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 for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi_guide/index-eng.php) The Brighton case definitions are also available. (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions/available-definitions.html)

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.

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PART 4

TETANUS TOXOID

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.

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

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

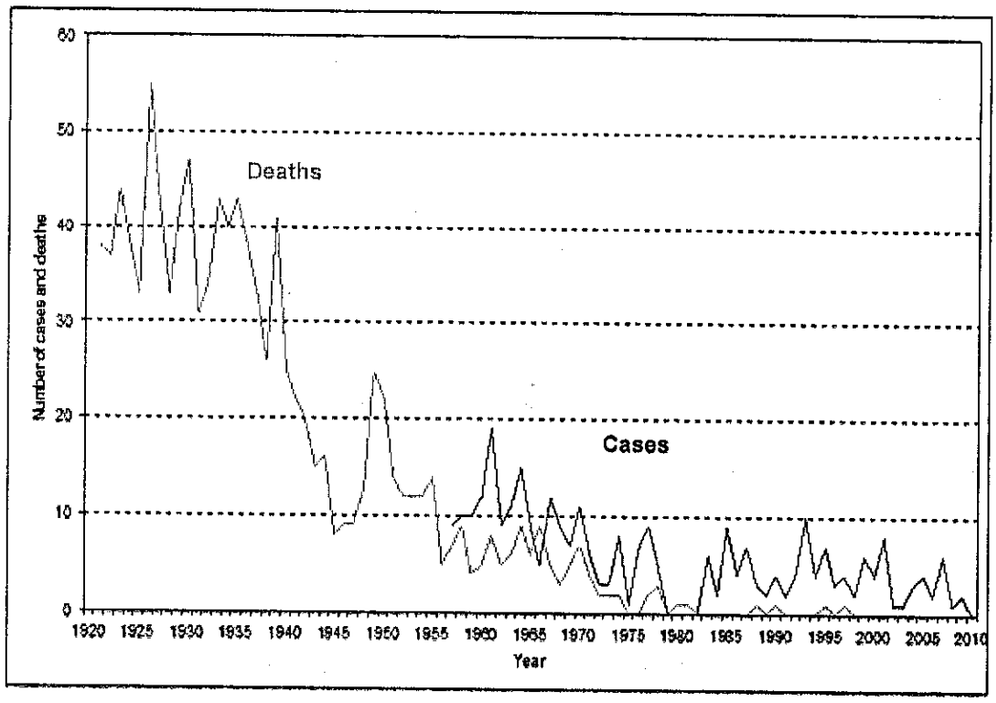
Global

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 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 or 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

History of tetanus immunization	Clean, minor wounds		All other wounds	
	Tetanus toxoid-containing vaccine*	TIg	Tetanus toxoid-containing vaccine*	TIg**
Unknown or less than 3 doses in a vaccine series	Yes	No	Yes	Yes
3 or more doses in a vaccine series and **less than 5 years** since last booster dose	No	No	No	No¶
3 or more doses in a vaccine series and **more than 5 years** but **less than 10 years** since last booster dose	No	No	Yes	No¶
3 or more doses in a vaccine series and **more than 10 years** since last booster dose	Yes	No	Yes	No¶

* 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

TIg: 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 (TIg) for prophylaxis

The recommended dose of HYPERTET® S/D (TIg) 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 (TIg) for treatment

When used in the treatment of tetanus, TIg 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-

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sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Passive Immunization Part 5 for additional general information.

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 +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 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.

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PART 4

TYPHOID VACCINE

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. (http://data.worldbank.org/about/country-classifications) 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. (http://data.worldbank.org/about/country-classifications) 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

- **TYPHERIX®** (*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/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

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

water; anatomic or functional asplenia (including sickle cell anemia), the presence of achlorhydria or the use of acid suppression therapy) and personal preference.

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[1]

	Vaccines		
	Parenteral inactivated vaccines (Typh-I)	**Oral, live attenuated vaccine** (Typh-O)	**Combined, parenteral inactivated vaccine** (HA-Typh-I)
Brand name	TYPHIM Vi® TYPHERIX®	Vivotif®	ViVAXIM®
Authorized for use in persons	2 years of age and older	5 years of age and older	16 years of age and older
Protection begins	14 days following vaccination	7 days following vaccination	14 days following vaccination
Dose and schedule	One dose: 0.5 mL	4 capsules taken on alternate days	One dose: 1.0 mL
Route of administration	Intramuscular injection	Oral	Intramuscular injection
Contraindications	Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container.	Pregnancy Individuals with hypersensitivity to any component of the vaccine or the enteric-coated capsule. Individuals with an acute gastrointestinal condition or inflammatory bowel disease and in immunocompromised persons.	Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container.
Re-immunization	Every 3 years	Every 7 years[3]	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.

1 Based on CATMAT *Statement on International Travellers and Typhoid*.
2 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.
3 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.

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