Travel vaccines: Update for Canadian pharmacists

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Introduction

Pretravel health assessments extend beyond vaccines, yet these play an integral role. Canadians made 31.3 million overnight departures abroad in 2016, and with recent expansion of pharmacists' authorization to administer vaccines across Canada, pharmacists with advanced training in travel medicine are well suited to fill a gap in providing guidance on safe and healthy travel practices, including administration of vaccines and personal protective measures (including personal safety, food and water precautions and bite avoidance).¹⁻⁴ Community pharmacists without specialized training can proactively inquire with patients about upcoming travel and offer to review and administer commonly recommended travel vaccines (or complete a vaccine series). They should, however, refer travellers with more complex itineraries (i.e., nonresort travel) to a specialized travel clinic. By being proactive, pharmacists can ensure adequate dosing prior to departure and/or be able to seek alternate options in the event of vaccine unavailability.

Canadian travel clinics face many challenges, particularly related to vaccine shortages, but pharmacists who strive to maintain a high level of competency in travel health and vaccination can alleviate the impact these challenges could have on travellers' health.³⁻⁵ This article will focus on recent updates and challenges regarding commonly recommended travel vaccines, including those for travellers' diarrhea, cholera, hepatitis A and B, typhoid, Japanese encephalitis, rabies, meningococcal meningitis and yellow fever, and are summarized in Table 1.

Travellers' diarrhea and cholera

Travellers' diarrhea (TD), affecting 30% to 70% of travellers, is the most common health complaint for travellers, and risks correlate strongly to destination, duration and type of travel.⁶ The most common causes of TD are bacterial (80%-90%), with

enterotoxigenic *Escherichia coli* (ETEC) being the predominant pathogen in 25% to 50% of all tested TD cases.^{7,8} TD is defined as 3 or more unformed stools in 24 hours and is usually mild and self-limiting.^{7,9}

The heat-labile enterotoxin (LT) strain of ETEC has antigenic commonalities to the recombinant B subunit of the cholera toxin in the oral cholera/ETEC-diarrhea vaccine (Dukoral).⁷⁻¹⁰ The vaccine is promoted in Canada to protect travellers against TD but may provide a false sense of security, as the actual efficacy of this vaccine for the prevention of all-cause TD is quite low, at only 6%.^{6,7} More evidence is required to definitively recommend this vaccine even in those high-risk travellers where TD can be more serious.^{6,7} A recent review found insufficient evidence to recommend this vaccine in TD prevention, citing a need for further research to create a vaccine to cover all antigenic variations of ETEC.¹¹

Travellers' perceptions and preferences can be considered when discussing this vaccine.^{6,12} To reduce their perceived risk of TD, travellers may be willing to pay close to \$100 CAN for a vaccine with minimal efficacy.^{6,10} TD self-management should still be reinforced for possible diarrheal illness during travel. Consult the Committee to Advise on Tropical Medicine and Travel (CATMAT) guidelines for TD prevention and management for additional guidance.⁶

General access to sanitary conditions for most travellers creates a very low risk of infection with *Vibrio cholerae* O1 (0.01%-0.001%/month of stay in risk areas), with most cases being mistaken for self-limiting bouts of TD.¹³⁻¹⁵ The use of the oral cholera/ETEC-diarrhea vaccine has shown to have high short-term (6 months) protection against *V. cholera* O1 at 85% to 90%, but over 3 years only an average of 63% efficacy as protection drops to <50% after the first year.¹³⁻¹⁵ Booster doses given within 2 years have shown to provide anamnestic

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DOI:10.1177/1715163519877899

