are usually introduced into the body through a wound that is contaminated with dust, soil or animal/human feces. *C. tetani* spores will germinate into bacilli in an anaerobic environment, such as necrotic tissue. The bacilli release a potent neurotoxin. The incubation period is generally 3 to 21 days (range, 1 day to several months). Since tetanus is caused by the neurotoxin, it is not transmitted person-to-person.

Risk factors

Cases of tetanus related to lacerations (most frequent), injection drug use, and animal bites have been reported as well as rare cases occurring after bowel surgery or aspiration of soil and feces. Cases may occur following small, insignificant wounds, especially when there is necrotic tissue present. It is often associated with blunt trauma or deep puncture wounds. Tetanus rarely occurs in fully vaccinated people and, if it does, it is usually mild.

Spectrum of clinical illness

Tetanus is characterized by muscle spasms, usually in a descending pattern beginning in the jaw muscles. As the disease progresses, prolonged frequent spasms may occur contributing to serious complications and death unless treatment is provided. Globally, tetanus is common in neonates who are delivered without adequate sterile procedures. The case fatality rate in the unvaccinated varies from 10% to over 80% and is highest in infants and the elderly.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

Tetanus occurs worldwide but occurs most frequently in agricultural regions and densely populated regions. A total of 9,683 cases of tetanus were reported to the World Health Organization (WHO) in 2010. Tetanus is relatively uncommon in most developed countries. Although neonatal tetanus has been eliminated in North America, it remains an important global issue. Not all cases of tetanus are preceded by a recognized wound or injury. In the United States between 2001 and 2008, there were no wounds or injuries in 22 (9.4%) of 223 cases of tetanus reported; 14 of the 22 cases were injection drug users.

National

Tetanus is rare in Canada (refer to Figure 1). Between 1990 and 2010, the number of cases reported annually ranged from 1 to 10, with an average of 4 per year. During this period, persons 60 years of age and older accounted for 48% of the cases and 59% were males. No cases were reported among neonates. The immunization status of the reported cases was not known. Only eight deaths due to tetanus have been reported since 1990, the last two were reported in 2009. There is limited evidence on the protective concentrations of tetanus antitoxin in the Canadian population. A serosurvey of adult blood donors in Toronto found that 17.5% of donors did not have protective levels of tetanus antitoxin. Factors associated with lack of immunity to tetanus include increasing age, birth outside Canada, and absence of immunization records.
Figure 1: Tetanus - number of cases and deaths, Canada, 1921-2010

PREPARATIONS AVAILABLE FOR USE IN CANADA

TETANUS TOXOID-CONTAINING VACCINES

- ADACEL® (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine). (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). (Tdap)
- BOOSTRIX®-POLIO (adsorbed vaccine containing tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine combined with inactivated poliomyelitis vaccine). (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). (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). (DTaP-IPV-Hib)
- QUADRACEL® (adsorbed vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine). (DTaP-IPV)
- Td ADSORBED adsorbed vaccine containing tetanus and reduced diphtheria toxoids). (Td)
- Td POLIO ADSORBED adsorbed vaccine containing tetanus and reduced diphtheria toxoids and inactivated poliomyelitis vaccine). (Td-IPV)
Tetanus toxoid is only available as a combination vaccine.

**TETANUS IMMUNE GLOBULIN**

- **HYPERTET® S/D** (tetanus immune globulin (human) solvent/detergent treated).

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 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**

**EFFICACY AND EFFECTIVENESS**

Protective antitoxin concentrations occur in virtually all healthy infants and children who receive primary tetanus immunization. Efficacy in standard pre-exposure and post-wound booster immunization regimens in adults has not been assessed in randomized trials but has been demonstrated in observational studies. Very rare cases of tetanus, which are usually mild but can range from mild or localized to severe disease, have been reported despite full immunization and the presence of toxin-neutralizing antibody.

**IMMUNOGENICITY**

It has been consistently demonstrated in study trials that one month after completion of a three dose primary series at least 99% of vaccinees have a protective antibody titre.

**RECOMMENDATIONS FOR USE**

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

Tetanus 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 to16 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 tetanus 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 Diphtheria 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 Persons 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. Neonatal tetanus may occur in infants born to unimmunized mothers under unhygienic conditions. 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 tetanus toxoid-containing preparation 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 tetanus toxoid-containing vaccine. Refer to Immunization of Persons in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS
Diphtheria-tetanus-pertussis-polio-Hib-containing preparations 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 in Immunocompromised persons in Diphtheria Toxoid in Part 4. For complex cases, referral to a physician with expertise in either or immunization or immunodeficiency is advised.

The antibody response to tetanus boosters given to adults with HIV or humoral immune deficiencies is suboptimal. Tetanus immunity is lost in approximately 50% of patients undergoing chemotherapy for lymphoma or leukemia.

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, including tetanus toxoid-containing preparations. Cases of Guillain Barré Syndrome (GBS) have been reported very rarely following administration of a tetanus toxoid-containing vaccine. Refer to Contraindications and Precautions for additional information. 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 tetanus toxoid-containing combination vaccines. 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 tetanus 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 PROPHYLAXIS
The most important goals of post-exposure prophylaxis are removing the source of toxin production and neutralizing any toxin which may have been released. The first goal is best achieved by timely, thorough wound cleaning. The second goal is achieved by high circulating concentrations of tetanus antibody which inactivate the toxin. Effective neutralizing antibody concentrations at the time of the injury can only be achieved by prior completion of the tetanus toxoid-containing vaccine series or immediate administration of tetanus immune globulin (TIG).

It is important to ascertain the number of doses of tetanus toxoid-containing vaccine previously received, any severe reaction experienced, and the interval since the last dose. Post-exposure prophylaxis of individuals who are previously unimmunized or incompletely immunized (unknown or less than 3 doses) and sustain more than a minor, clean wound should consist of both TIG and tetanus toxoid-containing vaccine (as appropriate for age and immunization history) given at different injection sites using separate needles and syringes. The vaccine series should be completed subsequently unless there is a contraindication. TIG provides immediate passive protection until the exposed person mounts an immune response to the tetanus toxoid-containing vaccine. Refer to Table 1 for additional information.

Previously immunized persons (3 or more doses) may require a booster dose of a tetanus toxoid-containing vaccine depending on the interval since the last booster and the type of wound. A booster dose of tetanus toxoid-containing vaccine is recommended at ten or more years for those with clean, minor wounds and at five or more years for all other wounds.

People who have a tetanus-prone injury and have experienced a severe injection site reaction following a tetanus toxoid-containing vaccine usually have very high serum antitoxin levels and should not receive routine or emergency booster doses of tetanus toxoid-containing vaccine for 10 years. A tetanus-prone injury can be defined as an injury significantly contaminated with material likely to contain either tetanus spores or the presence of necrotic tissue.

Some individuals with humoral immune deficiency (e.g., HIV, agammaglobulinemia or hypogammaglobulinemia) may not respond adequately to tetanus toxoid-containing vaccine. Individuals with humoral immune deficiency who have wounds that are not minor and clean should receive both TIG and tetanus toxoid-containing vaccine, regardless of the time elapsed since the last booster. Table 1 summarizes the recommended use of immunizing agents in wound management.
Table 1: Guide to tetanus prophylaxis in wound management

<table>
<thead>
<tr>
<th>History of tetanus immunization</th>
<th>Clean, minor wounds</th>
<th>All other wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetanus toxoid-</td>
<td>Tetanus toxoid-</td>
</tr>
<tr>
<td></td>
<td>containing vaccine*</td>
<td>containing vaccine*</td>
</tr>
<tr>
<td>Unknown or less than 3 doses in</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>a vaccine series†</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3 or more doses in a vaccine</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>series and less than 5 years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>since last booster dose</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3 or more doses in a vaccine</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>series and more than 5 years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>but less than 10 years since</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>last booster dose</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3 or more doses in a vaccine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>series and more than 10 years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>since last booster dose</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Refer to Recommendations for Use for specific tetanus toxoid-containing vaccine recommendation based on age.
** Given at different injection sites using separate needles and syringes
† Refer to Schedule
¶ Yes, if known to have a humoral immune deficiency state

Tlg: tetanus immune globulin

Persons who have recovered from tetanus disease should receive tetanus toxoid-containing vaccine as recommended for people who not had the disease. Because tetanus is caused by the toxins produced by the tetanus bacterium and not the bacterium itself, recovery from tetanus disease does not confer immunity.

**Tetanus immune globulin (Tlg) for prophylaxis**

The recommended dose of HYPERTET® S/D (Tlg) for adults and children 7 years of age and older is 250 units by deep intramuscular injection. In small children less than 7 years old the routine prophylactic dose of HYPERTET® S/D is 4 units/kg. However, it may be advisable to administer the entire contents of the vial or syringe of HYPERTET® S/D (250 units) regardless of the child’s size, since theoretically the same amount of toxin will be produced in the child’s body by the infecting tetanus organism as it will in an adult’s body.

**Tetanus immune globulin (Tlg) for treatment**

When used in the treatment of tetanus, Tlg should be administered intramuscularly in an effort to neutralize tetanus toxin in body fluids. It has no effect on toxin already fixed to nerve tissue. The optimal therapeutic dose has not been established.

Intramuscular injections are preferably administered in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal muscle should not be used as an injection site because of the risk of injury to the sciatic nerve.

Refer to Vaccine Safety 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-
VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose of tetanus toxoid-containing vaccine is 0.5 mL

Route of administration
Tetanus 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 tetanus 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 tetanus 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 tetanus-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 tetanus 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**

Currently, booster doses of Td vaccine are recommended every 10 years. There is new evidence that booster doses of Td vaccine may not be required every 10 years and this evidence is currently under review. 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 tetanus toxoid-containing vaccine.

**STORAGE REQUIREMENTS**

Store tetanus toxoid-containing preparations in a refrigerator at +2ºC to +8ºC and do not freeze. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information. Refer to Passive Immunization in Part 5 for information regarding immune globulin storage.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**

Tetanus 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 IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS**

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

**COMMON AND LOCAL ADVERSE EVENTS**

**Tetanus-toxoid containing vaccines**

Redness, swelling and pain at the injection site are the most common adverse reactions to childhood tetanus 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 tetanus 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.

**TIg**
Mild soreness at the injection site and slight temperature elevation may occur following TIg injection.

### 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. Anaphylaxis following vaccination with varicella-containing vaccine may occur but is very rare.

**Tetanus-toxoid containing vaccines**
Serious adverse events are rare following immunization with tetanus 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.

Serum sickness, brachial plexus neuropathy, encephalomyelitis and transverse myelitis have rarely been reported in association with tetanus vaccination.

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-containing vaccine. Persons experiencing severe injection site reactions usually have very high serum antitoxin concentrations and should not receive further routine doses of Td vaccine for at least 10 years.

**TIg**
Angioneurotic edema, nephrotic syndrome, and anaphylaxis after injection have been reported rarely.

### OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Trismus (inability to normally open the mouth) associated with tetanus toxoid immunization has rarely been reported. The pathogenesis is unexplained and it may be attributable to a reporting bias. Outcomes have been favourable.

Cases of Guillain-Barre Syndrome (GBS) or polyneuritis have been reported following administration of tetanus toxoid-containing vaccine and there has been one case report of relapsing GBS following each of three doses of vaccine. However, population studies have not supported a causal association.
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) (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

Tetanus 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 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 tetanus 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 tetanus 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 in Part 5 for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

The primary series of three doses tetanus 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.

SELECTED REFERENCES

Centers for Disease Control and Prevention. ACIP Provisional Recommendations for Health Care Personnel on use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) and use of Postexposure Antimicrobial Prophylaxis.


Centers for Disease Control and Prevention. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine in Adults Aged 65 Years and Older — Advisory Committee on Immunization Practices (ACIP), 2012.


Gautret P, Wilder-Smith A. Vaccination against tetanus, diphtheria, pertussis and poliomyelitis in adult travellers. Travel Med Infect Dis 2010;8:155-60.


Okaïs C, Gay C, Seon F et al. Disease-specific adverse events following nonlive vaccines: A paradoxical placebo effect or a nocebo phenomenon? Vaccine 2011;May 31. [Epub ahead of print]


Sanofi Pasteur Ltd. Product Monograph - ADACEL®, August 2009.

Sanofi Pasteur Ltd. Product Monograph - ADACEL®-POLIO, October 2010.


PART 4

TYPHOID VACCINE

- Epidemiology
- Preparations Authorized for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Typhoid fever is caused by *Salmonella enterica* subspecies *enterica* serovar *Typhi* (*S. typhi*).
|      | *S. typhi* is generally transmitted through ingestion of food and water contaminated with the feces of people with the disease or who are chronic *S. typhi* carriers.
|      | Clinical course ranges from mild illness with low-grade fever to severe systemic disease with abdominal perforation and extra-intestinal infection that, if untreated, may be fatal.
|      | There are 3 types of typhoid vaccines: parenteral (Typh-I), parenteral combined with hepatitis A (HA-Typh-I), and oral (Typh-O). These vaccines provide approximately 50% protection against clinical disease.
|      | Protection following Typh-I vaccine lasts for 3 years; protection following Typh-O vaccine lasts for about 7 years.
|      | The most commonly reported adverse events following immunization with Typh-I vaccine are injection site reactions (pain, swelling); following receipt of Typh-O vaccine are abdominal pain, nausea, diarrhea, vomiting, fever, headache and rash.

| Who | Typhoid immunization is recommended for most persons (2 years of age and older) travelling to South Asia (which includes Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka).
|     | Typhoid immunization is not routinely recommended for travel outside of South Asia; however, it might be considered for travellers to areas outside of South Asia (e.g., Africa) based on individual-specific risk factors (such as travelling children; travellers visiting friends and relatives; longer duration of travel; functional or anatomic asplenia, the presence of achlorhydria or the use of acid suppression therapy) and personal preference.
|     | Typhoid immunization is also indicated for laboratory personnel at risk of exposure and for people in close contact with carriers.
### How
- Give a single 0.5 mL dose of Typh-I vaccine for people 2 years of age and older.
- Give a single 1.0 mL dose of HA-Typh-I vaccine for people 16 years of age and older.
- Give one capsule on alternate days to a total of four capsules of Typh-O vaccine for people 5 years of age and older. Typh-O vaccine should be taken approximately one hour before, or two hours after a meal.
- Typh-O vaccine is contraindicated in pregnancy, individuals with an acute gastrointestinal condition or inflammatory bowel disease and in immunocompromised persons, including those with known HIV infection.
- Administration of oral cholera vaccine and Typh-O vaccine should be separated by at least 8 hours.
- Typh-O vaccine may be given concomitantly with or at any time before or after any parenteral vaccine.
- Typh-I vaccine and other travel vaccines may be given concomitantly.

