CHAPTER 5

Immunizations for Travelers

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Recommendations for travel immunizations are based on a risk assessment of each traveler's general health, trip itinerary, and knowledge of current health conditions at a given destination. Most travelers seek protection against vaccine-preventable diseases, yet their acceptance of the vaccines recommended for travel may depend largely on other concerns, such as number of doses and vaccine schedules, route of administration (oral vs. injection), and cost. Many first-time international travelers are surprised by the number of vaccines that may be advised for a given itinerary. On the other hand, experienced repeat travelers may be pleased by the availability of new vaccines that may be better tolerated, provide greater efficacy, and have a longer duration of protection compared with older products.

Travelers planning adventure or expedition travel, extended stays abroad, or whose work may necessitate multiple trips abroad with very short notice should be encouraged to seek advice for travel immunizations well in advance (up to 6 months) of anticipated departure. This allows time for optimal scheduling of vaccine doses and procurement of vaccines that may be in short supply or difficult to obtain. For travelers with little advance notice, accelerated schedules may be used for some travel vaccines, and multiple vaccine doses may be given at different sites on the same day, limited only by the recipient's anticipated tolerance for multiple injections and associated minor adverse side effects. Up to six live virus vaccines may be given on the same day without interfering with immune efficacy. **Table 5.1** lists some conditions that may cause vaccine interactions or interfere with the expected immune protection. In general, attenuated live virus vaccines and bacterial vaccines are contraindicated during pregnancy and in persons with altered immune competence (see Chapters 14-16). This chapter will cover the approach to adult travel immunizations. Pediatric travel immunizations are covered in Chapter 12.

ROUTINE IMMUNIZATIONS

Immunizations may be organized into three categories termed the "3 Rs": routine, required, and recommended. Routine vaccines are those vaccines usually given as part of national public health childhood immunization programs. Although most travelers seek pre-travel care for "travel" immunizations, documenting completion of the routine vaccines (or immunity to the given vaccine-preventable disease) and identifying recommended booster doses are just as important as the travel vaccines. Many low-resource countries are still working toward implementation of childhood immunization programs that cover 90% of the pediatric population, a public health goal identified by the World Health Organization (WHO) Expanded Program on Immunizations. Thus, during international travel, adult travelers may be exposed to vaccine-preventable communicable diseases that are no longer commonly transmitted in industrialized countries, such as measles, polio, and chickenpox. Dosage schedules for adult routine immunizations are given in **Table 5.2**.

TABLE 5.1 Vaccine Interactions

Vaccine	Interaction	Precaution
Immune globulin	Measles/mumps/rubella (MMR), varicella, polio, and hepatitis A vaccines	Give these vaccines at least 2 weeks before immune globulin (IG) or 3-11 months after IG, depending on IG product, indication, and dose received.
Oral typhoid vaccine	Antibiotic therapy	Do not administer oral typhoid vaccine concurrently with antibiotics.
Oral typhoid vaccine	Proguanil malaria chemoprophylaxis	Schedule an interval of at least 10 days between final dose of oral typhoid vaccine and proguanil (Malarone = atovaquone + proguanil).
Virus vaccines, live (MMR, oral polio, varicella, yellow fever)	Other live virus vaccines	Give live virus vaccines on same day, or separate doses by at least 1 month.
Virus vaccines, live (MMR, oral polio, varicella, yellow fever)	Tuberculin skin test (PPD)	Do skin test on same day as receipt of a live virus vaccine, or 4-6 weeks after, because live virus vaccines can impair the response to PPD skin test.

Updated from Jong, E.C., 1993. Immunizations for international travelers. In: The Travel Medicine Advisor. American Health Consultants, Atlanta.

The American Committee on Immunization Practices (ACIP) at the Centers for Disease Control and Prevention (CDC) is the federal agency that develops official guidelines for immunizations in the United States. Current recommendations for childhood immunizations include the following vaccines: combined diphtheria, tetanus, and (acellular) pertussis (Dtap), *Haemophilus influenzae* type b conjugate, hepatitis A, hepatitis B, influenza, measles/mumps/rubella, pneumococcal conjugate, poliovirus, rotavirus, and varicella. The standard immunizations recommended by the ACIP for administration to pre-adolescent children at 11-12 years of age include tetanus, diphtheria, and (acellular) pertussis (Tdap), meningococcal conjugate, and human papillomavirus (HPV) vaccines, as well as the second dose of measles, mumps, rubella (MMR) and varicella (chickenpox) vaccines if these had not yet been given (Chapter 12).

When individuals seek travel immunizations, this provides a natural opportunity for them to catch up on any missed doses of their routine immunizations. Adult travelers may be due for booster doses of vaccines for tetanus/diphtheria, polio (for travel to polio outbreak areas), and/or measles (if a second dose after infancy was not received). As varicella is a disease of young adults rather than children in many tropical countries, persons lacking a definite history of previous varicella infection or of having received two doses of varicella vaccine may benefit from primary immunization or should complete their immunization by receiving a second dose of varicella vaccine prior to travel.