TABLE 1 Travel vaccine update and summary

Vaccine*	Recommended age	Schedule	Duration of protection	Comments
Oral cholera/ETEC-diarrhea	<ul style="list-style-type: none"> ≥2 years 	<ul style="list-style-type: none"> 2 doses: 1-6 weeks apart 	<ul style="list-style-type: none"> 2 months to 2 years 	<ul style="list-style-type: none"> Low efficacy in preventing TD Consider in relief or health care workers in cholera outbreak conditions
Hepatitis A (pediatric and adult formulations available)	<ul style="list-style-type: none"> ≥6 months 	<ul style="list-style-type: none"> 2 doses: 0, 6-12 months 	<ul style="list-style-type: none"> Long-term/lifetime after series completion 	<ul style="list-style-type: none"> Brand-specific age recommendations
Hepatitis B (pediatric and adult formulations available)	<ul style="list-style-type: none"> ≥Birth >19 years 11 to <16 years[†] 	<ul style="list-style-type: none"> 3 doses: 0, 1, 6 months 4 doses: 0 days, 7 days, 21 days, 12 months (accelerated) 2 doses: 0, 6-12 months 	<ul style="list-style-type: none"> Long-term/lifetime after series completion 	<ul style="list-style-type: none"> Serology not routinely recommended Consider immunity in Canadians born after 1981 <5% do not respond to vaccination
Hepatitis A/B (pediatric and adult formulations available)	<ul style="list-style-type: none"> ≥6 months >19 years ≥6 months to <16 years[†] 	<ul style="list-style-type: none"> 3 doses: 0, 1, 6 months 4 doses: 0 days, 7 days, 21 d, 12 months 2 doses: 0, 6-12 months 	<ul style="list-style-type: none"> Long-term/lifetime after series completion 	<ul style="list-style-type: none"> Consider previous HB immunity prior to use of combined HAHB vaccine Ensure at least 4 full weeks prior to departure before initiating series
Typhoid (oral and Injectable formulations available)	<p>Oral</p> <ul style="list-style-type: none"> ≥6 years <p>Injectable</p> <ul style="list-style-type: none"> ≥2 years <p>Injectable combined with HA</p> <ul style="list-style-type: none"> ≥16 years 	<ul style="list-style-type: none"> 1 capsule on alternate days (total of 4 capsules) 1 dose 	<ul style="list-style-type: none"> 5 to 7 years 2 to 3 years 	<ul style="list-style-type: none"> Not generally indicated for routine travel to Mexico or Caribbean A booster for HA will be needed in 6-12 months if combination product used
Japanese encephalitis	<ul style="list-style-type: none"> ≥18 years ≥2 months to <3 years^{‡,33,36} ≥3 years^{‡,33,36} 	<ul style="list-style-type: none"> 2 doses: 0, 28 days 2 doses: 0, 7 days[‡] 2 half doses: 0, 28 days 2 doses: 0, 28 days 	<ul style="list-style-type: none"> 12-24 months 	<ul style="list-style-type: none"> Give a booster dose 12-24 months after first dose if still at risk Then: <ul style="list-style-type: none"> Give booster at 10 years for long-term immunity Seroconversion with 0, 7-day schedule[‡] found to be comparable to 0, 28-day schedule Disease severity higher in pediatrics to warrant consideration of vaccine use[‡]

(continued)

TABLE 1 (continued)

Vaccine*	Recommended age	Schedule	Duration of protection	Comments
Rabies	<ul style="list-style-type: none"> All 	<ul style="list-style-type: none"> 3 doses: 0, 7, 21-28 days (preexposure) 	<ul style="list-style-type: none"> Long-term demonstrated by anamnestic response 	<ul style="list-style-type: none"> ID dosing requires serological testing 2 weeks postseries and should not be used in immunocompromised clients or with concomitant chloroquine use[‡]
Meningococcal meningitis (conjugate polysaccharide formulations)	<ul style="list-style-type: none"> ≥2 to ≤55 years ≥56 years[‡] ≥3 months to 2 years⁶¹ 	<ul style="list-style-type: none"> 1 dose 2 doses: 3 months apart 	<ul style="list-style-type: none"> 5 years 	<ul style="list-style-type: none"> Brand-specific age recommendations Use in populations ≥56 years can be considered safe and effective based on limited data and expert opinion[‡]
Yellow fever	Full dose <ul style="list-style-type: none"> ≥ 9 months Fractional (1/5) dose [‡] <ul style="list-style-type: none"> ≥2 years 	<ul style="list-style-type: none"> 1 dose 1 dose 	<ul style="list-style-type: none"> Lifetime 1 year 	<ul style="list-style-type: none"> Despite new lifetime validity of full dose, reassessment every 10 years is advised Fractional dose offers similar protection to full dose for at least 1 year[‡]

ETEC, *Escherichia coli*; HA, hepatitis A; HAHB, hepatitis A and B vaccine; HB, hepatitis B; ID, intradermal; TD, travellers' diarrhea.

*Providers should refer to the *Canadian Immunization Guide* and product monographs for complete indications for clinic use, age-specific dosing schedules and contraindications.

[‡]Alternate pediatric dose using the adult formulation.

[‡]Considered an "off-label" use.