### Why
- The World Health Organization (WHO) has estimated that there are 21 million cases of typhoid a year. About 2% to 5% of untreated typhoid cases become chronic carriers.
- The case fatality rate is approximately 10% for untreated cases in low income settings and <1% for patients receiving care in high income countries.

Since the publication of the 2006 Canadian Immunization Guide:
- Recommendations for the use of typhoid vaccine in travellers have been revised.
- Recommendations for concomitant administration of oral typhoid vaccine and antimalarial drugs have been revised.
- Oral typhoid vaccine is no longer available in sachet format.

This chapter was developed with the Committee to Advise on Tropical Medicine and Travel (CATMAT) and is consistent with the CATMAT Statement on International Travellers and Typhoid. For additional information, refer to the CATMAT statement.

## EPIDEMIOLOGY

### DISEASE DESCRIPTION

**Infectious agent**
Typhoid fever is caused by a bacterium, *Salmonella enterica* subspecies *enterica* serovar Typhi (*S. typhi*).

**Reservoir**
Humans

**Transmission**
*S. typhi* is generally transmitted through ingestion of food and water contaminated with the feces of people with the disease or those who are chronic *S. typhi* carriers. The incubation period is usually 8 to 14 days (range, 3 days to more than 60 days). Individuals infected with *S. typhi* are infectious as long as they are excreting the bacilli, usually from the first week of infection until symptoms have resolved. However, 10% of untreated individuals excrete the bacilli for 3 months or more after initially contracting the disease and 2% to 5% of untreated individuals become asymptomatic chronic carriers.
**Risk factors**

The overall risk of developing typhoid during travel to typhoid endemic countries is very low (less than 1 case/100,000 travellers). The strongest and most consistent predictor of typhoid risk in travellers is destination of travel. The estimated risk of developing travel-associated typhoid is about: 1/3,500 travellers for travel to South Asia (high risk), 1/50,000-100,000 for travel to Sub-Saharan Africa and South America (intermediate risk), and less than 1/300,000 for travel to the Caribbean and Central America (low risk).

It is known that people with anatomic or functional asplenia (i.e. from sickle cell disease) are at increased risk of severe disease from encapsulated bacteria. Several studies have identified travelling children, longer duration of travel, the presence of achlorhydria or use of acid suppression therapy, and travellers visiting friends or relatives as factors that increase the risk of travel-associated typhoid. It is plausible that each of these factors may increase risk of typhoid. The incremental magnitude of risk that these factors contribute in addition to travel destination is unclear.

Although immunocompromised conditions, such as HIV infection, are recognized to predispose to more severe and complicated infections, in general they do not appear to be associated with an increased risk of *S. typhi* infection.

In Canada, chronic carriers pose the greatest public health risk, particularly when working in the food industry.

**Spectrum of clinical illness**

Typhoid fever is a systemic illness of varying severity. The clinical course ranges from mild illness with low-grade fever to severe systemic disease with abdominal perforation and extra-intestinal infection that, if untreated, may be fatal. Symptoms may include fever, headache, abdominal pain, nausea, vomiting, malaise, anorexia, bradycardia, splenomegaly, cough, rose spots on trunk, and constipation. The case fatality rate is approximately 10% for untreated cases in low income settings and <1% for patients receiving care in high income countries. Between 2% and 5% of typhoid cases become chronic carriers, sometimes shedding bacteria in stool for years.

**DISEASE DISTRIBUTION**

**Incidence/prevalence**

*Global*

*S. typhi* infection continues to be a chief cause of enteric disease and remains a significant public health issue in developing countries, principally among children. The WHO estimates the global incidence of typhoid fever to be 21 million cases per year with an associated 210,000 to 840,000 deaths annually. The highest incidence of typhoid fever is among children 17 years of age and younger who live in low and middle income countries. Globally, it is estimated that more than 90% of typhoid cases and deaths occur in Asian countries, predominantly in South Asia (e.g., India).

The incidence of typhoid fever is very low in high income countries. The majority of cases of typhoid fever in these countries occur among travellers returning from endemic areas in low and middle income countries. The estimated incidence of typhoid fever in returned travellers to high income countries ranges from 3 to 30 cases per 100,000.

*National*

In Canada, where most cases occur in travellers, there were a mean of 117 (range, 78 to 175) cases of typhoid reported annually (1999 to 2008); with a mean incidence rate of 0.36 per 100,000 population (range, 0.3 to 0.5/100,000). In a recent study in Quebec, the majority of typhoid cases...
reported by international travellers (34 of 36, 94%) were people who were travelling for the purpose of visiting family members or friends living abroad.

**PREPARATIONS AVAILABLE FOR USE IN CANADA**

**THYPHOID-CONTAINING VACCINES**

- **TYPERIX®** *(Salmonella typhi Vi capsular polysaccharide vaccine for injection), GlaxoSmithKline Inc. (Typh-I)*
- **TYPHIM Vi®** *(Salmonella typhi Vi capsular polysaccharide vaccine for injection), Sanofi Pasteur SA (manufacturer), sanofi pasteur Ltd. (distributor) (Typh-I)
- **VIVAXIM®** *(combined purified Vi polysaccharide typhoid and inactivated hepatitis A vaccine for injection), Sanofi Pasteur SA (manufacturer), sanofi pasteur Ltd. (distributor) (HA-Typh-I)
- **Vivotif®** *(live, oral, attenuated TY21A typhoid vaccine), Crucell Switzerland Ltd. (manufacturer), Crucell Vaccines Inc. (distributor) (Typh-O)*

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

**Efficacy, Effectiveness, and Immunogenicity**

**Efficacy and Effectiveness**

All vaccine efficacy studies were performed in populations living in endemic areas; these data have been extrapolated to travellers. Efficacy of typhoid vaccine (oral and intramuscular formulations) in preventing typhoid is approximately 50%. There are no authorized vaccines to protect against *S. paratyphi* infection (paratyphoid). Evidence suggests that oral typhoid vaccine provides some protection against paratyphoid; however, the evidence is insufficient to recommend the off-label use of typhoid vaccine for this indication.

**Immunogenicity**

**Typh-I vaccines**

Immunity following Typh-I vaccine is thought to last for 3 years.

**Typh-O vaccine**

Live, attenuated oral typhoid vaccine stimulates a cell-mediated immune response, as well as inducing both secretory and humoral antibody. Protective antibodies are detectable for about 7 years following receipt of Typh-O vaccine.

**Recommendations for Use**

**Children (2 to 17 years of age) and Adults (18 years of age and older)**

Most Canadian travellers visiting South Asia (including Afghanistan, India, Nepal Bangladesh, Maldives, Sri Lanka and Bhutan) should be offered typhoid vaccine.

Most Canadians travellers visiting destinations other than South Asia (e.g., Africa) should not routinely be offered typhoid vaccine. However, the decision of whether or not to offer typhoid vaccination for destinations other than South Asia should be carefully balanced against the presence of other factors that may increase the risk of travel-associated typhoid (such as travelling children; travellers visiting friends and relatives; longer duration of travel and prolonged exposure to potentially contaminated food and
Typhoid immunization is recommended for individuals with ongoing or intimate exposure (e.g., family member) to a chronic carrier of *S. typhi*.

Typhoid immunization is recommended for laboratory personnel regularly working with *S. typhi* in clinical or research laboratories. Technicians working in routine microbiology laboratories do not need to be vaccinated.

Typh-I vaccine is indicated for persons 2 years of age and older and Typh-O vaccine may be used in people 5 years of age and older. HA-Typh-I vaccine is indicated for people 16 years of age and older.

Refer to Schedule.

**PREGNANCY AND BREASTFEEDING**

No information is available on the safety of Typh-I vaccine in pregnancy; however, there is no theoretical reason to suspect an increased risk from inactivated vaccines. Typhoid vaccine should be considered in pregnant women like anyone else, when indicated due to place of travel, the presence of risk factors and personal preference. The appropriate vaccine for pregnant or breastfeeding women is inactivated Typh-I vaccine; pregnant women should not receive live vaccines, including Typh-O vaccine. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

**IMMUNOCOMPROMISED PERSONS**

Typh-I vaccine may be administered to immunocompromised persons if indicated; however, an adequate response may not be achieved. Typh-O vaccine should not be given to immunocompromised persons, including those with known HIV infection. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

**Household contacts**

Healthy persons vaccinated with Typh-O vaccine do not shed vaccine-strain organisms in their stool and secondary transmission to contacts does not occur.

Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

**TRAVELLERS**

Travellers are generally at low risk of typhoid fever. The strongest and most consistent predictor of typhoid risk in travellers is destination of travel. The estimated risk of developing travel associated typhoid is about: 1/3,500 travellers to South Asia (high risk), 1/50,000-100,000 for travel to Sub-Saharan African and South America (intermediate risk), and less than 1/300,000 for travel to the Caribbean and Central America (low risk).

Most Canadian travellers visiting South Asia (including Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka and) should be offered typhoid vaccine. The risk of typhoid is highest for persons travelling to India, Pakistan, and Bangladesh. Data suggest that most cases of typhoid occur when travellers stay more than two weeks.

Most Canadians travellers visiting destinations other than South Asia (e.g., Africa) should not routinely be offered typhoid vaccine. However, the decision of whether or not to offer typhoid vaccination for destinations other than South Asia should be carefully balanced against the presence of other factors that may increase the risk of travel-associated typhoid (such as travelling children; travellers visiting friends and relatives; longer duration of travel; anatomic or functional asplenia (including sickle cell anemia), the presence of achlorhydria or the use of acid suppression therapy) and personal preference.
Immunization is only modestly effective against typhoid and provides no protection against other fecal-oral diseases; therefore, all travellers should be advised to adhere to basic sanitation and food and water precautions irrespective of whether they are immunized against typhoid. Refer to Immunization of Travellers in Part 3 for additional general information.

WORKERS
Typhoid vaccine is recommended for laboratory personnel regularly working with *S. typhi* in clinical or research laboratories. Technicians working in routine microbiology laboratories do not need to be vaccinated. Refer to Immunization of Workers in Part 3 for additional general information.

OUTBREAK CONTROL
Typhoid immunization is not routinely recommended for the control or containment of typhoid outbreaks in Canada.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE (refer to Table 1)

*Typh-I vaccine*

Persons 2 years of age and older should receive a single 0.5 mL dose intramuscularly at least 14 days prior to potential exposure.

*Typh-O vaccine*

Persons 5 years of age and older should take one capsule on alternate days to a total of four capsules. All four capsules must be taken for optimal protection. Minor variations in dosing schedule are not expected to affect efficacy. However, if it is necessary to repeat the series because of a longer interval between doses (more than a week), the administration of an additional full course of vaccine is not harmful. Administer the capsules in accordance with the instructions in the manufacturer’s product leaflet. Immunization (ingestion of all 4 capsules) should be completed at least 7 days prior to potential exposure.

*HA-Typh-I vaccine*

Persons 16 years of age and older should receive a single 1.0 mL dose for primary immunization against typhoid at least 14 days prior to potential exposure. To provide long-term protection against hepatitis A, a booster dose of hepatitis A vaccine should be given 6 to 36 months later. Alternatively, HA-Typh-I vaccine can be given as a booster vaccine after 3 years in people who also require ongoing protection against typhoid fever. Refer to Hepatitis A Vaccine in Part 4 for additional information.
Table 1: Typhoid vaccines authorized for use in Canada

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Parenteral inactivated vaccines (Typh-I)</th>
<th>Oral, live attenuated vaccine (Typh-O)</th>
<th>Combined, parenteral inactivated vaccine (HA-Typh-I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>TYPHIM Vi®</td>
<td>Vivotif®</td>
<td>ViVAXIM®</td>
</tr>
<tr>
<td>Authorized for use in persons</td>
<td>2 years of age and older</td>
<td>5 years of age and older</td>
<td>16 years of age and older</td>
</tr>
<tr>
<td>Protection begins</td>
<td>14 days following vaccination</td>
<td>7 days following vaccination</td>
<td>14 days following vaccination</td>
</tr>
<tr>
<td>Dose and schedule</td>
<td>One dose: 0.5 mL</td>
<td>4 capsules taken on alternate days</td>
<td>One dose: 1.0 mL</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intramuscular injection</td>
<td>Oral</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container.</td>
<td>Pregnancy</td>
<td>Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container.</td>
</tr>
<tr>
<td>Re-immunization</td>
<td>Every 3 years</td>
<td>Every 7 years</td>
<td>Hepatitis A - boost with a single dose of hepatitis A vaccine 6 months to 36 months later for long term protection. Typhoid - re-immunize with a single dose of Typh-I vaccine every 3 years. HA-Typh-I vaccine can be used after 3 years if boosters are needed for both hepatitis A and typhoid.</td>
</tr>
</tbody>
</table>
Based on CATMAT Statement on International Travellers and Typhoid. Re-immunization should be carried out when a person remains at risk in conditions of repeated or continuous exposure. There is no data on continued protection in travellers.

CATMAT is aware that The Yellow Book - CDC Health Information for International Travellers 2012 advises repeat immunization with oral live typhoid vaccine every 5 years; however, this recommendation is consistent with the Health Canada Biologics and Genetic Therapies Directorate vaccine authorization for re-immunization every 7 years.

Refer to Vaccine Administration Practices in Part 1 for additional information.

BOOSTER DOSES AND RE-IMMUNIZATION

Periodic booster doses in persons at continued risk of typhoid may be expected to increase antibody titres and maintain protection. Booster doses should be offered when a person remains at risk in conditions of repeated or continuous exposure. For Typh-I vaccine, administer a booster dose every 3 years. For Typh-O vaccine, administer a booster of 4 doses every 7 years. For the combined HA-Typh-I vaccine, boost with a single dose of inactivated hepatitis A vaccine 6 months to 36 months later; a single dose of Typh-I vaccine may be given at or after 3 years; HA-Typh-I vaccine can be used after 3 years if boosters are needed for both hepatitis A and typhoid.

SEROLOGICAL TESTING

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

STORAGE REQUIREMENTS

Store typhoid vaccines in a refrigerator at +2°C to +8°C. Do not freeze. Protect TYPHERIX® and Typh-O vaccines from light. Protect Typh-O vaccine from moisture and high humidity. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

The administration of oral cholera vaccine and Typh-O vaccine capsules should be separated by at least 8 hours; Typh-O vaccine can be given concomitantly with or at any time before or after any parenteral vaccine. There is no known interaction between Typh-I vaccine and other travel vaccines, such as hepatitis A vaccine, yellow fever vaccine and 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

Typh-I vaccine
Common adverse events (1% to 10% of vaccinees) include: injection site tenderness, induration, redness or pain, fever, headache, general malaise or myalgia.

Typh-O vaccine
Common adverse events include: abdominal pain, nausea, diarrhea, vomiting, fever, headache and rash.

HA-Typh-I vaccine
Very common (more than 10% of vaccinees) adverse events include: injection site pain, induration, swelling and erythema; headache; myalgia and weakness. Common adverse events include: fever,
malaise, nausea, diarrhea and dizziness. Uncommon adverse events (0.1% to less than 1% of vaccinees) include: pruritus and rash.

