PART 4

INFLUENZA VACCINE

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.

SELECTED REFERENCES

Canadian Immunization Committee. *Recommendations on a Human Papillomavirus Immunization Program*. Accessed August 2011.

Centers for Disease Control and Prevention. *The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases*. 12th ed.; April 2011. Accessed August 2011.

Dunne EF, Nielson CM, Stone KM et al. *Prevalence of HPV infection among men: A systematic review of the literature*. J Infect Dis. 2006 10/15;194(0022-1899;8):1044-57.

Giuliano AR, Lazcano-Ponce E, Villa LL, et al. *The human papillomavirus infection in men study: Human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States*. Cancer Epidemiol Biomarkers Prev. 2008 08;17(1055-9965;8):2036-43.

Giuliano AR, Lu B, Nielson CM, et al. *Age-specific prevalence, incidence, and duration of human papillomavirus infections in a cohort of 290 US men*. J Infect Dis. 2008 09/15;198 (0022-1899;6):827-35.

GlaxoSmithKline Inc. *Product Monograph – CERVARIX™*. February 2010.

Kliewer EV, Demers AA, Elliott L et al. *Twenty-year trends in the incidence and prevalence of diagnosed anogenital warts in Canada*. Sex Transm Dis. 2009 06;36(1537-4521; 6):380-6.

Marra F, Ogilvie G, Colley L et al. *Epidemiology and costs associated with genital warts in Canada*. Sex Transm Infect. 2009 04;85(1472-3263; 2):111-5.

Merck Frosst Canada Ltd. *Product Monograph - GARDASIL®*. September 2010.

Moore RA, Ogilvie G, Fornika D et al. *Prevalence and type distribution of human papillomavirus in 5,000 British Columbia women-implications for vaccination*. Cancer Causes Control. 2009 05/29(1573-7225).

National Advisory Committee on Immunization. *Update on Human Papillomavirus (HPV) Vaccines*. Can Commun Dis Rep 2012;37 (ACS-7):1-62.

National Advisory Committee on Immunization. *Statement on Human Papillomavirus Vaccine*. Can Commun Dis Rep 2007;33(ACS-2):1-32.

Newall AT, Brotherton JM, Quinn HE et al. *Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia*. Clin Infect Dis. 2008 06/01;46(1537-6591; 11):1647-55.

Ogilvie GS, Taylor DL, Achen M et al. *Self-collection of genital human papillomavirus specimens in heterosexual men*. Sex Transm Infect. 2009 06;85(1472-3263; 1472-3263; 3):221-5.

Winer RL, Lee SK, Hughes JP et al. *Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students*. Am J Epidemiol 2003;157:218-26.

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.

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

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.

(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

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 and18-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

- 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. (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

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.

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).

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.

For additional information, refer to the National Advisory Committee on Immunization (NACI) Statements *Update on Human Papillomavirus (HPV) Vaccines* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php) and *Statement on Human Papillomavirus Vaccine*. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-02/index-eng.php)

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) to epithelial 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.

PART 4

HUMAN PAPILLOMAVIRUS VACCINE

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.

Kerzner B, Murray AV, Cheng E et al. *Safety and immunogenicity profile of the concomitant administration of ZOSTAVAX and inactivated influenza vaccine in adults aged 50 and older.* J Am Geriatr Soc 2007;55(10):1499-1507.

Klein NP, Holmes TH, Sharp MA et al. *Variability and gender differences in memory T cell immunity to varicella-zoster virus in healthy adults.* Vaccine 2006;24(33-34):5913-18.

Law BJ, Chateau D, Walld R et al. *Temporal trends in the annual population-based incidence of herpes zoster by age and gender: Manitoba, 1979-1998.* Can J Infect Dis Med Microbiol 2004;15:357-8.

MacIntyre CR, Egerton T, McCaughey M et al. *Concomitant administration of zoster and pneumococcal vaccines in adults ≥ 60 years old.* Abstract presented at the ICAAC/IDSA 2008 Joint Meeting, October 25-28, 2008, Washington, D.C.

Macaladad N, Marcano T, Guzman M et al. *Safety and immunogenicity of a zoster vaccine in varicella-zoster virus seronegative and low-seropositive healthy adults.* Vaccine 2007;25(11):2139-44.

Merck Frosst Canada Ltd. *Product Monograph - ZOSTAVAX®.* June 2010.

Mills R, Tyring SK, Lawless JF et al. *Safety, Tolerability and Immunogenicity of Zoster Vaccine in Subjects with a History of Herpes Zoster.* Vaccine 2010;28(25):4204-9.

National Advisory Committee on Immunization. *NACI statement on the recommended use of herpes zoster vaccine.* Can Commun Dis Rep 2010;36(ACS-1):1-19.