(memory-based) response, but that effect is lost after 2 years and the series should be restarted if at risk beyond this time.⁷

Use of this vaccine for cholera is generally reserved for populations at high risk of exposure in endemic or epidemic conditions.¹⁴ Travellers providing relief work and/or medical care to displaced persons (e.g., refugee camps or disaster relief) should be considered for vaccination against cholera.^{7,14,16} Of note, the commercially available preparation in Canada does not protect against *V. cholera* O139, most commonly found in India and Bangladesh.¹⁴

The oral vaccine can be used in patients ≥2 years and is available at pharmacies without a prescription in all provinces (except Quebec, where a prescription is required). The vaccine should be completed at least 1 week prior to travel and consists of 2 doses taken 1 to 6 weeks apart, with booster dose(s) required for subsequent travel.^{6,17}

Hepatitis A vaccine

Hepatitis A virus (HAV) is one of the most common infections acquired by travellers. Infection risk and travel are strongly correlated, with 44% to 55% of reported hepatitis A (HA) infections in Canada associated with international travel.^{15,18} Vaccine efficacy is high, even with a single dose, and reported 97% to 100% seroconversion with the second dose confers long-term protection.^{15,18} HA vaccines (Avaxim; Havrix) are generally considered safe and well tolerated.¹⁵

HA vaccine should be recommended to all nonimmune travellers to endemic areas as soon as travel is considered and

can be started as late as the day of travel and still be effective.¹⁹ While risk of severe infection is low in infants ≤12 months of age, vaccination with HA vaccine can be given safely, with comparable immunogenicity to those vaccinated ≥12 months of age. For infants travelling to areas with endemic HAV (including Canadian-born children of new Canadian parents), vaccination can be provided beginning at 6 months of age, a recommendation supported by the National Advisory Committee on Immunization.^{15,18,20}

Hepatitis B vaccine

Hepatitis B (HB) vaccine (Engerix B; Recombivax HB) was introduced into the universal school-based vaccination program in Canada in 1987 and is also included in routine vaccine schedules in many other countries—this is an important consideration when travellers present for travel health advice.^{21,22} For example, in Alberta, any individual born in 1981 or later would have been eligible to receive the vaccine from the public health vaccination program.²³ Provincially varying schedules can create some confusion, but a published schedule by province is available.²⁴

Canadian-born children travelling to countries with high endemicity of hepatitis B virus (HBV) with their Canadian immigrant parents to visit friends and relatives are at high risk of exposure and should be vaccinated if they were not given the vaccine in infancy.²⁵ Any nonimmune individual travelling to endemic countries, with any potential for possible exposure to blood or bodily fluids, should be vaccinated against HBV.²⁶

For most, completion of a 3- to 4-dose series of HB vaccine confers long-term or lifetime immunity.²⁵ Vaccine nonresponse does occur (<5% of those vaccinated) and a repeated series should be completed, along with serology 1 to 2 months after the last dose. Negative serology after the repeated series confirms nonresponse, and those individuals should be counselled on strict risk avoidance and postexposure follow-up.²⁷ Travellers with chronic renal disease or immunodeficiency should receive a series using double doses of the appropriate formulation of HB vaccine, along with serology 1 to 2 months after series completion.²⁵ Neither booster doses nor routine serology are routinely recommended in immunocompetent individuals. Despite low or undetectable titers, cell-mediated immune memory persists.²⁵

Combined hepatitis A and B vaccine

At times, travellers request specific vaccines, including the well-advertised combined hepatitis A and B vaccine (HAHB) vaccine (Twinrix). Time remaining before travel and previous HB vaccination status are important considerations. Previous HB vaccine recipients would only need to update HA. For those with no HB vaccine history, if there is insufficient time to ensure at least 2 to 3 doses within 3 to 4 weeks, it is recommended to administer the monovalent vaccines for HA and HB separately.¹⁹ Knowledge of alternate dosing schedules can ensure the protection of travellers during supply restraints. For example, adult HAHB vaccine can be used in pediatrics (1-15 years of age) as a 0, 6-month schedule.²⁵ Recommended age-dependent dosing schedules and available brands can be found by reviewing the *Canadian Immunization Guide*.^{15,25}