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. Anaphylaxis following vaccination with typhoid 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 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
Typhoid vaccine is contraindicated in persons with history of anaphylaxis after previous administration of the vaccine and in persons with suspected or proven hypersensitivity to any component of the vaccine or its container. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of vaccines available for use in Canada and their contents. For typhoid vaccines, potential allergens include:

- TYPHERIX® (rubber stopper in pre-filled syringe).
- TYPHIM Vi® (no known potential allergens).
- VIVAXIM® (neomycin).
- Vivotif® (gelatin).

Typh-O vaccine is contraindicated in pregnancy, individuals with an acute gastrointestinal condition or inflammatory bowel disease and in immunocompromised persons.

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

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

DRUG-DRUG AND DRUG-FOOD INTERACTIONS
The Typh-O vaccine series should be finished 3 days before commencing, or initiated 48- to 72 hours after completing, treatment with sulphonamides or other antibiotics active against S. typhi, or antimalarials. Exceptions include chloroquine, mefloquine and malarone, as these antimalarials do not affect the immune response to Typh-O vaccine and can be administered at the same time as, or at any interval before or after Typh-O vaccine.

Typh-O vaccine should be taken approximately one hour before, or two hours after a meal. Alcoholic beverages should not be consumed one hour before or two hours after taking Typh-O vaccine.

Typh-I, HA-Typh-I or Typh-O vaccines can be given before, concurrently with, or after immune globulin products.

OTHER CONSIDERATIONS
INTERCHANGEABILITY OF VACCINES
Although there are no data regarding the interchangeability of typhoid vaccines, it is presumed that boosting can be performed with any of the available formulations regardless of the vaccine used initially. The boosting interval should correspond to the interval established for the preceding vaccine (i.e., 3 years.
after Typh-I vaccine; 7 years after Typh-O vaccine) Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

SELECTED REFERENCES


PART 4

VARICELLA (CHICKENPOX) VACCINE

- Epidemiology
- Preparations for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine and Immune Globulin Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

<table>
<thead>
<tr>
<th>What</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary varicella zoster virus infection causes varicella (chickenpox) and reactivated infection results in herpes zoster (shingles).</td>
<td></td>
</tr>
<tr>
<td>Complications are more common in adolescents, adults and immunocompromised people. Children with impaired immunity are at risk of severe varicella and death.</td>
<td></td>
</tr>
<tr>
<td>Varicella-containing vaccine is available as univalent varicella vaccine or combined multivalent measles-mumps-rubella-varicella (MMRV) vaccine.</td>
<td></td>
</tr>
<tr>
<td>Univalent varicella vaccine or varicella zoster immune globulin (VarIg) may be used for varicella post-exposure immunization, depending on the circumstances.</td>
<td></td>
</tr>
<tr>
<td>The efficacy of varicella vaccines in children is estimated to be 94.4% following a single dose and 98.3% following a second dose.</td>
<td></td>
</tr>
<tr>
<td>Reactions to varicella vaccines are generally mild and include pain, swelling and redness at the injection site in 10% to 20% of recipients; low-grade fever in 10% to 15%; and a varicella-like rash in 3% to 5% of vaccinees after the first dose and 1% after the second dose.</td>
<td></td>
</tr>
<tr>
<td>Reactions to MMRV vaccine include pain and redness at the injection site and/or low-grade fever in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C), occur in 1% to less than 10% of vaccinees and can occur 7 to 21 days after receipt of vaccine. Febrile seizures following vaccination with a varicella-containing vaccine should be reported as an Adverse Events Following Immunization.</td>
<td></td>
</tr>
<tr>
<td>Univalent varicella or MMRV vaccine is recommended for immunization of healthy children aged 12 months to 12 years of age</td>
<td></td>
</tr>
<tr>
<td>Univalent varicella vaccine is recommended for susceptible adolescents (13 to 17 years of age) and susceptible adults (18 to 49 years of age).</td>
<td></td>
</tr>
<tr>
<td>Priority groups for varicella immunization include susceptible:</td>
<td></td>
</tr>
<tr>
<td>- Non-pregnant women of childbearing age</td>
<td></td>
</tr>
<tr>
<td>- Household contacts of immunocompromised people</td>
<td></td>
</tr>
<tr>
<td>- Health care workers</td>
<td></td>
</tr>
<tr>
<td>- Adults who may be exposed occupationally to varicella (e.g., people who work with</td>
<td></td>
</tr>
</tbody>
</table>
young children)
- Immigrants and refugees from tropical regions
- People receiving chronic salicylate therapy (e.g., acetylsalicylic acid [ASA]).
- People with cystic fibrosis
- Susceptible adults exposed to a case of varicella
- Do not immunize pregnant women with varicella-containing vaccine. Pregnancy should be avoided for at least 4 weeks after receipt of vaccine.
- Administer MMRV vaccine in the routine manner to children who have a history of anaphylactic hypersensitivity to eggs.
- Univalent varicella vaccine may be considered for patients with select immunodeficiency disorders. MMRV vaccine has not been studied in persons with impaired immune function, including primary or secondary immunodeficiency disorders, and so is not recommended for this group.

### How
- For routine childhood immunization, administer the first dose of varicella-containing vaccine (univalent varicella or MMRV) at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter.
- For children aged 12 months to 12 years of age not immunized on the routine schedule, the recommended interval between 2 doses of any varicella-containing vaccine is at least 3 months. A minimum interval of 6 weeks between doses of varicella-containing vaccine may be used if rapid, complete protection is required. Adolescents (13 to 17 years of age) and adults (under 50 years of age) who may be susceptible to varicella (refer to Susceptibility and immunity for a definition of susceptible) should be tested for antibodies against varicella. If varicella susceptible, administer two doses of univalent varicella vaccine, at least 6 weeks apart. Adolescents and adults (under 50 years of age) who have received only one dose of varicella vaccine should be offered a second dose. For adults 50 years of age and older, refer to Herpes Zoster (Shingles) Vaccine in Part 4 for recommendations.
- Avoid salicylates (e.g., acetylsalicylic acid [ASA]) for 6 weeks after varicella vaccination.
- Varicella-containing vaccine may be administered concomitantly with other routine childhood vaccines at different injection sites using separate needles and syringes.

### Why
- Varicella occurs worldwide.
- Children up to 12 years of age with varicella disease who are otherwise healthy account for 80% to 85% of varicella-associated physician visits, 85% to 90% of hospitalizations, and nearly 50% of fatal cases.

Since the publication of the 2006 Canadian Immunization Guide:
- New recommendations have been made regarding a two-dose varicella vaccination schedule for healthy children.
- New recommendations have been made about the use of univalent varicella vaccine in human immunodeficiency virus (HIV)-infected individuals.
- A new combined multivalent vaccine (measles-mumps-rubella-varicella [MMRV]) has become available for healthy children aged 12 months to 12 years of age.
- Changes in the minimum interval between varicella-containing vaccines have been recommended to make the intervals more consistent between varicella-containing products.
- Herpes zoster vaccine has become available for older adults. Refer to Herpes Zoster (Shingles) Vaccine in Part 4 for additional information.

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent
Varicella (chickenpox) is a generalized viral disease caused by varicella zoster virus (VZV), a deoxyribonucleic acid (DNA virus) of the Herpesvirus family.

Reservoir
Humans

Transmission
VZV is spread by the airborne route as well as by direct contact with the virus shed from skin lesions. The attack rate among susceptible contacts in household settings is estimated at 65% to 87%. The incubation period is from 10 to 21 days after exposure, usually 14 to 16 days. Infectiousness begins 1 to 2 days before onset of the rash and lasts until the last lesion has crusted.

Risk factors
Varicella has been considered to be a benign disease in otherwise healthy children up to 12 years of age. Risk of severe varicella infection increases with age. Adults and, in particular, pregnant women are at increased risk of severe disease. However, because most infections occur in children up to 12 years of age in unvaccinated communities, the majority of severe cases occur in this age group. Children up to 12 years of age account for 80% to 85% of varicella-associated physician visits, 85% to 90% of hospitalizations, and nearly 50% of fatal cases. Children with impaired immunity are at risk of severe varicella and death.

Seasonal/temporal pattern
Varicella disease increases during the school year and decreases sharply during summer vacation.

Spectrum of clinical illness
Symptoms of varicella include low-grade fever, mild constitutional symptoms, and a generalized, pruritic rash, with lesions at different stages that progress rapidly from macules to papules to vesicular lesions before crusting. The main complications of varicella include secondary bacterial skin and soft tissue infections, bacteremia, pneumonia, osteomyelitis, septic arthritis, necrotizing fasciitis, toxic shock-like syndrome, cerebellar ataxia, stroke and encephalitis. Varicella increases the risk of severe invasive group A streptococcal infection in previously healthy children by 40- to 60-fold. Complications are more common in adolescents, adults and people with conditions that compromise their immune system who have higher rates of pneumonia, encephalitis and death.

Congenital varicella syndrome is rare when infection occurs before the 13th or after the 20th week of gestation. The risk is approximately 2% when infection occurs at between 13 and 19 weeks of gestation. Congenital infection results in a wide clinical spectrum, which may include low birth weight, ophthalmic abnormalities, skin scarring, limb atrophy, cerebral atrophy and a variety of other anomalies. Maternal varicella occurring in the 5 days before to 2 days after birth is associated with severe neonatal varicella in 17% to 30% of infants, with high case fatality for the newborn.

Varicella case fatality rates are highest among adults (30 deaths/100,000 cases) followed by infants under 1 year of age (7 deaths/100,000 cases) and those aged 1 to 19 years (1 to 1.5 deaths/100,000 cases). In Canada, 70% of the 59 varicella related deaths in the years 1987 to 1997 (pre-vaccine) occurred in those over 15 years of age. Between 2000 and 2009, a total of 10 pediatric deaths due to varicella were reported by the Immunization Monitoring Program ACTive (IMPACT) system, with a range of 0 to 3 deaths per year.
DISEASE DISTRIBUTION

Incidence/prevalence

Global

Varicella occurs worldwide and, in countries without vaccination programs, it is mainly a disease of childhood, developing in 50% of children by the age of 5 years and 90% by the age of 12 years. The epidemiology of varicella is similar among developed countries such as the United Kingdom (UK), the United States (US), and Canada. No significant gender difference has been found. People from tropical regions (including South Asia, South East and East Asia) are less likely to acquire immunity in childhood and, therefore, have higher rates of susceptibility as adults.

In the US, there were approximately 4 million varicella cases annually before varicella vaccine was licensed in 1995. The incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly in the post-vaccine era. Varicella-related hospitalizations in the US decreased from 2.3-5 per 100,000 population (1993-1995) to 0.3-1.3 per 100,000 population (2001-2002) and ambulatory care visits for varicella declined by 59%. In 2000, the number of varicella-related deaths in the US had declined by 78% in the under-20-year age group and by 63% in the 20-year to 49-year age group, as compared with the pre-vaccine years, 1990 to 1994.

National

In the pre-vaccine era, it is estimated that there were approximately 350,000 varicella cases and 1,500 to 2,000 varicella-related hospitalizations each year in Canada. However, assessing the effect of varicella immunization programs on the incidence of the disease is difficult as varicella infections are significantly under-reported, with less than 10% of the expected cases reported annually. Canadian studies have found decreases in the burden of varicella following the introduction of immunization programs. Alberta saw a significant decline in disease incidence compatible with a vaccination program effect. Following introduction of publicly funded varicella vaccination in Ontario, varicella-related hospitalizations, emergency department use, and visits to physicians’ offices decreased 53%, 43% and 45% respectively.

Information on pediatric hospitalized cases and deaths are available from the IMPACT system for the periods 1990 to 1996 and 1999 to 2009. These data indicate that the majority of hospitalizations occur in previously healthy children. Among these cases, children younger than 10 years of age were mainly affected and accounted for 16.5% (less than 1 year of age) and 75.5% (1 to 9 years of age) of the total hospitalizations. Since 2004, the annual average number of varicella hospitalizations at IMPACT centers has dropped from 300 (2000 to 2004) to 114 (2005 to 2009).

PREPARATIONS AVAILABLE FOR USE IN CANADA

VARICELLA-CONTAINING VACCINES

- **VARIVAX® III**: live, attenuated, univalent varicella virus vaccine, (Oka/Merck), Merck Canada Inc. (Var)
- **VARILRIX®**: live, attenuated, univalent varicella virus vaccine, (Oka/GSK), GlaxoSmithKline Inc. (Var)
- **PRIORIX-TETRA®**: live, attenuated, combined measles, mumps, rubella and varicella vaccines, GlaxoSmithKline Inc. (MMRV)

VARICELLA ZOSTER IMMUNE GLOBULIN

- **VariZIG™**: varicella zoster immune globulin (human), Cangene Corporation (VarIg)
For complete prescribing information, consult the product leaflet or information contained within Health Canada’s authorized product monographs available through the Drug Product Database at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php. Refer to Table 1 and Table 2 in General Considerations in Part 1 for lists of all vaccines and passive immunizing agents available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

The rate of breakthrough varicella disease in vaccinees following one dose of varicella vaccine has been estimated at 7.2% over a 10-year follow-up period. American data estimate the overall effectiveness of a single dose vaccination program to be between 70% and 90% in preventing varicella disease of any severity, and 95% in protecting against severe varicella for at least 7 to 10 years after immunization. However, despite high vaccination coverage, limitations of the single dose regimen in achieving varicella control have been identified in the US. Primary vaccine failure and waning immunity appear to be responsible for breakthrough disease.

A two-dose primary schedule for children 12 months to 12 years of age has improved varicella control. In a 10-year prospective study, the cumulative risk of breakthrough disease was 3.3-fold lower in children who received two doses of varicella vaccine compared to children who received one dose. The estimated vaccine effectiveness was 98.3% after two doses, significantly higher than after one dose (94.4%). The 2-dose regimen was 100% efficacious against severe varicella.

There are no data regarding the efficacy of MMRV vaccine.

IMMUNOGENICITY

In healthy children 12 months to 12 years of age, a single univalent varicella vaccine dose results in a seroconversion rate of 98% at 4 to 6 weeks after vaccination with antibodies persisting in 98% at 5 years and 96% at 7 years after vaccination. A second dose of a univalent varicella vaccine in children produces an improved immunologic response that is correlated with improved protection. In adults and adolescents 13 years of age and older, two vaccine doses administered 4 to 8 weeks apart result in seroconversion rates of 99% at 4 to 6 weeks after the second dose, with persistence of antibodies 5 years later in 97%.