National Advisory Committee on Immunization. An Advisory Committee Statement (ACS). National Advisory Committee on Immunization (NACI): *Update on the use of herpes zoster vaccine.* Public Health Agency of Canada, January 2014 (Catalogue no. HP40-92/2014E-PDF).

National Advisory Committee on Immunization. *Update on varicella.* Can Commun Dis Rep 2004;301-26.

Oxman MN, Levin MJ, Johnson GR et al. *A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults.* N Engl J Med 2005;352(22):2271-2284.

Russell ML, Schopflocher DP, Svenson L et al. *Secular trends in the epidemiology of shingles in Alberta.* Epidemiol Infect 2007;135(6):908-913.

Tseng HF, Chi M, Smith N et al. *Herpes zoster vaccine and the incidence of recurrent herpes zoster in an immunocompetent elderly population.* J Infect Dis 2012;206(2):190-96.

Yawn BP, Wollan PC, Kurland MJ et al. *Herpes zoster recurrences more frequent than previously reported.* Mayo Clin Proc 2011;86(2):88-93.

Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012; Jul 4;308(1):43-9.

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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

American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, et al. (editors). *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Brisson M, Edmunds WJ, Law B et al. *Epidemiology of varicella zoster virus infection in Canada and the United Kingdom* Epidemiol Infect 2001;127(2):305-14.

Brisson M, Pellisier JM, Camden S et al. *The potential cost-effectiveness of vaccination against herpes zoster and post-herpetic neuralgia*. Hum Vaccin 2008;4(3):238-45.

Centers for Disease Control and Prevention. *Prevention of Herpes Zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP)*. MMWR Morb Mortal Wkly Rep 2008;57(RR-5):1-30.

Centers for Disease Control and Prevention. *The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases*. Updated 11th ed.; May 2009. Accessed October 2010 at: http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm

Edgar BL, Galanis E, Kay C et al. *The burden of varicella and zoster in British Columbia 1994-2003: baseline assessment prior to universal vaccination*. Can Commun Dis Rep 2007;33(11):1-15.

Hales CM, Harpaz R, Joesoef MR, Bialek SR; *Examination of Links Between Herpes Zoster Incidence and Childhood Varicella Vaccination*. Annals of Internal Medicine 2013;159(11):739-745.

Table 1: Immunosuppressive medication

Immunosuppressive medication	Example brand name (company)
6-mercaptopurine*	PURINETHOL®(Novopharm Ltd.)
Alemtuzumab	MabCampath®(Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)
Anti-thymocyte globulin	Thymoglobulin®(Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)
Azathioprine*	IMURAN (Triton Pharma Inc.)
Basiliximab	SIMULECT™ (Novartis Pharmaceuticals Canada Inc.)
Cyclophosphamide	PROCYTOX (Baxter Corp.) CYTOXAN
Cyclosporine	NEORAL™ (Novartis Pharmaceuticals Canada Inc.)
High-dose systemic corticosteroids (20 mg/day or more of prednisone or its equivalent for an adult) for 14 days or more*	
Leflunomide	ARAVA®(Sanofi-Aventis Canada Inc.)
Methotrexate*	
Mitoxantrone	
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	
Mycophenolate mofetil	CellCept® (Hoffman-LaRoche Ltd.)
Sirolimus	Rapamune® (Pfizer Canada Inc.)
Tacrolimus	Prograf® (Astellas Pharma Canada Inc.)
Non-TNF biologic immunosuppressives used in inflammatory disease	Orencia™ (Bristol-Myers Squibb Canada) RITUXAN® (Hoffman-LaRoche Ltd.)

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

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)

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.

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 world-wide 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.

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.

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 immunuosuppressive 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, inhaled, or locally injected (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.

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.

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.

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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.

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.

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PART 4

HERPES ZOSTER (SHINGLES) VACCINE

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

For additional information, refer to the National Advisory Committee on Immunization (NACI) *Statement on the recommended use of herpes zoster vaccine* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-1/index-eng.php) and *Update on the use of herpes zoster vaccine*. (http://www.phac-aspc.gc.ca/naci-ccni/hzv-vcz-eng.php)

Losonsky GA, Wasserman SS, Stephens I et al. *Hepatitis B vaccination of premature infants*. Pediatrics 1999;103(2): E14.

McMahon B, Bruden DL, Petersen K et al. *Antibody levels and protection after hepatitis B vaccination: results of a 15-year follow-up*. Ann Intern Med. 2005;142:333-41.

Merck Frosst Canada Ltd. *Product Monograph - RECOMBIVAX HB®*. March 2009.

National Advisory Committee on Immunization. *Statement on the recommended use of pentavalent and hexavalent vaccines*. Can Comm Dis Rep. 2007;33(ACS-1):1-15.

Navas E, Salleras L, Gisbert R et al. *Efficiency of the incorporation of the hepatitis A vaccine as a combined A+B vaccine to the hepatitis B vaccination programme of preadolescents in schools*. Vaccine 2005;23(17-18): 2185-9.