Typhoid vaccine

Available vaccines against the fecal-oral transmission of *Salmonella typhi* have only moderate efficacy, ranging from 50% to 70%. Vaccination is indicated for travellers visiting those areas of highest risk found in South Asia and can be considered in areas of Southeast Asia and Africa for travellers with higher-risk itineraries (e.g., backpacking and long duration of travel). Because of the low risk of typhoid in South America, the Caribbean and Mexico, typhoid vaccines are not usually indicated.²⁸⁻³⁰ Risk factors for typhoid disease include longer duration of travel, achlorhydria, travellers visiting friends and relatives, rural itineraries and adventurous eating habits.²⁸⁻³⁰ These, as well as patient preference, cost and frequency of travel, should be taken into account when recommending typhoid vaccine and when choosing a dosage form.²⁹

A single dose of injectable typhoid vaccine (Typh-I) or injectable typhoid vaccine combined with HA (HA-Typh-I) will confer protection for 2 to 3 years, and oral typhoid (Typh-O) given as 4 capsules on alternate days will confer immunity for approximately 5 to 7 years.^{28,31} Both the injectable and oral vaccines are generally safe and well tolerated and considered protective within 7 to 10 days after vaccination.³⁰ Three

commercially available vaccines are available for typhoid fever in Canada: Typh-I (Typhim-Vi), HA-Typh-I (Vivaxim) and Typh-O (Vivotif).³⁰

Japanese encephalitis vaccine

Japanese encephalitis virus (JEV) is a *Flavivirus* common in many Asian countries, where it is considered a public health issue requiring routine vaccination.³² The night-biting *Culex* mosquito transmitting JEV breeds in large pools of water, including areas in which flood irrigation is practiced, such as rice fields. The risk for travellers is considered low but risk increases based on duration of travel, location, season and planned activities during travel. While most cases are asymptomatic (making the reported incidence lower than the actual incidence), the case fatality rate is reported to be 20% to 30%, with long-term neurological sequelae reported in as high as 50% of survivors.³²⁻³⁴ Pharmacists recommending this vaccine should have a good knowledge of seasonal variances in risk based on geographic climate.^{31,35}

The vero cell JEV vaccine JEV-VC (Ixiaro), available in Canada, has shown favourable response. Although actual overall prevention rates are not known, it is assumed that protection can be expected when combined with strict personal protective measures based on the presence of antibodies in at least 95% of vaccinees a month after vaccination with 2 doses 28 days apart.³⁴

In Canada, JEV-VC vaccine has been approved for use in adults ≥ 18 years using a dose on day 0 and day 28. Boosters at 12 to 24 months have been recommended for travellers still at risk of exposure, and a single booster at 10 years has been proposed to confer long-term or lifetime immunity.³² Recently, JEV-VC has been approved for use in the United States in children ≥ 2 months of age (half a dose recommended for children aged ≥ 2 months to <3 years) on days 0, 28.^{33,36} In Canada, this would still be considered “off-label.” However, since safety and efficacy are similar in pediatric and adult populations, the vaccine should be considered for pediatric travellers to endemic areas, as disease severity is high in this population.^{32,36}

Last-minute travellers often complicate the travel health assessment process, since ideally, initiation of JEV-VC should occur 6 weeks prior to departure to establish protective antibody levels. Recently, a rapid dosing schedule for adults aged 18 to 65 years has been approved for use in the United States (considered “off-label” in Canada), with a dose on day 0 and day 7 completed at least 1 week before risk of exposure, with seroconversion comparable to the 0- and 28-day schedule.^{32,37}

Rabies vaccine

Rabies exposure from the bite or scratch of an infected mammal is a serious event and, if left untreated, is fatal.³⁸ Limitations to preexposure vaccination include cost, time to travel and low perception of actual risk. Travellers at higher risk of exposure should be encouraged to vaccinate, including

travellers visiting friends and relatives (especially young children), expatriates/long-term travellers, travellers engaging in high-risk activities (e.g., cave exploration, animal care) and travellers to high-risk areas with limited or no rabies immune globulin and vaccine.^{38,39}

Intramuscular rabies vaccine given on days 0, 7, and 21 or 28 is safe and immunogenic in healthy travellers.^{40,41} Booster doses and serology are not routinely recommended except in those at sustained high risk. Immunity is considered long term, as demonstrated by anamnestic responses to booster doses.⁴¹ Intradermal (ID) dosing can be used with similar response, but serologic testing should be performed at least 2 weeks postseries if this route is used. While ID use reduces the cost to travellers, the time to vaccinate and obtain serology can exceed 7 weeks.^{42,43} The vial must be used within 6 hours of reconstitution, however, which creates challenges to maximize the number of patients vaccinated to reduce waste.^{39,40,42,43} ID dosing should not be used in immunocompromised travellers or with concomitant chloroquine use.^{40,43}