In a study of 12-month-old children, a single dose of MMRV vaccine resulted in a seroconversion rate for measles, mumps, rubella and varicella of 98%, 97%, 98% and 93%, respectively. The seroconversion rates and geometric mean titres for individual components were not significantly different from those achieved after measles-mumps-rubella (MMR) plus a univalent varicella vaccine or MMR vaccine alone. A study of children receiving two doses of MMRV vaccine during the second year of life noted seropositivity for measles, mumps, rubella and varicella of 99%, 97.4%, 100% and 99.4% respectively by the third year post-vaccination. Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies following MMRV vaccinations are under evaluation.

RECOMMENDATIONS FOR USE

HEALTHY CHILDREN (12 months to 12 years of age)

Two doses of varicella-containing vaccine (univalent varicella or MMRV) should be given for routine immunization of children and for immunization of children who have missed varicella immunization on the routine schedule.

Children with a history of varicella disease occurring before 12 months of age should receive routine immunization with two doses of varicella-containing vaccine after 12 months of age, because varicella disease at less than 12 months of age has been associated with an increased risk of a second episode of varicella. Children who receive one dose of varicella-containing vaccine and subsequently develop
laboratory confirmed breakthrough infection do not require a second dose of a varicella-containing vaccine for varicella protection.

**ADOLESCENTS (13 to 17 years of age)**
Adolescents without contraindications who may be susceptible to varicella (refer to **Susceptibility and immunity** for a definition of susceptible) should be serologically tested for varicella antibodies because the majority of such adolescents will be immune. If the adolescent is shown to be serologically susceptible to varicella, the person should receive two doses of a univalent varicella vaccine (as MMRV is not authorized in this age group) a minimum of 6 weeks apart. In adolescents with documentation of receiving only one dose of a varicella-containing vaccine, a second dose should be offered.

**ADULTS (18 years of age and older)**
Adults (under 50 years of age) without contraindications who may be susceptible to varicella (refer to **Susceptibility and immunity** for a definition of susceptible) should be serologically tested for varicella antibodies because the majority of such adults will be immune. If an adult under the age of 50 years is shown to be serologically susceptible to varicella, the person should receive two doses of univalent varicella vaccine. Adults (under 50 years of age) who received only one dose of varicella vaccine should be offered a second dose.

In adults aged **50 years and older**, routine serologic testing is not recommended. Nearly all Canadians 50 years of age and older, will have had prior varicella exposure even if the person does not remember having had chickenpox or herpes zoster. In the rare circumstance that an adult aged 50 years and over is known to be serologically susceptible to varicella based on previous testing for another reason, and is without contraindications, the individual should be vaccinated with two doses of univalent varicella vaccine. For other adults 50 years of age and over, refer to **Herpes Zoster (Shingles) Vaccine** in Part 4 for additional information.

**Susceptibility and immunity**
A self-reported history of varicella is considered a reliable history of varicella disease in individuals born before 2004 (with the exception of health care workers). For children born in 2004 or later and health care workers, a health care provider diagnosis of varicella or herpes zoster is necessary to be considered a reliable history of varicella disease.

Individuals who have one or more of the following are considered immune to varicella. Individuals who do not have ANY of the following are considered susceptible to varicella:

- Self-reported history of varicella if born before 2004 (except for health care workers)
- For those born in 2004 or later and for health care workers, a health care provider diagnosis of varicella or herpes zoster
- Documented evidence of immunization with two doses of a varicella-containing vaccine
- A history of laboratory confirmed varicella infection
- Laboratory evidence of immunity

Recipient of hematopoietic stem cell transplant should be considered susceptible in the post-transplantation period regardless of a history of varicella disease or vaccination, or positive serologic test results.

**PRIORITY GROUPS**
The following groups are priorities for varicella immunization if susceptible:

- **Women of childbearing age**. Varicella-containing vaccine should not be given during pregnancy. Refer to **Pregnancy and lactation**.
- **Household contacts of immunocompromised people**. Refer to **Immunocompromised persons**.
- **Health care workers** and others who may be exposed occupationally to varicella (e.g., teachers of young children, child care workers). Refer to **Workers**.
- **Immigrants and refugees from tropical regions** who are more likely to be susceptible to varicella. Refer to Persons new to Canada.
- People receiving **chronic salicylate therapy** (medications derived from salicylic acid, e.g., acetylsalicylic acid [ASA]) because of an association between wild-type varicella disease, salicylate therapy and Reye’s syndrome. Refer to **Drug interactions** for additional information regarding the avoidance of salicylate therapy following varicella vaccination.
- People with **cystic fibrosis**, because varicella disease may cause a transient worsening of lung function.
- **Persons exposed to a case** of varicella. Refer to **Post-exposure immunization**.

Refer to **Schedule**.

**PERSONS WITH INADEQUATE IMMUNIZATION RECORDS**

Children and adults, who are susceptible to varicella, including those lacking adequate documentation of immunization, should be started on an immunization schedule appropriate for their age and risk factors. Varicella-containing vaccine may be given regardless of possible previous receipt of the vaccine because adverse events associated with repeated immunization have not been demonstrated. Refer to **Immunization of Children and Adults with Inadequate Immunization Records** in Part 3 for additional general information.

**PREGNANCY AND LACTATION**

Immunity to varicella should be reviewed in women of reproductive age and vaccination should be recommended to susceptible non-pregnant women. Women should delay pregnancy by at least 4 weeks following vaccination with a univalent varicella vaccine.

Varicella-containing vaccine is contraindicated in pregnancy because there is a theoretical risk to the fetus; however, there is no evidence to demonstrate a teratogenic risk from the vaccine. Termination of pregnancy should not be recommended following inadvertent immunization with varicella vaccine on the basis of fetal risks following maternal immunization. Incidents of inadvertent varicella immunization during pregnancy, or of pregnancy occurring within 3 months after immunization with VARIVAX® III, should be reported to the registry maintained by Merck Canada Inc., Medical Services (telephone: 1-800-684-6686). GlaxoSmithKline Inc. does not maintain a pregnancy outcome registry for VARILRIX®.

Women who are breastfeeding and individuals in households where there is a newborn can be vaccinated with a univalent varicella vaccine.

Refer to **Contraindications and Precautions**. Refer to **Immunization in Pregnancy and Breastfeeding** in Part 3 for additional general information.

**PATIENTS/RESIDENTS IN HEALTH CARE INSTITUTIONS**

Most residents of long-term care facilities will be immune to varicella. Postpartum women susceptible to varicella should be vaccinated before discharge. Refer to **Immunization of Patients in Health Care Institutions** in Part 3 for additional general information.

**IMMUNOCOMPROMISED PERSONS**

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised person, approval from the individual’s attending physician should be obtained before vaccination. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

In Canada, only VARILRIX® has received authorization for the vaccination of select groups of immunocompromised people; however, VARIVAX® III may also be used. MMRV vaccine has not been studied in persons with impaired immune function, including primary or secondary immunodeficiency disorders, and so is not recommended for this group.
In immunosuppressed people, antibody testing may be considered 6 to 8 weeks after the last dose of univalent varicella vaccine is given. Local antibody assays may not be sensitive enough to detect antibody after vaccination. For the purposes of post-exposure prophylaxis, an immunosuppressed person with a negative test should be considered non-immune. Therefore, if antibody is not detectable, consider offering immunocompromised persons VarIg upon subsequent exposures to wild-type varicella. Refer to Figure 1, Table 1 and Post-exposure immunization.

Family or medical history
People who have a suspicious history for immunodeficiency disorders (e.g., known or suspected family history of congenital immunodeficiency disorder or HIV infection, or a history of failure to thrive and recurrent infections) should not be immunized until they have been fully investigated and T cell dysfunction ruled out.

Congenital (primary) immunodeficiency
Live vaccines are generally not recommended for patients with congenital immunodeficiency states although some exceptions exist.

B cell deficiency
Univalent varicella vaccine should be considered if the individual is not receiving regular immune globulin replacement therapy, which may affect the efficacy of the vaccine. People with isolated humoral immunoglobulin deficiency disorders and known intact T cell systems may be vaccinated with two doses of univalent varicella vaccine at least 3 months apart.

T cell, natural killer T cell, and mixed cellular and antibody defects (e.g., Severe Combined Immune Deficiency [SCID])
All live vaccines, including varicella-containing vaccine, are contraindicated in people with defects in T cell function.

Phagocytic and neutrophil disorders (e.g., congenital neutropenia, leukocyte adhesion and migration defects, chronic granulomatous disease)
Children with phagocytic or neutrophil disorders may be vaccinated with two doses of univalent varicella vaccine at least 3 months apart.

Complement deficiency
Persons with complement deficiency disorders may be vaccinated with two doses of univalent varicella vaccine at least 3 months apart. Because immunity can decrease over time, assessment of antibody titres and re-immunization, if needed, should be considered.

Acquired (secondary) immunodeficiency
Malignant hematologic disorders
Varicella-containing vaccine is contraindicated in individuals with severe immunodeficiency due to conditions such as: blood dyscrasias, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Varicella-containing vaccine is contraindicated in people undergoing immunosuppressive treatment for acute leukemia. Children with Acute Lymphocytic Leukemia (ALL) may be vaccinated with univalent varicella vaccine if the disease has been in remission for at least 12 months, the child's total lymphocyte count is at least $1.2 \times 10^9/L$, the child is not receiving radiation therapy, and maintenance chemotherapy can be withheld for at least 1 week before to 1 week after immunization. Two doses of univalent varicella vaccine may be given, at least 3 months apart.
**Malignant solid tumours**

Varicella-containing vaccine is contraindicated in people undergoing immunosuppressive treatment for any malignant solid tumours.

**Hematopoietic stem cell transplantation (HSCT - autologous or allogeneic)**

- Pre-transplantation: People awaiting HSCT should not receive varicella-containing vaccine. Vaccination of donors immediately before stem cell harvest is not recommended because there is no evidence that immunity can be transferred from the donor to the recipient and there are no safety data.
- Post-transplantation: Antibody titres to vaccine-preventable diseases decline after HSCT if the recipient is not re-vaccinated. Vaccination of seronegative HSCT recipients with one dose of univalent varicella vaccine may be considered at two years or more after transplantation provided there is no evidence of chronic graft-versus-host disease, immunosuppression has been discontinued for at least 3 months, and the person is deemed to be immunocompetent by a transplant specialist. Serologic status should be checked prior to vaccination and vaccine administered to serologically varicella susceptible persons only. Safety and immunogenicity data are not available regarding administration of more than one dose of varicella-containing vaccine after HSCT.

**Solid organ transplantation**

Varicella vaccination is recommended before transplantation for susceptible (as determined by serology) children and adults. Ideally, and if time permits, two doses of univalent varicella vaccine should be given at least 3 months apart with the last dose being given at least 6 weeks prior to transplantation. If time does not permit administration of a two-dose series, one dose of univalent varicella vaccine should be given and the transplant delayed by at least 4 weeks. The person should not be receiving immunosuppressive treatment at the time of vaccination. Varicella-containing vaccine is not recommended after solid organ transplantation.

**Immunosuppressive therapy**

Vaccination status for varicella should be reviewed for immunocompetent persons who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency.

If indicated, varicella vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy (e.g., high-dose systemic corticosteroids [2 mg/kg per day or more of prednisone or its equivalent 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 live vaccines. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of live vaccines. The interval between discontinuation of immunosuppressive drugs and varicella vaccine administration may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors. If immunosuppressive therapy cannot be stopped, live vaccines are generally contraindicated, although the risk-to-benefit ratio may favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of varicella infection.

Corticosteroid therapy is not a contraindication to administering a live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 20 mg of prednisone or equivalent per day for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).
**HIV-infected**

An infectious disease specialist/immunologist should be consulted for advice on varicella immunization in HIV-infected people. Varicella vaccine is contraindicated in persons with advanced HIV/AIDS. The safety and immunogenicity of MMRV vaccine in HIV-infected individuals has not been evaluated, and MMRV vaccine is not routinely recommended.

- **Children:** HIV-infected children 12 months of age and older, and with CDC clinical category N, A, or B and immunologic category 1 or 2 (i.e., CD4 percentage ≥15%) may receive two doses of a univalent varicella vaccine 3 to 6 months apart. Univalent varicella vaccine may be administered concomitantly with measles-mumps-rubella (MMR) vaccine at different injection sites using separate needles and syringes. Refer to [Measles Vaccine], [Mumps Vaccine] and [Rubella Vaccine] in Part 4 for additional information.

- **Adolescents and adults:** There are no published data on the use of varicella vaccine in susceptible HIV-infected adolescents and adults. HIV-infected adolescents and adults should be asked for a history of varicella disease or vaccination (refer to [Susceptibility and immunity]), and if negative for both, serology should be requested to confirm susceptibility. Based on expert opinion, immunization with two doses of univalent varicella vaccine administered 3 months apart may be considered for susceptible HIV-infected adolescents and adults with CD4 cell count ≥200 x 10^6/L and CD4 percentage ≥15%.

**Household contacts**

Susceptible household contacts of immunocompromised people should receive varicella-containing vaccine as appropriate for age and risk factors. If the vaccine recipient develops a varicella-like rash, the rash should be covered and the vaccinee should avoid direct contact with the immunocompromised person for the duration of the rash. Secondary transmission from people with post-vaccination varicella-like rashes can occur rarely.

Refer to [Post-exposure immunization] and [Contraindications and Precautions]. Refer to [Immunization of Immunocompromised Persons] in Part 3 for additional general information.

**PERSONS WITH CHRONIC DISEASES**

**Hyposplenism or asplenia**

Hyposplenic or asplenic (congenital absence, surgical removal or functional [e.g., sickle cell disease]) individuals should receive two doses of univalent varicella vaccine, at least 3 months apart.

**Chronic renal disease/dialysis**

Varicella vaccine is recommended for individuals with chronic renal disease or undergoing dialysis. Two doses of univalent varicella vaccine may be given, at least 3 months apart.

**Neurologic disorders**

People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including varicella-containing vaccine.

**Autoimmune diseases**

Although definitive data are lacking, individuals with autoimmune disease not being treated with [immunosuppressive drugs] are not considered significantly immunocompromised and should receive varicella immunization following consultation with a physician. The nature of the person’s underlying disease should be considered. Rheumatic disease modifying agents such as hydroxychloroquine, sulfasalazine, or auranofin are not considered immunosuppressive.

The safety and efficacy of live, attenuated vaccines during [low dose intermittent or maintenance therapy with immunosuppressive drugs] (other than corticosteroids) for autoimmune disease is...
unknown. These drugs include therapeutic monoclonal antibodies, especially the anti-tumour necrosis factor agents adalimumab, infliximab, and etanercept and others (azathioprine, methotrexate, leflunomide, and abatacept). These have been reported to cause reactivation of latent tuberculosis infection and predisposition to other opportunistic infections. Therefore, until additional information becomes available, avoidance of live vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent.

Refer to *Immunization of Persons with Chronic Diseases* in Part 3 for additional general information.
Figure 1: Varicella vaccination for immunocompromised persons

Consult with attending physician before vaccination.
If necessary, refer to a specialist with expertise in immunization and/or immunodeficiency. Refer to Immunocompromised persons.