Public Health Agency of Canada. *An integrated protocol to manage health care workers exposed to bloodborne pathogens*. Can Comm Dis Rep. 1997;23S2.

Roberton D, Marshall H, Nolan T et al. *Reactogenicity and immunogenicity profile of a two-dose combined hepatitis A and B vaccine in 1-11-year-old children*. Vaccine 2005(43);23:5099-105.

Shefer A, Atkinson W, Friedman C et al. *Immunization of Health-Care Personnel Recommendations of the Advisory Committee on Immunization Practices*. MMWR 2011;60:1-46

Talecris Biotherapeutics Inc. *Product Monograph - HyperHEP B™ S/D*. September 2006.

Watson B, West DJ, Chilkatowsky A et al. *Persistence of immunologic memory for 13 years in recipients of a recombinant hepatitis B vaccine*. Vaccine 2001;19:3164-8.

Zhongjie S, Yang Y, Wang H et al. *Breastfeeding of Newborns by Mothers Carrying Hepatitis B Virus A Meta-analysis and Systematic Review*. Arch Pediatri Adolesc Med 2011;165(9): 837-46.

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SELECTED REFERENCES

American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, et al. (editors). Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Ascherio A, Zhang S, Hernan M et al. *Hepatitis B vaccination and the risk of multiple sclerosis.* N Engl J Med. 2001;344:327-32.

Banatvala J, VanDamme P, Oehen S et al. *Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory.* Vaccine. 2001;19:877-85.

Cangene Corp. *Product Monograph – HepaGam B*™. April 2009.

Centers for Disease Control and Prevention. *The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases.* Updated 11th ed.; May 2009. http://www.cdc.gov/vaccines/pubs/pinkbook/index.html

Committee to Advise on Tropical Medicine and Travel. *Statement on hepatitis vaccines for travellers.* Can Comm Dis Rep. 2008;34(ACS-2):1-24.

Committee to Advise on Tropical Medicine and Travel. *Statement on international adoption.* Can Comm Dis Rep. 2010;36(ACS-15):1-17.

Confavreau C, Suissa S, Saddier P et al. *Vaccinations and the risk of relapse of multiple sclerosis.* N Engl J Med. 2001;344:319-26.

Duval B, Boulianne G, De Serres G. *Should children with isolated anti-HBs or anti-HBc be immunized against hepatitis B virus?* JAMA. 1997;287:1064.

Duval B, Gilca V, Boulianne N et al. *Comparative long-term immunogenicity of two recombinant hepatitis B vaccines and the effect of a booster dose given after 5 years in a low endemicity country.* Pediatr Infect Dis J. 2005;24:213-8.

Duval B, Gilca V, Boulianne N et al. *Immunogenicity of two paediatric doses of monovalent hepatitis B or combined hepatitis A and B vaccine in 8-10-year-old children.* Vaccine 2005;23(31):4082-87.

FitzSimons D, François G, Hall A et al. *Long-term efficacy of hepatitis B vaccine, booster policy, and impact of hepatitis B virus mutant.* Vaccine 2005;23:4158-66.

Flynn P, Cunningham C, Rudy B et al. *Hepatitis B Vaccination in HIV-Infected Youth: A Randomized Trial of Three Regimens.* J Acquir Immune Defic Syndr 2011;56(4):325-32.

Gilca V, De Serres G, Boulianne N, et al. *Antibody kinetics among 8-10 years old respondents to hepatitis B vaccination in a low endemic country and the effect of a booster dose given five or ten years later.* Vaccine 2009;27(43):6048-53.

GlaxoSmithKline Inc. *Product Monograph - ENGERIX®-B.* September 2008.

GlaxoSmithKline Inc. *Product Monograph - INFANRIX hexa*™. July 2008.

GlaxoSmithKline Inc. *Product Monograph – TWINRIX®.* September 2008.

Jarroson L, Kolopp-Sarda M, Aguilar P et al. *Most humoral non-responders to hepatitis B vaccines develop HBV-specific cellular immune responses.* Vaccine 2004;22:3789-96.

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 HBIg 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.

- 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.

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.

Recipients	Vaccine														
	Monovalent hepatitis B						DTaP-HB-IPV-Hib			HAHB					
	RECOMBIVAX HB®			ENGERIX®-B			INFANRIX hexa™			TWINRIX®			TWINRIX® Junior		
	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)
Dialysis – chronic renal failure and some immunocompromised – 20 years of age and older	40 (adult dialysis formulation) *or*	1.0 *or*	0, 1, 6	40	2.0	0, 1, 2, 6	Not indicated			Not indicated			Not indicated		
	10 (standard formulation)	4.0	0, 1, 6												