Meningococcal meningitis

The risk to travellers for acquiring *Neisseria meningitidis* is low, but implications of infection with invasive meningococcal disease (IMD) are high, with case fatality rates >10%.¹³ Approximately 20% of survivors suffer long-term sequelae, including brain damage, limb loss and hearing and/or learning disabilities.^{13,44} Five serogroups most commonly associated with invasive disease include A, B, C, Y and W-135, and their prevalence will vary by continent.⁴⁵⁻⁴⁷ Indications for vaccination of travellers using the quadrivalent meningococcal vaccine (Men-ACYW135) will depend on destination, activities, patient characteristics and host condition.⁴⁸

Conjugate Men-ACYW135 vaccines have shown to be more effective than polysaccharide vaccines, and the 3 available conjugate vaccines (Menveo, Menactra and Nimenrix) can be used interchangeably in travellers between the ages of 2 and 55 years.^{45,47} Available evidence demonstrates that they can also be used (off-label) in those ≥56 years.⁴⁵ Repeated doses are to be given every 5 years if still at risk.^{45,47} Beginning in 2002, proof of vaccination with Men-ACYW135 is required for all those wanting to enter Saudi Arabia for Hajj and Umrah pilgrimages.^{45,46,49} Vaccination with the conjugate vaccine is preferred and should occur within 3 years to 10 days before entry into the country.^{45,48}

Available vaccines and their schedules (including for travellers <2 years) can be found in the *Canadian Immunization Guide*.⁴⁷

Yellow fever vaccine

Yellow fever (YF) is a *Flavivirus* transmitted by day-biting *Aedes* or *Haemagogus* mosquitos, with a 3- to 6-day incubation period, and is endemic and intermittently epidemic in Africa and South America.^{50,51} Risk to travellers varies by destination

and season and can be difficult to quantify. In severe infections, fatality rates are high, even with aggressive supportive treatments.⁵¹ In addition to personal protective measures, vaccination should be considered in certain travellers after performing a thorough risk assessment. Risk of severe adverse vaccine reactions should be weighed with actual risk of disease vs entry requirements, and travellers with absolute contraindications should not be vaccinated.^{50,51} Protection after vaccination is to be considered lifetime and boosters not recommended except for travellers visiting areas with current outbreaks or those who are HIV positive if it has been >10 years since their primary dose.⁵²

YF vaccination and official documentation must be received at designated YF vaccination centres, which are becoming more prevalent in Canada.⁵³ Pharmacies can become designated centres, provided they specify a nominated health care practitioner with prescribing authority to ensure requirements are met.⁵⁴ Notably, recent YF vaccine supply restraints have limited vaccine accessibility to travellers.⁴ However, in 2017, Health Canada supported the use of fractional dosing of YF vaccine to extend available supply.^{53,55} Using 1/5 the dose has been shown to provide similar protection as a full dose, for at least 1 year.⁵⁵

Consult CATMAT guidelines for using fractional YF dosing.⁵⁴

Pharmacists poised for future expansion of travel vaccination services

The availability, accessibility and public trust in pharmacists place the profession in a unique position to offer pretravel consultation for patients.⁴ Moreover, recent expansion in scope of pharmacy practice has presented an opportunity for pharmacists to play a larger role in providing vaccination services for travellers in community pharmacies or travel clinics.³ Notably, the majority (or all) of the travel vaccines covered in this article fall within current (or pending) scope of practice for pharmacists in most jurisdictions outside of Nunavut and Northwest Territories, where pharmacists do not yet have immunizing authority.⁵⁶⁻⁵⁹

A recent study conducted in Alberta has demonstrated positive patient health status and high satisfaction (94%) with care received following a pretravel consultation at a pharmacist-managed travel clinic.⁴ In this study, a total of 280 vaccines were recommended across 103 study participants, with the vast majority (79%) of these vaccines administered in the clinic. These results provide evidence to support continued expansion of pharmacists' scope in pretravel health, including vaccination, and suggest the need for future efforts to expand advanced training in travel medicine. Ultimately, pharmacy-based delivery of travel vaccines promises to improve patient access to recommended vaccines, thereby protecting travellers' health and potentially reducing the global burden of infectious disease.⁶⁰ ■

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