- Persons with severe immunodeficiency
- Persons with T cell defects
- Persons with natural killer T cell defects
- Persons with combined T and B cell deficiencies
- Persons with mixed cell-mediated antibody defects
- Persons with advanced HIV/AIDS
- Persons on immunosuppressive treatment for malignant solid tumours
- Persons with blood dyscrasias
- Persons with lymphomas
- Persons with malignant neoplasms affecting the bone marrow or lymphatic systems
- Persons with active leukemia

Vaccination is NOT RECOMMENDED. Further safety and efficacy studies are needed

- Persons with conditions requiring chronic immunosuppressive therapy
- After solid organ transplantation

Vaccination is CONTRAINDICATED

AIDS - acquired immunodeficiency syndrome
ALL - acute lymphocytic leukemia
HSCT - hematopoietic stem cell transplant
HIV - human immunodeficiency virus
Var – univalent varicella vaccine
VZV - varicella zoster virus
VZV IgG – varicella zoster virus antibody

Persons 2 years or more after HSCT

HIV-infected children with CDC clinical category N, A or B, and immunologic category 1 or 2 (CD4 percentage ≥ 15%)

HIV-infected adolescents and adults with CD4 cell count ≥ 200 x 10^6/L and percentage ≥ 15%

May vaccinate with 2 doses of Var. vaccine at least 3 months apart

May consider vaccination with 1 dose of Var. vaccine

May vaccinate with 2 doses of Var. vaccine 3 to 6 months apart

May vaccinate with 2 doses of Var. vaccine 3 months apart

Consider checking VZV serology (VZV IgG) using local antibody tests 6 to 8 weeks after last dose.

VZV IgG positive

VZV IgG negative

Consider offering VarIg on subsequent exposures to wild-type varicella
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 as necessary. People from tropical regions are more likely to be susceptible to varicella and should be a priority for varicella immunization. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS

Varicella immunization should be offered to susceptible workers (refer to Susceptibility and immunity for a definition of susceptible) including health care workers, child care workers, and teachers of young children. These groups are at occupational risk of exposure or may transmit disease to susceptible individuals. For health care providers, a self-reported history of varicella is not reliable to be considered immune. A health care provider diagnosis of varicella or herpes zoster is required for immunity to be considered reliable based on clinical presentation. If a health care provider diagnosis is not available, serologic testing is required to document immunity. Two doses of varicella vaccine are recommended for susceptible workers as is the case for all susceptible adults. A second dose of varicella vaccine should be offered to workers who would have received only one dose of vaccine.

Health care workers with a post-vaccine rash at the injection site may continue to work if the rash is covered. Those with a varicella-like rash not confined to the injection site should be excluded from work in high-risk patient care areas (e.g., where there are premature infants and immunocompromised patients) until lesions are crusted. Vaccinees with a post-vaccination varicella-like rash rarely transmit the vaccine-associated virus.

Refer to Immunization of Workers in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION (refer to Table 1)

Significant exposures to VZV

The following situations are significant exposures to VZV:

- Continuous household contact (living in the same dwelling) with a person with varicella
- Being indoors for more than 1 hour with a case of varicella
- Being in the same hospital room for more than 1 hour, or more than 15 minutes of face-to-face contact with a patient with varicella
- Touching the lesions of a person with active varicella
- Close exposure to a person with herpes zoster. Refer to Post-exposure immunization in Herpes Zoster (Shingles) Vaccine in Part 4 for additional information.

Univalent varicella vaccine

Univalent varicella vaccine given as soon as possible and within 3 and up to 5 days after exposure has been shown to be approximately 90% effective in preventing or reducing the severity of varicella and is the post-exposure management of choice for susceptible, healthy, non-pregnant persons. Varicella vaccination is not indicated for post-exposure management of infants less than 12 months of age, as the vaccine is not authorized for this age group and these infants are generally protected by maternal antibodies. Adults who previously received at least 1 dose of varicella-containing vaccine before 12 years of age or two doses thereafter should not be serologically tested as they are likely to be immune to varicella and commercially available antibody tests are usually not sensitive enough to detect post-vaccination antibody concentrations. Those who received only one dose of varicella-containing vaccine should be offered a second dose. There are no data on the use of MMRV vaccine in varicella post-exposure or outbreak situations.
Varicella zoster immune globulin

The decision to administer VarIg should be based on fulfilling all of the following criteria:

- The exposed person is susceptible to varicella.
- There has been a significant exposure to VZV. Refer to Significant exposures to VZV.
- The person is at increased risk of severe varicella. Refer to Persons at increased risk of severe varicella.
- Post-exposure immunization with univalent varicella vaccine is contraindicated.

If VarIg is being considered, consultation with an infectious diseases/infection control specialist is advised.

**Persons at increased risk of severe varicella**

VarIg is recommended for the following persons at increased risk of severe varicella if significant exposure has occurred:

- **Susceptible pregnant women** exposed to varicella should be evaluated for a history of varicella vaccination or disease. In the absence of such a history, immunity should be assessed by serologic testing as soon as possible. Exposed susceptible pregnant women should not be given vaccine; VarIg should be offered as soon as possible and within 96 hours of exposure to reduce potential maternal morbidity. If serology results cannot be obtained within 96 hours, VarIg should be administered to pregnant women who are presumed to be susceptible. Susceptible pregnant women should be given univalent varicella vaccine after delivery, assuming the recommended interval has passed since VarIg was administered. For recommendations on the interval between administration of VarIg and vaccination with varicella-containing vaccine, refer to Recent Administration of Human Immune Globulin Products in Part 1.

- **Newborn infants of mothers who develop varicella** during the 5 days before to 48 hours after delivery.

- **Neonatal or pediatric intensive care settings.** For the management of significant varicella exposure in a neonatal or pediatric intensive care setting, consultation with the infectious diseases/infection control specialist regarding the potential use of VarIg is advised.

- **Susceptible immunocompromised persons.** Those receiving regular monthly infusions of 400 mg/kg or more of intravenous immune globulin and whose most recent dose was within 3 weeks before exposure do not require VarIg. Monthly infusion of intravenous immune globulin maintains concentrations of varicella antibody comparable to that achieved with VarIg. For immunocompromised persons who are outside the 96-hour post-exposure window for VarIg administration, antiviral therapy from days 7 to 14 post-exposure could be considered. Refer to Immunocompromised persons.

- **Susceptible HIV-infected persons.** Based on expert opinion, if not severely immunocompromised (CD4 cell count ≥ 200 x 10^6/L and percentage ≥ 15%), post-exposure vaccination is indicated. If only one dose of vaccine had been administered previously, completion of the series with a second dose is indicated. Post-exposure vaccination is contraindicated if severely immune suppressed (CD4 cell count < 200 x 10^6/L or CD4 percentage < 15%); VarIg is indicated in such patients and should be administered as soon as possible, and within 96 hours of exposure to varicella. VarIg is not routinely necessary for HIV-infected persons without severe immune suppression who have completed an appropriate two-dose vaccination series or who have had natural varicella infection. Previously immunized HIV-infected children may demonstrate significant waning of immunity at 1 to 2 years after receiving 2 doses of varicella vaccine; however, it is unknown if this implies an inability to mount an anamnestic response after exposure to varicella disease. In the event of breakthrough varicella, a specialist should be promptly consulted regarding the need for antiviral therapy.

- **Recipients of HSCT** should be considered susceptible in the post-transplantation period regardless of a history of varicella disease or vaccination, or positive serologic test results.
Such persons should be offered Varlg after exposure to varicella. Refer to **Susceptible immunocompromised persons** for additional information.

Varlg is of maximal benefit if administered within 96 hours after first exposure. However, since the exact timing of transmission is unknown, it may be used within 96 hours of the most recent exposure. If more than 96 hours have elapsed since the last exposure, the benefit of administering Varlg is uncertain. Protection conferred by Varlg lasts approximately 3 weeks. Subsequent exposures occurring more than 3 weeks after a dose of Varlg require additional doses of Varlg if the criteria for Varlg administration, as specified above, are met.

The recommended dose of Varlg is 125 IU/10 kg of body weight up to a maximum of 625 IU. The minimum dose is 125 IU. Varlg should be given by the intramuscular (IM) route. Intravenous administration is also possible in certain circumstances but is associated with additional safety considerations. For complete prescribing information, consult the product leaflet or information contained within Health Canada’s authorized product monographs available through the Drug Product Database. If Varlg is being considered, consultation with an infectious diseases/infection control specialist is advised.

Refer to **Passive Immunization** Part 5 for additional general information.

### Table 1: Varicella post-exposure management for susceptible* individuals

<table>
<thead>
<tr>
<th>Post-exposure intervention</th>
<th>Healthy, non-pregnant (12 months of age** and older)</th>
<th>Pregnant</th>
<th>Immunocompromised****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinate with varicella vaccine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Check VZV IgG</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>If VZV IgG negative, administer Varlg***</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Refer to **Susceptibility and immunity** for definition of susceptible.

** Refer to **Varicella zoster immune globulin** for information regarding newborns of mothers who develop varicella during the 5 days before to 48 hours after delivery.

*** If serology results cannot be obtained within 96 hours, Varlg should be administered

**** In case of hematopoietic stem cell transplant (HSCT), administer Varlg regardless of VZV IgG result

### OUTBREAK CONTROL

Post-exposure immunization is useful in preventing or limiting varicella outbreaks in hospitals, child care facilities and homeless shelters. Serologic testing for susceptibility is not necessary prior to immunization in an outbreak situation. There are no data on the use of MMRV vaccine in outbreak situations. Refer to **Post-exposure immunization**.
VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE (refer to Table 1)

Dose
Each dose is 0.5 mL.

Route of administration
Univalent varicella vaccine should be administered subcutaneously (SC). Although the intramuscular (IM) route is not recommended, there is evidence that it is not necessary to repeat a dose of univalent varicella vaccine if it is inadvertently given IM. MMRV vaccine should be administered SC or IM. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Healthy children (12 months to 12 years of age)
For routine immunization of children aged 12 months to 12 years, two doses of varicella-containing vaccine (univalent varicella or MMRV) should be administered. The first varicella-containing vaccine dose should be administered at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter. The recommended interval between two doses is at least 3 months, however a 6-week interval can be used if rapid complete protection is required.

Two doses of varicella-containing vaccine (univalent varicella or MMRV) should be administered to children less than 13 years of age who were not routinely immunized with varicella-containing vaccine. The recommended interval between doses is at least 3 months. A minimum interval of 6 weeks between doses of varicella-containing vaccine may be used for catch-up immunization if rapid, complete protection is required. In deciding on the timing of the second dose, vaccine providers should consider factors such as the prevalence of varicella in the community, the current age of the child and attendance at a child care centre or school. The choice of vaccines and minimum interval for the second dose will depend on the vaccines and number of doses previously administered. Refer to Table 2 and Table 3. The minimum interval between doses of varicella-containing vaccines has been simplified and differs from previous NACI statements.
### Table 2: Recommended options for children (12 months to 12 years of age) not routinely immunized with varicella-containing vaccine

<table>
<thead>
<tr>
<th>Prior immunization</th>
<th>Recommended options for immunization</th>
</tr>
</thead>
</table>
| 0 dose MMR & 0 dose univalent varicella | 2 doses MMRV (with the two doses at least 3 months apart*)  
OR  
2 doses of MMR* and univalent varicella* (with the two doses at least 3 months apart*) |
| 1 dose MMR & 1 dose univalent varicella | 1 dose MMRV (at least 3 months after univalent varicella*)  
OR  
1 dose of MMR* and univalent varicella* (at least 3 months after prior univalent varicella*) |
| 1 dose MMR & 0 dose univalent varicella | 1 dose MMRV (at least 6 weeks after the prior MMR), followed by 1 dose univalent varicella (at least 3 months after MMRV*)  
OR  
1 dose univalent varicella (at least 4 weeks after the prior MMR), followed by 1 dose MMRV (at least 3 months after univalent varicella*) |
| 2 doses MMR & 1 dose univalent varicella | 1 dose univalent varicella (at least 4 weeks after the last MMR AND at least 3 months after the prior univalent varicella*) |
| 2 doses MMR & 0 dose univalent varicella | 2 doses univalent varicella (given at least 4 weeks after the last MMR, with a minimum interval of 3 months between the two doses of univalent varicella*) |
| 1 dose MMRV & 0 dose univalent varicella | 1 dose MMRV (at least 3 months after the prior MMRV*)  
OR  
1 dose each of MMR* and univalent varicella* (at least 3 months after the prior MMRV*) |
| 1 dose MMR & 1 dose MMRV | 1 dose of univalent varicella (at least 4 weeks after prior MMR or at least 3 months after the prior MMRV*) |

* MMR and univalent varicella vaccines may be given concomitantly at different injection sites using separate needles and syringes. If not given concomitantly, administration of MMR and univalent varicella vaccines must be separated by at least 4 weeks.

+ If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between 2 doses may be used.

**Adolescents (13-17 years of age)**

Adolescents with unknown susceptibility status should be serologically tested for varicella antibodies because most will be immune. Healthy, varicella-susceptible adolescents should receive two doses of univalent varicella vaccine given at least 6 weeks apart.

**Adults (18 years of age and older)**

Adults, under 50 years of age, with unknown susceptibility status should be serologically tested for varicella antibodies because most will be immune. Healthy, varicella-susceptible adults should receive two doses of univalent varicella vaccine administered at least 6 weeks apart. Refer to **Recommendations for use**.

In general, adults 50 years of age and older, are presumed to be immune to varicella. Routine serology is not recommended in this age group. Herpes zoster vaccine is recommended in people 60 years of age and older without contraindications and may be used in people 50-59 years of age without contraindications. Refer to **Herpes Zoster (Shingles) Vaccine** in Part 4 for additional information.
Table 3: Recommended number of doses of varicella-containing vaccine and minimum intervals for selected groups, by vaccine

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy children 1-12 years of age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Univalent Varicella</td>
</tr>
<tr>
<td></td>
<td>2 doses ≥ 3 months apart*</td>
</tr>
<tr>
<td>Healthy adolescents ≥ 13 years of age &amp; adults</td>
<td>MMRV</td>
</tr>
<tr>
<td></td>
<td>2 doses ≥ 6 weeks apart</td>
</tr>
<tr>
<td></td>
<td>No data, not recommended</td>
</tr>
<tr>
<td>Catch-up (unimmunized), aged ≥ 12 months-12 years</td>
<td>Univalent Varicella</td>
</tr>
<tr>
<td></td>
<td>2 doses ≥ 3 mois d'intervalle*</td>
</tr>
<tr>
<td>Post-exposure (unimmunized), aged ≥ 12 months-12 years</td>
<td>MMRV</td>
</tr>
<tr>
<td></td>
<td>2 doses ≥ 3 months apart*</td>
</tr>
<tr>
<td></td>
<td>No data, not recommended</td>
</tr>
<tr>
<td>Select immunocompromised groups meeting prerequisites, aged ≥ 12 months</td>
<td>Univalent Varicella</td>
</tr>
<tr>
<td></td>
<td>2 doses ≥ 3 months apart</td>
</tr>
<tr>
<td></td>
<td>No data, not recommended</td>
</tr>
<tr>
<td>At least 2 years post-HSCT, aged ≥ 12 months</td>
<td>MMRV</td>
</tr>
<tr>
<td></td>
<td>1 dose (no data for 2 doses)</td>
</tr>
<tr>
<td></td>
<td>No data, not recommended</td>
</tr>
</tbody>
</table>

<sup>a</sup> Children with varicella-like illness that occurred before 12 months of age should be vaccinated after age 1 year with age-appropriate schedule

* If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between 2 doses may be used.