† 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

Recipients	Vaccine														
	Monovalent hepatitis B						DTaP-HB-IPV-Hib			HAHB					
	RECOMBIVAX HB®			ENGERIX®-B			INFANRIX hexa™			TWINRIX®			TWINRIX® Junior		
	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)
Dialysis, chronic renal failure and some immunocompromised children under 16 years of age	double the µg dose for healthy child of same age		3 or 4 dose schedule	double the µg dose for healthy child of same age		3 or 4 dose schedule	Not indicated			Not indicated			Not indicated		
Dialysis, chronic renal failure and some immunocompromised 16 to 19 years of age	double the µg dose for healthy child of same age		3 or 4 dose schedule	40	2.0	0, 1, 2, 6	Not indicated			Not indicated			Not indicated		
Adults															
16 to 19 years of age	5	0.5	0, 1, 6**	10¥	0.5	0, 1, 6 *or* 0, 1, 2, 12	Not indicated			20	1.0	0, 1, 6 *or* 0, day 7, day 21, month 12	Not indicated		
20 years of age and older	10	1.0	0, 1, 6**	20	1.0	0, 1, 6 *or* 0, 1, 2, 12 *or* 0, day 7, day 21, month 12	Not indicated			20	1.0	0, 1, 6 *or* 0, day 7, day 21, month 12	Not indicated		

Table 3: Dosages and schedules for hepatitis B-containing vaccines

Recipients	Vaccine																	
	Monovalent hepatitis B						DTaP-HB-IPV-Hib			HAHB								
	RECOMBIVAX HB®			ENGERIX®-B			INFANRIX hexa™			TWINRIX®			TWINRIX® Junior					
	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule (Months: 1st dose = month 0)	µg HBsAg	mL	Schedule	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)	µg HBs Ag	mL	Schedule (Months: 1st dose = month 0)			
Infants and children																		
Infants of HB-negative mothers	2.5	0.25	0, 1, 6**	10	0.5	0, 1, 6 *or* 0, 1, 2, 12	10	0.5	Months of 2, 4, 6, 12- *or* 2, 4, 6 *or* 2, 4, 12-23	Not indicated			Not indicated					
Infants of HB-positive mothers	5	0.5	0, 1, 6**	10	0.5	0, 1, 6 *or* 0, 1, 2, 12	Not indicated before 6 weeks of age			Not indicated			Not indicated					
12 months to 24 months of age	2.5	0.25	0, 1, 6**	10	0.5	0, 1, 6 *or* 0, 1, 2, 12	10	0.5	Months: 1st = month 0) 0, 2, 4, 10- *or* 0, 2, 4 *or* 0, 2, 10-21	20	1.0	0, 6-12	10	0.5	0, 1, 6			
24 months to less than 11 years of age	2.5	0.25	0, 1, 6**	10	0.5	0, 1, 6 *or* 0, 1, 2, 12	May be given to children aged 24 months to 7 years, if necessary			20	1.0	0, 6-12	10	0.5	0, 1, 6			
11 to 15 years of age (inclusive)	10	1.0	0, 4-6	20	1.0	0, 6	Not indicated			20	1.0	0, 6-12	10	0.5	0, 1, 6			
	5	0.5	0, 1, 6**	10*	0.5	0, 1, 6 *or* 0, 1, 2, 12												
16 to 19 years of age (inclusive)	5	0.5	0, 1, 6**	10*	0.5	0, 1, 6 *or* 0, 1, 2, 12	Not indicated			Not indicated			10	0.5	0, 1, 6			

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.

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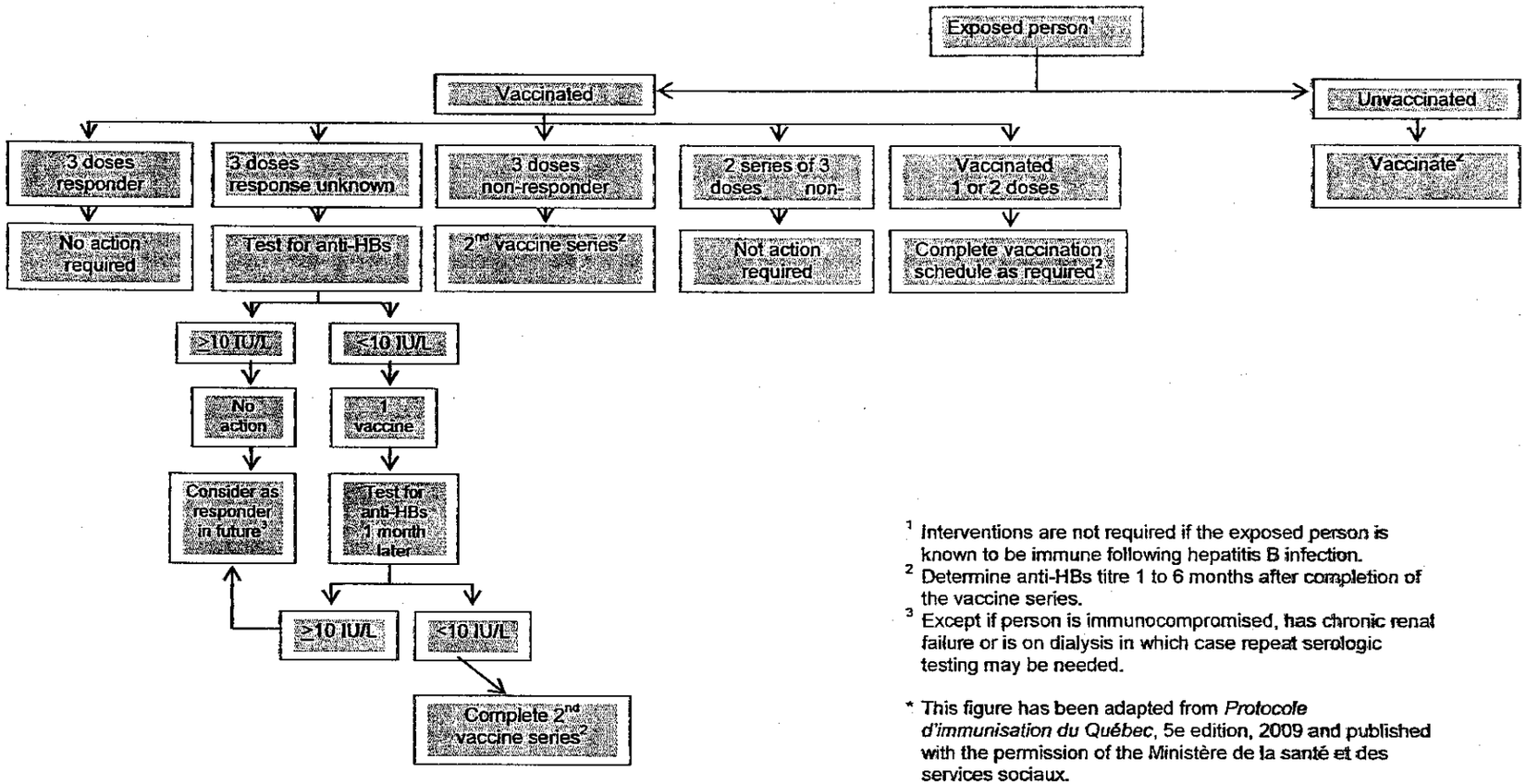
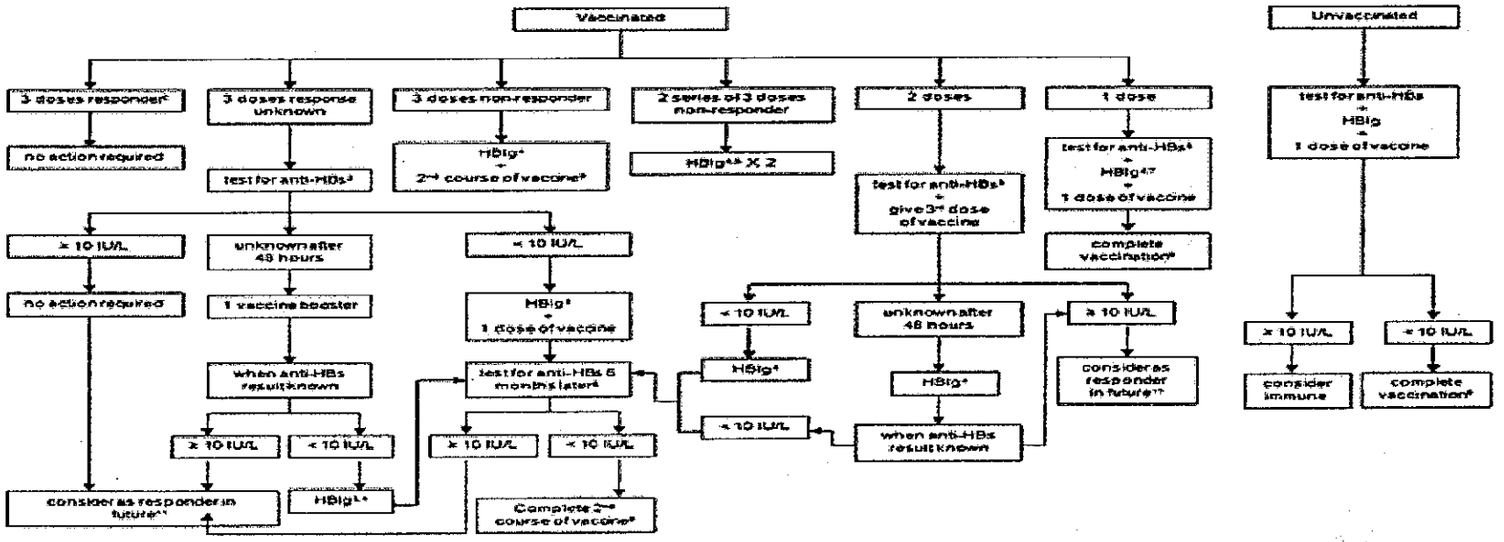
Figure 3*: Management of individuals with percutaneous or mucosal exposure to an uninfected or low risk source



[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.