**BOOSTER DOSES AND RE-IMMUNIZATION**

Re-immunization with varicella-containing vaccine after age and risk appropriate vaccination is not necessary. Herpes zoster vaccine is recommended for persons 60 years of age and older without contraindications and may be used in persons 50 to 59 years of age without contraindications. Refer to **Herpes Zoster (Shingles) Vaccine** in Part 4 for additional information.

**SEROLOGICAL TESTING**

**PRE-IMMUNIZATION**

Serologic testing is not recommended in children (12 months to 12 years of age) before receiving a varicella-containing vaccine. In adolescents and adults (13 to less than 50 years of age) who may be susceptible to varicella (refer to **Susceptibility and immunity** for a definition of susceptible) serologic testing should be performed before immunization as the majority of such individuals will be immune and will not require varicella vaccine. Individuals 50 years of age and over are presumed to be immune unless known to be varicella-susceptible based on serology previously drawn for other purposes. Routine serology is not recommended in this age group.

**POST-IMMUNIZATION**

Serologic testing is not recommended for healthy children. Previously vaccinated individuals who are inadvertently tested are likely to be immune to varicella even if there is no detectable antibody. Commercially available varicella antibody tests, such as the enzyme-linked immunosorbant assay (ELISA) and latex agglutination (LA), may not have sufficient sensitivity to detect antibody after vaccination, although they are useful for establishing immunity after wild-type infection.
Immunocompromised people who are vaccinated with univalent varicella vaccine may have antibody testing performed 6 to 8 weeks after the last dose (refer to Figure 1). However, local antibody tests may not be sensitive enough to detect antibody after immunization. The glycoprotein ELISA (gpELISA) test is more sensitive, but is not routinely available.

**STORAGE REQUIREMENTS**

VARILRIX®: Store the vaccine in a refrigerator at +2°C to +8°C. The diluent may be stored in the refrigerator or at ambient temperature (maximum +25°C). The freeze-dried vaccine is not affected by freezing.

VARIVAX® III: Store the vaccine at +2°C to +8°C or colder. The vaccine may be stored in a freezer; if subsequently transferred to a refrigerator, the vaccine should not be refrozen. Protect from light. The vial of diluent should be stored separately at room temperature (+20°C to +25°C) or in the refrigerator (+2°C to +8°C).

PRIORIX-TETRA™: Store the vaccine and diluent in a refrigerator at +2°C to +8°C and do not freeze. Protect the vaccine from light.

Refer to *Storage and Handling of Immunizing Agents* in Part 1 for additional general information. Refer to *Passive Immunization* Part 5 for information regarding Varlg storage requirements.

**SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES**

Varicella-containing vaccine may be administered concomitantly with routine childhood vaccines or live intranasal influenza vaccine (LAIV). Different injection sites and separate needles and syringes must be used for concomitant parenteral injections. If not given concomitantly, a minimum interval of 4 weeks is recommended between administration of two live vaccines. These recommendations are to address the hypothetical risk of interference from the vaccine given first on the vaccine given later. Recommended intervals between varicella-containing vaccines are provided in *Table 3*. Refer to *Timing of Vaccine Administration* in Part 1 for additional general information.

**VACCINE AND IMMUNE GLOBULIN SAFETY AND ADVERSE EVENTS**

Refer to *Vaccine Safety and Adverse Events Following Immunization* Part 2 for additional general information.

**COMMON AND LOCAL ADVERSE EVENTS**

**Univalent varicella vaccine**

Reactions to univalent varicella vaccine are generally mild and include injection site pain, swelling and redness in 10% to 20% of recipients. A low-grade fever has been documented in 10% to 15% of vaccinees. A varicella-like rash occurs at the injection site or is generalized in 3% to 5% of vaccinees after the first dose and 1% after a second dose. The rash usually appears within 5 to 26 days after immunization. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus, health care providers should obtain specimens from the vaccinee to ensure varicella disease is not confused with a reaction to vaccination.

The safety profile of a 2-dose regimen is comparable to that of a single dose: the incidence of injection site reactions observed within 3 days after vaccination was slightly higher after dose 2 (25.4%) than after dose 1 (21.7%), while fever incidence (which can occur 7 to 21 days after receipt of vaccine) was 7% after dose 1 and 4% after dose 2, and varicella-like rash incidence after dose 1 was 3%, compared with 1% after dose 2. Febrile seizures should be reported following varicella-containing vaccines.
MMRV vaccine
Pain and redness at the injection site and/or low-grade fever occur in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C), occur in 1% to less than 10% of vaccinees. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus, health care providers should obtain specimens from the vaccinee to ensure varicella disease is not confused with a reaction to vaccination.

VarIg
Reactions to VarIg are rare. The most frequent treatment related adverse events are pain at the injection site (17%), headache (7%), and rash (5%).

Rubella-containing vaccines
Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with rubella-containing vaccine, such as MMRV. It lasts for about 1 to 3 weeks, and rarely recurs. This is more common in post-pubertal females, among whom arthralgia develops in 25% and arthritis in 10% after immunization with rubella-containing vaccine. There is no evidence of increased risk of new onset, chronic arthropathies or neurologic conditions.

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. Anaphylaxis following vaccination with varicella-containing vaccine may occur but is very rare.

Univalent varicella vaccine
Most reported serious adverse events have not been proven to be caused by the vaccine, with the exception of rare events linked to the varicella vaccine strain among immunocompromised individuals or those with other serious medical conditions.

MMR and MMRV vaccines

*Immune Thrombocytopenic Purpura (ITP)*
Rarely, ITP occurs within 6 weeks after immunization with MMRV vaccine. In most children, post-immunization thrombocytopenia resolves within three months without serious complications. In individuals who experienced ITP with the first dose of MMRV vaccine, serologic status may be evaluated to determine whether an additional dose of vaccine is needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases.

*Encephalitis*
Encephalitis has been reported in association with administration of measles vaccine in approximately 1 per million doses distributed in North America which is much lower than that observed with natural measles disease (1 per 1,000 cases).

*Febrile seizures*
Recent studies have found a higher risk of febrile seizures with the first dose of a MMRV vaccine (ProQuad®, Merck, not authorized for use in Canada) when compared to the concomitant administration of MMR and univalent varicella vaccine. Data from the US estimated that the risk of febrile seizures in the 5 to 12 days following the first dose of this MMRV vaccine is 1 for every 2,600 vaccinated children aged 12 to 23 months. Experience with the MMRV vaccine available in Canada is more limited; however, one study showed a statistically non-significant increased risk of febrile seizures with MMRV vaccine compared to MMR and varicella given as two separate vaccines administered concomitantly. Close surveillance and further investigation are underway.
VarItg
There is a remote risk of an anaphylactic reaction to VarItg in individuals with hypersensitivity to blood products.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Herpes zoster
Herpes zoster has been reported after varicella immunization due to reactivation of either the vaccine or wild-type strain. The risk of herpes zoster developing is 4-fold to 12-fold lower in vaccinated as compared with unvaccinated children under 10 years of age. The risk of herpes zoster after vaccination with MMRV vaccine is unknown.

Transmission of vaccine virus
Transmission of vaccine strain virus from a healthy vaccinee is very rare. There have been few documented cases, all associated with a rash in the vaccinee.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)
Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with varicella-containing vaccine
- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with varicella-containing vaccine
- 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.


CONTRAINDICATIONS AND PRECAUTIONS
Varicella-containing vaccines and VarItg are contraindicated in persons with a history of anaphylaxis after previous administration of the product and in persons with proven immediate or anaphylactic hypersensitivity to any component of the product (with the exception of egg allergy for MMRV vaccine [see below]) or its container. Refer to Table 1 and Table 2 in General Considerations in Part 1 for lists of all vaccines and passive immunizing agents available in Canada and their contents. For varicella-containing vaccines, potential allergens include:

- PRIORIX-TETRA™: egg protein; neomycin sulphate
- VARILRIX®: neomycin sulphate
- VARIVAX® III: neomycin, porcine gelatin

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.

The measles and mumps components of MMRV vaccine are produced in chick embryo cell culture and may contain traces of egg protein. The amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is not recommended prior to vaccination. MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens’ eggs. Prior egg ingestion is not a prerequisite for immunization. For all vaccines, immunization should be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.
Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Vaccination with univalent varicella vaccine may be considered in select disorders. Refer to Immunocompromised persons.

Varicella-containing vaccines are contraindicated during pregnancy. Refer to Pregnancy and lactation.

VARIVAX® III is contraindicated in individuals with active, untreated tuberculosis. Initiating anti-tuberculous therapy is advisable before administering varicella-containing vaccines. Tuberculosis may be exacerbated by natural measles infection. However, there is no evidence that measles-containing vaccine such as MMRV has such an effect.

A history of febrile seizures or a family history of seizures is not a contraindication for the use of MMRV vaccine.

Administration of varicella-containing vaccine should be postponed in persons with moderate or severe acute illness and should be delayed by at least 4 weeks (ideally 6 weeks, if feasible) following measles infection. Persons with minor acute illness (with or without fever) may be vaccinated.

Following MMRV vaccine, transmission of measles, mumps and rubella vaccine viruses from vaccinees to susceptible contacts has not been documented and transmission of varicella vaccine virus may occur very rarely between healthy vaccinees who develop a varicella-like rash and susceptible contacts.

It is recommended to avoid the use of salicylates for 6 weeks after immunization with varicella-containing vaccine. Refer to Drug Interactions.

Persons with specific immunoglobulin A (IgA) deficiency have increased potential for developing antibodies to IgA after receipt of blood products including VarIg and could have anaphylactic reactions to subsequent administration of blood products containing IgA, such as VarIg.

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

**DRUG INTERACTIONS**

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of varicella-containing vaccine and should not restart antiviral therapy until 14 days after.

The measles component in MMRV vaccine can temporarily suppress tuberculin reactivity, resulting in false-negative results. The effect of other live virus vaccines, such as univalent varicella vaccine on tuberculin reactivity is unknown. Until data are available, if tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) is required, it should be done on the same day as immunization or delayed for at least 4 weeks after varicella vaccination. Vaccination with measles and/or varicella-containing vaccine may take place at any time after tuberculin skin testing has been performed and read.

Varicella-containing vaccine manufacturers recommend avoidance of salicylate therapy (medications derived from salicylic acid, e.g., acetylsalicylic acid [ASA]) for 6 weeks after varicella immunization because of an association between wild-type varicella, salicylate therapy and Reye’s syndrome. Health care providers should weigh the theoretical risks associated with varicella vaccine against the known risks associated with wild-type varicella infection. Because adverse events have not been reported with the use
of salicylates after varicella immunization, people with conditions requiring chronic salicylate therapy should be considered for immunization, with close subsequent monitoring.

Passive immunization with human immune globulin or receipt of most blood products can interfere with the immune response to varicella-containing vaccine. These vaccines should be given at least 14 days prior to administration of an immune globulin preparation or blood product or delayed until the antibodies in the immune globulin preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an immune globulin preparation or blood product is less than 14 days, immunization should be repeated. The recommended interval between administration of an immune globulin preparation or blood product and subsequent immunization with a live vaccine such as varicella varies, depending on the immune globulin preparation or blood product. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to varicella-containing vaccines. Refer to Recent Administration of Human Immune Globulin Products in Part 1 for additional general information.

OTHER CONSIDERATIONS

SURVEILLANCE

Virus identification from clinical specimens (e.g., vesicle scraping) by laboratory methods in order to differentiate wild type from vaccine-derived VZV should be considered when:

- A severe post-vaccination rash occurs
- A previously vaccinated child develops varicella (breakthrough varicella) that requires admission to hospital
- Herpes zoster occurs in a previously immunized (especially immunocompromised) individual
- A varicella-like illness occurs in an immunized health care worker with subsequent spread in the health care setting
- A varicella-like illness develops in a pregnant or immunocompromised contact of a recent vaccinee with a varicella-like rash

Polymerase chain reaction testing to differentiate vaccine-derived from wild type varicella virus can be performed by the National Microbiology Laboratory in Winnipeg.

INTERCHANGEABILITY OF VACCINES

For a two-dose schedule, it is recommended that the same manufacturer’s univalent varicella vaccine or MMRV vaccine be used to complete the schedule unless there are unavoidable barriers (e.g., the vaccine used for the first dose is not available). Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

SELECTED REFERENCES


http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm


PART 4

YELLOW FEVER VACCINE

- Epidemiology
- Preparations Available for Use in Canada
- Efficacy, Effectiveness and Immunogenicity
- Recommendations for Use
- Vaccine Administration
- Serologic Testing
- Storage Requirements
- Simultaneous Administration with Other Vaccines
- Vaccine Safety and Adverse Events
  - Common and local adverse events
  - Contraindications and precautions
- Other Considerations
- Selected References

KEY INFORMATION (refer to text for details)

| What | Yellow Fever (YF) virus is transmitted to humans through the bite of an infected mosquito. |
| What | YF is endemic and intermittently epidemic in sub-Saharan Africa and tropical South America. |
| What | Risk for acquiring YF is low for most travellers, particularly those staying in highly developed major urban areas. |
| What | YF is unique among diseases in that there are international health regulations which outline the requirements for proof of vaccination when travelling to specific countries. In Canada, YF vaccine is only available at Yellow Fever Vaccination Centres designated by the Public Health Agency of Canada (PHAC). |
| What | YF vaccine has a seroconversion rate of 95% to 99%; immunity persists for more than 10 years following vaccination. |
| What | The most common adverse events following YF vaccination are pain, inflammation and swelling at the injection site; weakness; headache; and myalgia. |

| Who | YF vaccine is recommended for healthy persons 9 months of age to less than 60 years of age. YF vaccine may be considered in infants 6 to 8 months of age and in people aged 60 years and over travelling to areas where risk of YF is highest (endemic or transitional regions). |
| Who | YF vaccine is recommended for laboratory personnel who work with YF virus. |

| How | One dose of YF vaccine should be administered. |
| How | The *International Certificate of Vaccination or Prophylaxis* becomes valid 10 days after primary vaccination and immediately upon revaccination. |
| How | In general, immunocompromised persons, pregnant or lactating women, and persons with a history of thymus disease should not receive YF vaccine. |
| How | Re-immunization is recommended every 10 years for immunocompetent people, if indicated. |
Why

- YF immunization (documented by an *International Certificate of Vaccination or Prophylaxis*) is required to enter certain countries in Africa and South America regardless of the traveller’s country of origin. Other countries require YF vaccination of travellers if the traveller has passed through endemic areas.
- Since 1970, there have been nine cases of YF reported in unvaccinated travellers from the United States and Europe who visited YF endemic areas of Africa and South America. Eight of the nine travellers died.