Figure 2*: Management of individuals with percutaneous or mucosal exposure to an infected or high risk source[1]



[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

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.

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 than10 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.

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

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.

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.

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

Maternal HBsAg status	Recommendation
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

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

All adults and children who have immigrated to Canada from areas where there is a high prevalence of HB
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.
Children and workers in child care settings in which there is a child or worker who has acute HB or is an HB carrier
Household and sexual contacts of acute HB cases and HB carriers
Household or close contacts of children adopted from HB-endemic countries if the adopted child is HBsAg positive
Populations or communities in which HB is highly endemic
Residents and staff of institutions for the developmentally challenged
Staff and inmates of correctional facilities
Persons with lifestyle risks for infection, including: • persons who have unprotected sex with new partners • persons who have had more than one sexual partner in the previous 6 months • persons with a history of sexually transmitted infections • persons seeking evaluation or treatment for a sexually transmitted infection • persons who engage in high risk sexual practices • persons who use injection drugs • men who have sex with men (MSM)
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.
Hemophiliacs and other people receiving repeated infusions of blood or blood products.
Persons with chronic renal disease or who are undergoing chronic dialysis (hemodialysis or peritoneal dialysis)
Persons with congenital immunodeficiencies
Persons who have undergone hematopoietic stem cell transplantation (HSCT) or are awaiting solid organ transplant
HIV-infected persons
Travellers to HB endemic areas
Health care workers, emergency service workers, and others with potential occupational exposure to blood, blood products and bodily fluids that may contain HB virus
Any person who wishes to decrease his or her risk of HB

Post-exposure

HB vaccination and one dose of hepatitis B immune globulin (HBIg) administered within 24 hours after birth are 85% to 95% effective in preventing HB infection in exposed neonates. Studies have demonstrated the efficacy of HBIg and/or HB vaccine in percutaneous or mucosal exposure to HB-positive blood or sexual exposure to HB-positive persons. A single dose of HBIg 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

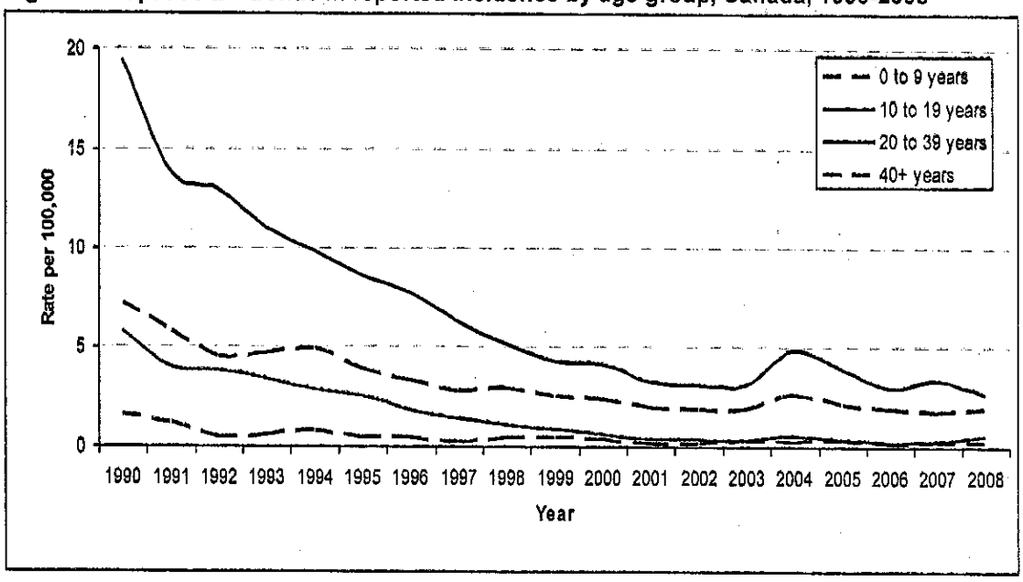
HB-containing vaccine should be given for routine immunization of infants or children and for immunization of children and adolescents who have missed HB immunization on the routine schedule. The age at which HB-containing vaccine is offered varies from jurisdiction to jurisdiction. In jurisdictions 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.

Figure 1: Hepatitis B - trends in reported incidence by age group, Canada, 1990-2008



PREPARATIONS AVAILABLE FOR USE IN CANADA

HEPATITIS B-CONTAINING VACCINES

- **ENGERIX®-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.

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).

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 *Hepadnavirdiae* 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

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PART 4

HEPATITIS B VACCINE

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: o Infants born to HB-infected mothers o persons potentially exposed to blood or bodily fluids containing HB virus o 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.

Merck Canada Inc. *Product Monograph - VAQTA®*. May 2011.

Navas E, Salleras L, Gisbert R et al. *Efficiency of the incorporation of the hepatitis A vaccine as a combined A+B vaccine to the hepatitis B vaccination programme of preadolescents in schools*. Vaccine 2005;23(17-18): 2185-9.

Pham B, Duval B, De Serres G et al. *Seroprevalence of hepatitis A infection in a low endemicity country: a systematic review*. BMC Infect Dis. 2005;5:56.

Roberton D, Marshall H, Nolan T et al. *Reactogenicity and immunogenicity profile of a two-dose combined hepatitis A and B vaccine in 1-11-year-old children*. Vaccine 2005(43);23:5099-105.

Sagliocca L, Amoroso P, Stroffolini T et al. *Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial*. Lancet. 1999;353(9159):1136-39.

Sanofi Pasteur Ltd. *Product Monograph - AVAXIM®*. February 2011.

Sanofi Pasteur Ltd. *Product Monograph - AVAXIM®– Pediatric*. November 2011.

Sanofi Pasteur Ltd. *Product Monograph - ViVAXIM®*. February 2011.

Scheifele D. *Hepatitis A vaccine: the growing case for universal immunization of children*. Expert Opin Pharmacother.2005;6:157-64.

Talecris Biotherapeutics Inc. *Product Monograph - GamaSTAN® S/D*. September 2006.

Vento S, Garofano T, Renzini C et al. *Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis*. N Engl J Med. 1998;388:286-90.

Werzberger A, Kuter B, Shouval D et al. *Anatomy of a trial: a historical view of the Monroe inactivated hepatitis A protective efficacy trial*. J Hepatol. 1993;18(Suppl. 2):S46-S50.

Wu J, Zou S, Giulivi A. *Hepatitis A and its control*. In: Bloodborne Pathogens Division, Health Canada. *Viral hepatitis and emerging bloodborne pathogens in Canada*. Can Commun Dis Rep. 2001;27(S3):7-9.

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SELECTED REFERENCES

American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, et al. (editors). Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Bryan J, Henry C, Hoffman A et al. *Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines.* Vaccine 2001;19:743-50.

Centers for Disease Control and Prevention. *Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices* (ACIP). MMWR Morb Mortal Wkly Rep 2006;55(No. RR-7); 1-23.

Centers for Disease Control and Prevention. *The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases*. Updated 11th ed.; May 2009.

Centers for Disease Control and Prevention. *Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Morbid Mortal Wkly Rep. 2007;56(41):1080–4.

Committee to Advise on Tropical Medicine and Travel. *Statement on hepatitis vaccines for travellers.* Can Comm Dis Rep. 2008;34(ACS-2):1-24.

Committee to Advise on Tropical Medicine and Travel. *Statement on international adoption.* Can Comm Dis Rep. 2010;36(ACS-15):1-17.

Dagan R, Leventhal A, Anis E et al. *Incidence of hepatitis A in Israel following universal immunization of toddlers.* JAMA 2005;294:202-10.

De Serres G, Duval B, Shadmani R et al. *Ineffectiveness of the current strategy to prevent hepatitis A in travelers.* J Travel Med 2002;9(1):10-6.

De Serres G, Laliberte D. *Hepatitis A among workers from a waste water treatment plant during a small community outbreak.* Occup Environ Med 1997;54:60-2.

Deshaies M, Dion R, Valiquette L et al. *Immunization against hepatitis A during an outbreak in a Jewish orthodox community Quebec 1997-1998.* Can Commun Dis Rep. 1998;24:145-51.

Duval B, De Serres G, Ochnio J et al. *Nationwide Canadian study of hepatitis A antibody prevalence among children eight to thirteen years old.* Pediatr Infect Dis J. 2005;24:514-19.

Duval B, Gilca V, Boullanne N et al. *Immunogenicity of two paediatric doses of monovalent hepatitis B or combined hepatitis A and B vaccine in 8-10-year-old children.* Vaccine 2005;23(31):4082-87.

Fiore AE. *Hepatitis A transmitted by food.* Clin Infect Dis. 2004;38:705-15.

GlaxoSmithKline Inc. *Product Monograph - HAVRIX®.* July 2011.

GlaxoSmithKline Inc. *Product Monograph – TWINRIX®.* December 2011.

Hockin J, Isaacs S, Kittle D et al. *Hepatitis A outbreak in a socially contained religious community in rural southern Ontario.* Can Commun Dis Rep. 1997;23:161-66.

McMahon B, Beller M, Williams J et al. *A programme to control an outbreak of HAV in Alaska by using an inactivated hepatitis A vaccine.* Arch Pediatr Adolesc Med. 1996;150:733-39.

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 vaccinee 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.

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.

Table 3: Dosages and schedules for Hepatitis A-containing vaccines

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

* 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.