Since the publication of 2006 *Canadian Immunization Guide*:

- The Word Health Organization (WHO) and the United States Centers for Disease Control and Preventions (CDC) have harmonized the mapping of yellow fever (YF) risk areas
- Recommendations for YF vaccination of travellers have been updated
- Transmission of YF virus via blood products after vaccination of the donor has been reported
- Transmission of vaccine strain of YF virus to an infant through breastfeeding has been reported and recommendations for YF vacation of lactating mothers have been revised.

For further information, refer to the Committee to Advise on Tropical Medicine and Travel (CATMAT) *Statement for Travellers and Yellow Fever* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-11/index-eng.php)

**EPIDEMIOLOGY**

**DISEASE DESCRIPTION**

**Infectious agent**
Yellow fever (YF) is caused by a ribonucleic acid (RNA) virus from the family *Flaviviridae*.

**Reservoir**
Humans and non-human primates

**Transmission**
YF virus is transmitted to humans through the bite of an infected mosquito, primarily *Aedes* or *Haemogogus* species. The incubation period is 3 to 6 days. Humans infected with YF virus experience the highest levels of viremia and are infectious to mosquitoes shortly before the onset of fever and for 3 to 5 days afterwards. Because of the high level of viremia in humans, bloodborne transmission of YF virus can occur through transfusion of blood products, intravenous drug use and needlestick injuries. Probable transmission of vaccine strain YF virus from a mother to her infant through breastfeeding has been reported. Vaccine-associated viremia occurs 4 to 10 days after primary YF vaccination and lasts for up to 5 days. Sustained transmission is not possible in Canada because the recognized mosquito vectors are not present.

**Risk factors**
A traveller’s risk for acquiring YF is determined by multiple factors including: immunization status, use of personal protection measures against mosquito bites, location of travel, duration of exposure, activities while travelling, and local rate of virus transmission. The risk for acquiring YF is low for most travellers, particularly those staying in highly developed major urban areas. Greater risk exists for travellers who:

- visit rural or jungle areas;
- stay for longer periods of time; and
- participate in outdoor activities such as recreation or fieldwork.

For example, risk is greater for travellers who stay in a rural area of an endemic country for over two weeks, whereas risk is low for travellers staying in an urban area in a transitional country for one week.

**Seasonal/temporal pattern**

In West Africa and South America, YF virus transmission is usually associated with the mid-to-late rainy season when the number of mosquitoes generally increases. However, YF virus can be transmitted during the dry season.

**Spectrum of clinical illness**

Clinical presentation of YF varies in severity from asymptomatic to fatal. When symptomatic, YF is typically characterized by an acute onset of symptoms including fever, chills, headache, backache, muscle pain, joint pain, nausea, vomiting, photophobia, mild jaundice, and epigastric pain. In about 85% of YF cases, the disease resolves when the acute symptoms subside. For others, after a brief remission lasting anywhere between hours to a day, symptoms worsen and the disease advances, eventually leading to renal failure, haemorrhagic symptoms, and thrombocytopenia. Treatment is symptomatic and supportive.

**DISEASE DISTRIBUTION**

**Incidence/prevalence**

**Global**

The World Health Organization (WHO) estimates that approximately 200,000 YF cases occur annually, with up to 30,000 deaths. YF is endemic and intermittently epidemic in sub-Saharan Africa and tropical South America. In South America, transmission of YF virus occurs mainly in forest areas rather than in urban areas. In Africa, the majority of outbreaks have been reported from West Africa. The mosquito vectors are present in Asia; however, there have been no documented cases of transmission.

Since 1970, there have been nine cases of YF reported in unvaccinated international travellers from the United States and Europe who visited YF endemic areas of Africa and South America. Eight of the nine travellers died. One case of YF has been documented in a vaccinated traveller.

The risk of YF varies widely within areas of transmission. One mathematical model suggested that for an unimmunized person taking a two week trip to an area of epidemic YF activity the risk of becoming ill from YF could be as high as 1:267 and the risk of death from YF could be as high as 1:1,333. Although the actual risk for most travelers is probably less, it is very hard to quantify. It is for this reason that revised guidelines were required in order to make it easier for health care providers to give advice and care to travellers.

YF is unique among diseases in that there are international health regulations which outline the requirements for proof of vaccination when travelling to specific areas. In 2011, the WHO published revised recommendations for YF vaccination for international travellers, in consultation with international travel medicine experts. The revisions include:

- Updated criteria for the designation of areas with risk for YF virus activity. The classification of geographical areas, according to risk of transmission of YF, was outlined in four categories: endemic, transitional, low potential for exposure, and no risk. Table 1 contains a list of endemic and transitional countries with risk of YF transmission and Table 2 provides a list of countries with low potential for exposure to YF virus.
Countries and geographic areas with a risk of YF transmission were reassessed with the new criteria, and vaccine recommendations were made based on the level of risk. Refer to Travellers section as to how these criteria are applied.

Minor changes have been made to rules regarding travellers rapidly transiting (less than 12 hour stay) through airports in regions of yellow fever transmission and then entering countries with no history of disease but potential for transmission (primate population and suitable insect vectors).

Table 1: Endemic and transitional countries** with a risk of yellow fever transmission by continent, 2011

<table>
<thead>
<tr>
<th>Africa</th>
<th>Central and South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>Guinea</td>
</tr>
<tr>
<td>Benin</td>
<td>Guinea-Bissau</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Kenya†</td>
</tr>
<tr>
<td>Burundi</td>
<td>Liberia</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Mali†</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>Mauritania†</td>
</tr>
<tr>
<td>Chad†</td>
<td>Niger†</td>
</tr>
<tr>
<td>Congo†</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>Rwanda</td>
</tr>
<tr>
<td>Democratic Republic of the Congo†</td>
<td>Senegal</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>Sierra Leone</td>
</tr>
<tr>
<td>Ethiopia†</td>
<td>Sudan†</td>
</tr>
<tr>
<td>Gabon</td>
<td>Togo</td>
</tr>
<tr>
<td>Ghana</td>
<td>Uganda</td>
</tr>
</tbody>
</table>

* Designation of regions with risk of YF transmission is subject to change. **Travellers and health care providers should refer to current information available from the World Health Organization (WHO).† Countries in bold-type require proof of YF vaccination and are subject to change. Additional countries require proof of YF vaccination from travellers arriving from an endemic country. †Only a portion of the country has risk of yellow fever transmission. Refer to the WHO map of the areas in the Americas where YF vaccination is recommended (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_americas.png) or the map of the areas in Africa where YF vaccination is recommended. (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_africa.png)

Table 2: Countries** with low potential for exposure to yellow fever virus, 2011

<table>
<thead>
<tr>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eritrea†</td>
</tr>
<tr>
<td>São Tomé and Principe</td>
</tr>
<tr>
<td>Somalia†</td>
</tr>
<tr>
<td>Tanzania</td>
</tr>
<tr>
<td>Zambia†</td>
</tr>
</tbody>
</table>

* Travellers and healthcare providers can view areas at risk for yellow fever transmission on maps through the World Health Organization (WHO). (http://www.who.int/ith/chapters/ith2011annexs.pdf)† Countries in bold-type require proof of YF vaccination and are subject to change.
† These countries are classified as having "low potential for exposure to YF virus" in only some areas; the remaining areas of these countries are classified as having no risk of exposure to YF virus.

Designation of regions with risk of YF transmission is subject to change. Some countries require yellow fever vaccination if traveling from or transiting through a country with risk of YF transmission. View a complete listing of country-specific requirements available from the CDC (http://wwwnc.cdc.gov/travel/page/2012-yellow-book-updates.htm) or the WHO. (http://www.who.int/ith/chapters/ith2012en_countrylist.pdf)

**National**

To date, there have been no cases of YF reported in Canada. YF is a nationally and internationally notifiable disease; therefore, cases diagnosed in Canada must be urgently reported through local public health officials.

**RECENT OUTBREAKS**

Yellow fever outbreaks are reported in the WHO Disease Outbreak News. (http://www.who.int/csr/don/en/index.html)

**PREPARATIONS AVAILABLE FOR USE IN CANADA**

In Canada, YF vaccine is only available at Yellow Fever Vaccination Centres designated by the Public Health Agency of Canada (PHAC). A list of Yellow Fever Vaccination Centres in Canada can be obtained from the Public Health Agency of Canada (http://www.phac-aspc.gc.ca/tmp-pmv/yf-fi/index-eng.php) or telephone at: (613) 957-8739 or email to: yfinfj@phac-aspc.gc.ca

**YELLOW FEVER VACCINE**

- **YF-VAX®** (live, attenuated, yellow fever vaccine), sanofi pasteur Ltd. (YF)

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**

Efficacy studies of YF vaccine have not been performed; however, unpublished reports comparing YF incidence among vaccinated and unvaccinated populations during a 1986 epidemic in Nigeria estimated vaccine effectiveness to be approximately 85%.

**Immunogenicity**

More than 80% of persons immunized with YF vaccine develop neutralizing antibodies 10 days after vaccination and more than 99% by 28 days after vaccination. Immunity persists for more than 10 years.

**Recommendations for Use**

**Healthy Infants and Children (9 months to 17 years of age)**

YF vaccine is recommended for healthy children 9 months of age and older travelling to areas where YF is considered endemic or transitional (refer to Table).
YF vaccine is contraindicated in infants less than 6 months of age because of an increased risk of post-vaccination encephalitis; travel to YF endemic or transitional countries should be discouraged for children less than 6 months of age. If travel to an YF endemic or transitional country is unavoidable, the need for protection from mosquitoes at all times should be emphasized.

In children 6 to 8 months of age YF vaccination is generally not recommended due to continued increased risk of adverse events and decreased immunogenicity. Whenever possible, infants aged 6 to 8 months should not travel to countries where YF is transmitted. If travel is unavoidable, the decision to vaccinate needs to balance the risk of YF exposure with the risks of vaccination. Although the risk of serious adverse neurologic events is less than that of infants less than six months of age, it is still higher than that of infants 9 months and older. At 9 months of age, the risk of serious adverse events becomes much lower and antibody response improves, thus improving the safety and efficacy profiles of the YF vaccine.

If an infant receives YF vaccine at 6 to 8 months of age, and subsequently travels after 9 months of age, serology should be done (if available), and a booster dose considered. Personal protective measures should be emphasized.

**ADULTS (18 years of age and older)**

YF vaccine is recommended for laboratory personnel who work with YF virus and for healthy adult travellers less than 60 years of age travelling to areas where YF is considered endemic or transitional (refer to Table 1).

Persons 60 years of age and older should be considered for primary YF vaccination only if travel to areas where YF is considered endemic or transitional cannot be avoided and a high level of protection against mosquito exposure is not feasible. Serious adverse reactions in older vaccinees have only occurred in primary vaccinations. Booster doses of YF vaccine may be given to people over 60 years of age. Refer to Other reported adverse events and conditions for additional information.

Refer to Travellers and Schedule for additional information.

**PREGNANCY AND LACTATION**

In general, YF vaccine, like other live viral vaccines, should be avoided in pregnancy. Pregnant or lactating women should be considered for YF immunization only if they are travelling to endemic or transitional areas, travel cannot be postponed, and a high level of protection against mosquito exposure is not feasible. While the effects of YF vaccine in pregnancy are not well documented, many pregnant women have received the vaccine without significant adverse events. In one study of women exposed to YF vaccine early in pregnancy there was slight increased risk noted for minor malformations (mainly skin) in the babies; no increased risk of major malformations was found. Inadvertent immunization of women in pregnancy is not an indication for termination of pregnancy.

Seroconversion rates are lower in pregnant women who are immunized, especially in the third trimester. Antibody titres should be checked post-immunization to ensure appropriate immune response in women who remain at risk for YF. If serology is not available and a woman is travelling to an endemic country after completion of her pregnancy, revaccination prior to travel should be considered.

If pregnant women must travel to a country that requires documentation for YF but is not endemic or transitional, a waiver or Certificate of Medical Contraindication to Vaccination should be provided. Refer to Travellers for additional information.

Probable transmission of vaccine strain of YF virus from a mother to her infant through breastfeeding has been reported; therefore, in general, lactating mothers should not be vaccinated. Refer to Contraindications and Precautions for additional information. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.
**IMMUNOCOMPROMISED PERSONS**

In general, immunocompromised persons should not receive YF vaccine because of the risk of disease caused by the vaccine strain. When considering immunization of an immunocompromised person, approval from the individual's attending physician should be obtained before vaccination. For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

For the immune suppressed traveller, the potential risks associated with administering the YF vaccine should be weighed against the potential benefits. Where there is a country-specific vaccine requirement but the risks associated with vaccine administration outweigh the medical benefits, a Certificate of Medical Contraindication to Vaccination should be provided. Travellers thought to have mild to moderate degrees of immune suppression who will be at significant risk for acquiring YF (e.g., travel to an area of endemic or transitional transmission risk), should be offered YF vaccine and advised of the theoretical risks. Profoundly immune suppressed travellers who, in spite of being informed of the risks, plan a trip to an area of active YF risk, should obtain advice from a travel medicine expert and should rigorously adhere to mosquito protection measures.

**Acquired (secondary) immunodeficiency**

* **Malignancies**

YF vaccine is contraindicated in people with leukemia, lymphoma, thymoma, and generalized malignancies.

* **Hematopoietic stem cell transplantation (HSCT- autologous or allogeneic)**

HSCT recipients may receive YF vaccine if clearly indicated, if the recipient is at least 24 months post-transplant, has not received immunosuppressive medications for at least three months, and has no active graft versus host disease for the past three months. Persons should be considered immunocompetent by their HSCT specialist.

* **Solid organ transplantation**

Solid organ transplant recipients should not receive YF vaccine at any time after transplantation.

* **Immunosuppressive therapy**

YF vaccine is contraindicated for persons whose immunologic response is either suppressed or modulated by current or recent radiation therapies or drugs (e.g., high-dose systemic corticosteroids [2 mg/kg per day for a child or 20 mg/day or more of prednisone or its equivalent for an adult] for 14 days or more; chemotherapy; radiation therapy; azathioprine; cyclosporine; cyclophosphamide; infliximab).