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Table 2: Options for completing hepatitis A vaccination series in adults, children and adolescents

Adult presents with history of:	Option: to complete HA series
1 dose adult HAHB vaccine	2 doses adult HAHB vaccine OR 2 doses adult HA vaccine*1,*2
2 doses adult HAHB vaccine	1 dose adult HAHB vaccine OR 1 dose adult HA vaccine*1,*2
1 dose adult HA vaccine	1 dose adult HA vaccine OR 2 doses adult HAHB vaccine*1
Child or adolescent*3 presents with history of:	**Options to complete HA series**
1 dose pediatric/adolescent HAHB vaccine	2 doses pediatric/adolescent HAHB vaccine*4 OR 2 doses pediatric/adolescent HA vaccine*1,*2
1 dose adult HAHB vaccine	1 dose adult HAHB vaccine unless 16 years or older*5 OR 1 dose pediatric/adolescent HA vaccine*1,*2
2 doses pediatric/adolescent HAHB vaccine	1 dose pediatric/adolescent HAHB vaccine*4 OR 1 dose pediatric/adolescent HA vaccine*1,*2
2 doses adult HAHB vaccine	No additional doses needed unless 16 years of age or older*5
1 dose pediatric/adolescent HA vaccine	1 dose pediatric/adolescent HA vaccine

*1 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.

*2 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.

*3 Refer to Table 3 for schedule and age cut-offs for each product.

*4 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.

*5 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.

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.

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.

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.

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)

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)

Travellers to or immigrants from HA endemic areas. Refer to Travellers.
Household or close contacts of children adopted from HA endemic countries
Populations or communities at risk of HA outbreaks or in which HA is highly endemic (e.g., some aboriginal communities).
Persons with lifestyle risks for infection, including those who use illicit drugs (injectable and non-injectable) and men who have sex with men (MSM).
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.
People with haemophilia A or B receiving plasma-derived replacement clotting factors.
Military personnel and humanitarian relief workers likely to be posted 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.
Any person who wishes to decrease his or her risk of HA.

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.

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.

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

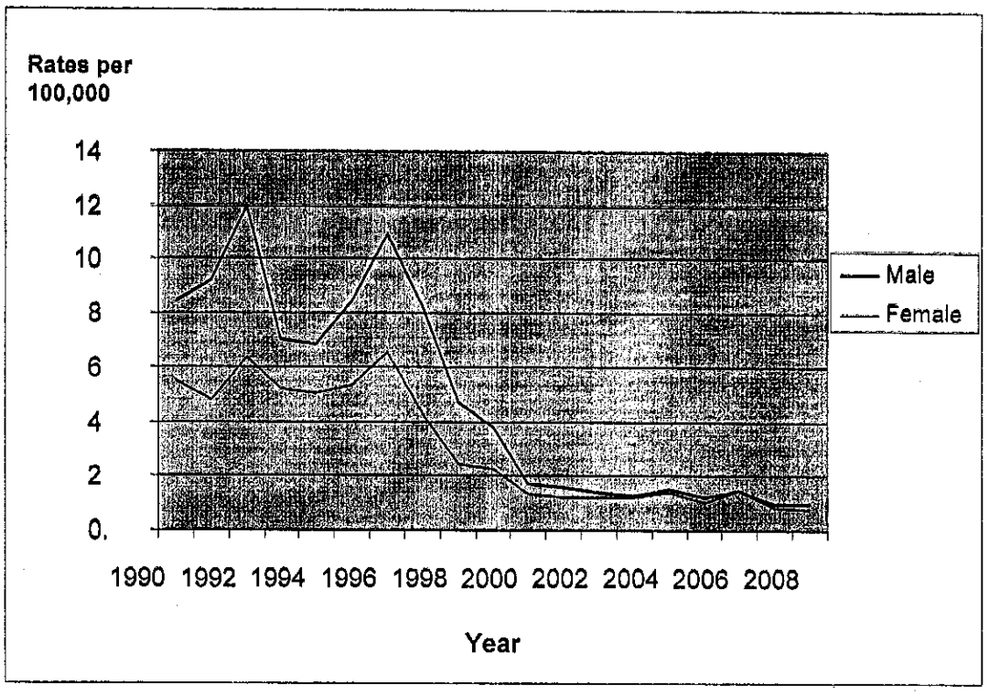
Global

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_ITHRiskMap.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.

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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

PART 4

HEPATITIS A VACCINE

KEY INFORMATION (refer to text for details)

What	• In Canada, risk factors for hepatitis A (HA) infection include: o Travel to HA endemic countries o Household or close contact with an acute HA case o Men who have sex with men (MSM) o Illicit drug use o Populations or communities that have high endemic rates of HA or are at risk of HA outbreaks o 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: o household and sexual contacts of people infected with HA o contacts in group child care centres and kindergartens o 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.

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