If indicated, YF vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy. 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 live vaccines. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of live vaccines.

Corticosteroid therapy is not a contraindication to administering a live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 2 mg/kg/day for a child or less than 20 mg/day of prednisone or its equivalent for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).

* **HIV-infected**

A specialist in HIV infection should be consulted for advice on YF immunization in HIV-infected people. YF vaccine may be considered for people who have asymptomatic HIV infection and who
are not severely immunosuppressed (i.e., CD4 count greater than 200 x 10^6/L) but vaccination should take place well in advance of travel in order to monitor potential adverse events, and antibody titres should be considered to assess efficacy of the vaccination. Persons with HIV respond suboptimally to YF vaccine with lower antibody titres, more often demonstrate non-protective titres, and may experience a more rapid decline in antibody titres following vaccination. Booster doses may be required.

- Refer to Booster doses and re-immunization, Serologic testing, and Contraindications and Precautions for additional information. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

PERSONS WITH CHRONIC DISEASES

Hyposplenism or asplenia
Persons with hyposplenism or asplenia (congenital absence, surgical removal or functional [e.g., sickle cell disease]) may receive YF vaccine, if indicated.

Chronic renal disease/dialysis
Persons with chronic renal disease or undergoing dialysis may receive YF vaccine, if indicated.

Autoimmune diseases
Although definitive data are lacking, individuals with autoimmune disease not being treated with immunosuppressive drugs are not considered significantly immunocompromised and may receive YF immunization following consultation with a physician. Rheumatic disease modifying agents such as hydroxychloroquine, sulfasalazine, or auranofin are not considered immunosuppressive.

The safety and efficacy of live vaccines during low dose intermittent or maintenance therapy with immunosuppressive drugs (other than corticosteroids) for autoimmune disease is unknown. These drugs include therapeutic monoclonal antibodies, especially the anti-tumour necrosis factor agents adalimumab, infliximab, and etanercept and others (azathioprine, methotrexate, leflunomide, and abatacept). These have been reported to cause reactivation of latent tuberculosis infection and predisposition to other opportunistic infections. Therefore, until additional information becomes available, avoidance of live vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent.

Thymus disease
There is an association between YF vaccine-associated viscerotropic disease (YEL-AVD) and a history of thymus disease. Therefore, YF vaccine is not generally recommended for persons with a history of thymoma, thymectomy or myasthenia gravis. Refer to Other reported adverse events and conditions for additional information.

TRAVELLERS

YF vaccine is recommended for healthy travellers (9 months to less than 60 years of age) passing through, visiting or living in areas where YF is considered endemic or transitional (refer to Table 1) or if YF immunization is required to enter the country (refer to Table 1 and Table 2).

Transit times of 12 hours or less in an international airport poses very low risk for YF virus transmission irrespective of the YF risk classification of the country in which the airport is located. Thus, such a transit typically does not warrant vaccination. Recent updates in international health agreements suggest that travellers fitting this strict criteria are not required to be vaccinated. This includes those travellers transiting to a country with an entry requirement for YF vaccination but no history of endemic disease. Defining specific entry requirements is under the control of each individual country. Some countries will not allow entry without proper documentation of vaccination or certificate of medical contraindication. Travellers without proper documentation may be denied entry or subjected to vaccination at the airport.
This should be considered during review of itineraries and pre-travel counseling. If there is concern that lack of documentation will put the traveller at risk, yet vaccination is not medically indicated, then providing a medical certificate of contraindication may be considered. Unfortunately, some countries may deny entry despite proper documentation of medical contraindication to vaccination.

YF vaccination is generally not recommended in areas where there is low potential for YF virus exposure (refer to Table 2). However, vaccination might be considered for a small subset of travellers to these areas who are at increased risk of exposure to mosquitoes because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Vaccination is not recommended for travellers whose itineraries are restricted to areas with no risk.

The decision to immunize a traveller against YF should take into account the traveller’s itinerary and the associated risk for exposure to YF virus, the requirements of the country to be visited (including stopovers and airport transit), individual risk factors (e.g., age, immune status), and the potential for serious adverse events following vaccination. Vaccine providers should check either the CDC or WHO website for an updated list of countries considered endemic or transitional for YF and/or requiring YF vaccination for entry.

Under the WHO’s International Health Regulations, YF immunization (documented by an International Certificate of Vaccination or Prophylaxis) is required to enter certain countries in Africa and South America regardless of the traveller’s country of origin. Other countries require YF vaccination of travellers if the traveller has passed through endemic areas. In some Asian and tropical countries where YF disease does not exist but the transmitting mosquito is present, immunization is required for travellers arriving from an endemic country to prevent importation of the disease. Some countries do not require YF vaccination of infants younger than a certain age (e.g., less than 1 year).

The International Certificate of Vaccination or Prophylaxis is valid for 10 years, beginning 10 days after primary immunization and immediately after re-immunization, if re-immunized within the 10 year period. Travellers requiring the certificate but in whom the YF vaccine is medically contraindicated (refer to Contraindications and Precautions) can be provided with an International Certificate of Medical Contraindication to Vaccination by the Yellow Fever Vaccination Centre following an individual risk assessment. Travellers without a valid International Certificate of Vaccination or Prophylaxis or a Certificate of Medical Contraindication to Vaccination may be denied entry into a country requiring such documentation, quarantined, or offered immunization at the point of entry (e.g., at the airport), potentially putting the health of traveller at risk.

In Canada, only Yellow Fever Vaccination Centre clinics designated by PHAC can provide the International Certificate of Vaccination or Prophylaxis or International Certificate of Medical Contraindication to Vaccination. A list of Yellow Fever Vaccination Centres (http://webqa.phac-aspc.gc.ca/tmp-pmv/yf-fj/index-eng.php) can be obtained from Public Health Agency of Canada (PHAC) (http://www.phac-aspc.gc.ca/tmp-pmv/yf-fj/index-eng.php) or telephone at: (613) 957-8739 or email to: yfinfofj@phac-aspc.gc.ca

Additional and updated information regarding countries with risk of yellow fever transmission and requirements for YF vaccination is available from local public health officials, PHAC or the WHO:

- A Yellow Fever Fact Sheet is available from PHAC. (http://www.phac-aspc.gc.ca/tmp-pmv/info/yf-fj-eng.php)
- View areas in the Americas where YF vaccination is recommended available through the WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_americas.png) View the map of the areas in Africa where YF vaccination is recommended available from the WHO. (http://gamapserver.who.int/mapLibrary/Files/Maps/ITH_YF_vaccination_africa.png)
- View the list of country-specific yellow fever vaccination requirements and WHO recommendations available through the WHO. (http://www.who.int/ith/chapters/ith2012en_countrylist.pdf)
Refer to Immunization of Travellers in Part 3 for additional general information.

WORKERS
Laboratory personnel who work with YF virus should receive YF vaccine. Refer to Immunization of Workers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose
Each dose is 0.5 mL.

Route of administration
YF vaccine should be administered subcutaneously. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule
One dose of YF vaccine should be administered.

BOOSTER DOSES AND RE-IMMUNIZATION
Re-immunization is recommended every 10 years for immunocompetent individuals, if indicated. Re-immunization boosts antibody titre, although evidence from several studies suggests that immunity persists for at least 30 to 35 years after a single dose and probably for life. If vaccine is appropriate for an immunocompromised person, serologic testing and revaccination (if indicated based on serology results) should be considered two to five years post-immunization.

SEROLOGICAL TESTING
Serologic testing is not recommended for non-pregnant healthy persons before or after receiving YF vaccine. For immunocompromised persons, serologic testing should be considered two to five years post-immunization. For women vaccinated during pregnancy, antibody titres should be checked post-immunization to ensure appropriate immune response in those who remain at risk for YF. An antibody titre of greater than 1:10 indicates immunity.

STORAGE REQUIREMENTS
Store YF vaccine in a refrigerator at +2°C to +8°C. Do not freeze. Refrigerate the reconstituted vaccine and use within 1 hour following reconstitution. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES
YF vaccine may be administered concomitantly with the following vaccines: measles, mumps, rubella, polio, diphtheria, tetanus, pertussis, hepatitis B, hepatitis A, oral cholera, and oral or parenteral typhoid. Different injection sites and separate needles and syringes must be used for concomitant parenteral injections. If not given concurrently, a minimal interval of 4 weeks is recommended between administration of YF vaccine and other live parenteral vaccines. Oral typhoid or oral cholera vaccine can be administered at any interval before or after YF vaccine. There are no data available regarding possible interference between YF vaccine and rabies, human papillomavirus, Japanese encephalitis, live attenuated influenza, or varicella 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 comparative study, 71.9% of subjects vaccinated with YF vaccine reported one or more non-serious adverse events assessed as related to vaccination. Injection site reactions were reported by 5.7% to 39.4% of subjects (pain at the injection site 39.4%; inflammation 29.4%; edema 19.9% and other injection site reaction 5.7%). Systemic reactions were reported by 10.1% to 31.4% (chills 10.1%; fever 14.0%; weakness 29.5%; headache 31.4%; myalgia 25.1% and malaise 17.8%) of subjects up to 10 days post vaccination.

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. Hypersensitivity reactions including rash, urticaria, asthma and anaphylaxis are very rare, with observations over the past decades of an incidence of less than 1 per million. However, reporting rates to the United States Vaccine Adverse Event Reporting System based on two reviews 10 years apart were higher: 0.8 per 100,000 doses distributed in the earlier study and 1.8 in the more recent study. The primary risk factor appears to be gelatin and egg protein sensitivity.

Two additional serious adverse events, YF vaccine associated neurotropic disease (YEL-AND) and YF vaccine associated viscerotropic disease (YEL-AVD), are described below.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

YF vaccine-associated neurotropic disease (YEL-AND)

YEL-AND is a group of clinical syndromes that includes meningoencephalitis (neurotropic disease), acute disseminated encephalomyelitis, Guillain Barré syndrome, and acute bulbar palsy. Neurotropic disease occurs as a result of YF vaccine virus invasion of the central nervous system (CNS). The other syndromes are autoimmune manifestations in which antibodies and/or T-cells produced in response to the vaccine cross-react with neuronal epitopes leading to CNS or peripheral nerve damage. The clinical course is typically brief with generally complete recovery. Fatality is rare. YEL-AND can present in any age group, between 4 and 23 days post vaccination (typically 7 to 21 days) and is seen almost exclusively in primary vaccine recipients. Children less than six months of age and older persons are at greater risk for YEL-AND. The US CDC reports an incidence of YEL-AND of 0.8 per 100,000 doses administered. The rate is double for those 60 to 69 years of age (1.6 per 100,000 doses) and almost 4 times higher in those over 70 years of age (2.3 per 100,000 doses). When infants and elderly are not given the vaccine, recent surveillance data suggest population-based incidence rates drop close to zero.

YF vaccine-associated viscerotropic disease (YEL-AVD)

YEL-AVD is characterized by severe illness and multi-organ failure. It resembles wild-type YF infection with onset within 2 to 5 days of vaccination. The risk of YEL-AVD increases with age. Incidence is estimated to be 1.0-1.1 per 100,000 for those 60-69 years of age; 2.3-3.2 per 100,000 for those over 70 years of age; and 0.1 per 100,000 for those less than 60 years of age. The case fatality rate is 65% overall and is higher in women than men (90% vs. 50%). YEL-AVD is seen almost exclusively in primary vaccine recipients. Extensive investigations of cases suggest that YEL-AVD is linked to various host factors including older age, and thymus disease (thymoma, myasthenia gravis, thymectomy), and is not associated with a change in virulence of the vaccine virus.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:
- YF vaccine-associated neurotropic disease
- YF vaccine-associated viscerotropic disease
- 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.


CONTRAINDICATIONS AND PRECAUTIONS
YF 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 in Canada in Part 1 for a list of all vaccines available for use in Canada and their contents. For YF-VAX® vaccine, potential allergens include chick protein, egg protein, gelatin, and latex in the stopper of diluent vial.

Individuals requiring YF immunization who have suspected hypersensitivity or non-anaphylactic allergy to vaccine components, should be referred to an allergist for evaluation.

Infants
In general, infants under the age of 9 months should not be vaccinated against YF. Infants less than six months of age are at greater risk for YEL-AND following YF vaccination and should not receive YF vaccine. However, the Advisory Committee on Immunization Practices (ACIP) in the United States recommends that for infants 6 to 8 months of age travelling to an endemic or transitional area, when travel is unavoidable, the decision to vaccinate needs to balance the risks of YF virus exposure with the risk for adverse events following vaccination.

Persons 60 years of age and older
Persons 60 years of age and older are at greater risk for YEL-AND and YEL-AVD following primary YF vaccination; therefore, primary YF vaccination is not generally recommended. Booster doses may be given.

Pregnancy and breastfeeding
The effects of live YF vaccine in pregnancy are not well documented and vaccination should be avoided if possible. If a pregnant woman must travel to a highly endemic or epidemic area, the risk of actually contracting the disease may outweigh the risks of vaccination to the mother and fetus.

Probable transmission of vaccine strain of YF virus from a mother to her infant through breastfeeding has been reported; therefore, in general, lactating mothers should not be vaccinated. Until recently, there was only a theoretical risk of transmission of the live virus in breast milk and no cases reported despite many breastfeeding women having been immunized during emergency vaccination campaigns. Two recent cases have documented the possibility of transmission through breast milk. A case in Brazil demonstrated laboratory confirmed evidence of yellow fever virus transmission in breast milk. In Canada, there was a case of yellow fever in an infant who had been breast fed by a recently vaccinated mother, which was highly suggestive of breast milk transfer. These two cases should raise the level of caution when considering vaccinating women who are actively breastfeeding. If there is no risk of acquiring yellow fever in the region to be visited, a waiver of vaccination should be given. If travel is to a highly endemic area, then the risks of vaccination should be weighed against the risk of disease.

Immunocompromised persons
In general, YF vaccine should not be given to immunosuppressed individuals. Refer to Immunocompromised persons.

| 12 | CANADIAN IMMUNIZATION GUIDE • YELLOW FEVER VACCINE |
**Thymus disease**

There is an association between YEL-AVD and a history of thymus disease; therefore, YF vaccine is not generally recommended for persons with a history of thymoma, thymectomy or myasthenia gravis.

**Acute illness**

Administration of YF 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.

**DRUG INTERACTIONS**

The effect of YF vaccine on tuberculin reactivity is unknown. Until data are available, if tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) is required, it should be done on the same day as immunization or delayed for at least 4 weeks after YF vaccination. Vaccination with YF vaccine may take place at any time after tuberculin skin testing has been performed and/or read.

**OTHER CONSIDERATIONS**

**INTERCHANGEABILITY OF VACCINES**

Persons who receive YF vaccines in countries other than the US and Canada should be considered protected against YF. Refer to [Principles of Vaccine Interchangeability](#) in Part 1 for additional general information.

**SELECTED REFERENCES**