Hepatitis A Vaccine as a Routine Immunization

Hepatitis A is the most common vaccine-preventable disease associated with travel and should be a high priority for those over the age of 1 year who have not previously received it or had the natural disease. In 1999, the ACIP recommended that hepatitis A vaccine be administered to all 2-year-olds living in 11 Western states in the United States, where heightened transmission of hepatitis A virus infections was occurring. In 2006, the ACIP issued a new recommendation for hepatitis A immunization of all children at 1 year of age. Thus, hepatitis A vaccine is now a standard immunization for children but should be considered a travel vaccine for older children and adults.

TABLE 5.2 Dosage Schedules for Adult Routine Immunizations

Vaccine	Primary Series	Booster Interval
Influenza virus, inactivated	One dose[a] IM or SC	Annual immunization with current vaccine
Influenza virus, live attenuated	One application by nasal inhalation	Annual immunization with current vaccine
Measles/mumps/rubella[b] (for children >15 months and adults)	One dose[a] SC	Boost measles vaccine at 12-18 years old; if a second dose was not received after childhood, boost measles vaccine once in adult life before international travel for people born after 1957 and before 1980
Pneumococcus conjugate (13 valent)	One dose SC	Give one dose at 65 years of age or older, preferably 6-12 months before the pneumococcus polysaccharide (23 valent) vaccine. (See text for alternate schedules)
Pneumococcus polysaccharide (Pneumovax) (23-valent)	One dose[a] SC	One booster 5 years after the first dose if the primary dose was received at <65 years of age
Poliomyelitis, enhanced inactivated (killed vaccine, safe for all ages)	Give doses[a] one and two SC or IM 4-8 weeks apart; give dose three 6-12 months after dose two	Give a booster dose once to people before travel in areas at risk if 5 or more years since the last dose of vaccine
Tetanus and diphtheria toxoids adsorbed (Td) (for children >7 years of age and for adults)	Three doses[a] SC or IM; give doses one and two 4-8 weeks apart, give dose three 6-12 months later	Routine booster dose every 10 years
Combined tetanus, diphtheria, and (acellular) pertussis (Tdap) (Adacel)	One dose at 11-12 years of age to boost childhood combined diphtheria, tetanus and (acellular) pertussis (Dtap) immunization	Give a single dose to boost childhood immunity; may substitute Tdap once for one of the adult Td booster doses
Varicella[b] (Varivax) (for children >13 years of age and for adults)	Two doses[a] SC given 4-8 weeks apart	None; give a second dose of vaccine if only one dose was received in childhood.

[a]See manufacturer's package insert for recommendations on dosage.
[b]May be contraindicated in patients with any of the following conditions: pregnancy, leukemia, lymphoma, generalized malignancy, immunosuppression from HIV infection or treatment with corticosteroids, alkylating drugs, antimetabolites, or radiation therapy.
IM, Intramuscularly; *SC*, subcutaneously.
Adapted from Jong, E.C., 1993. Immunizations for international travelers. In: The Travel Medicine Advisor. American Health Consultants, Atlanta.

Hepatitis B Vaccine as a Routine Immunization

Hepatitis B vaccine was incorporated into the recommended childhood immunization schedule in 1990. Adults born before 1990 may require the full three-dose hepatitis B vaccine primary series as a catch-up vaccine for protection against inadvertent exposures associated with travel.

Influenza Vaccine

Annual immunization against viral influenza is recommended by the ACIP for all persons 6 months of age or older who do not have medical contraindications to the vaccine. The influenza viruses undergo minor mutations of surface antigens from season to season in a process termed "antigenic drift"; thus the influenza vaccine is re-formulated each year in between flu seasons, according to WHO guidelines, to provide protection against strains of the influenza virus predicted to be in circulation during the season ahead. The newly formulated influenza vaccines are usually released in the early fall.

Both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) products are available. The inactivated influenza vaccines are given by intramuscular (IM) or intradermal (ID) injection. The LAIV is approved for use in persons 2-49 years old and is administered by intranasal application. Both IIV and LAIV are effective in adults. If the flu season has already started in the community, susceptible persons should be immunized with either flu vaccine type that is immediately available. (See Chapter 12 for details on pediatric recommendations.) An IIV administered by ID injection is approved for use in persons 18-64 years. The elderly >65 years old may have a decreased response to IIV; a high-dose IIV formulated for this age group should be used.

Despite the recommendation for universal immunization against viral influenza, flu vaccine coverage rates in the general population remain suboptimal. Flu vaccine should be recommended to all international travelers because prolonged air travel, fatigue, and exposure to crowds in various closed environments may predispose them to air-borne infections. The CDC identified a particular risk for viral influenza infections among travelers during the summer sailing season of Alaska cruise ship tours. The risk is thought to be associated with exposure of susceptible travelers to influenza-infected persons among the other travelers and tourist industry staff, particularly those from the Southern Hemisphere where the seasonal climate patterns are opposite to those in the Northern Hemisphere.

If flu vaccine is unavailable for travelers during their travel season, the inclusion in the traveler's medical kit of one of the antiviral drugs active against influenza virus, either oseltamivir (Tamiflu®, chemoprophylaxis or early treatment) or zanamivir (Relenza®, early treatment), should be discussed with the travelers who will be at potential risk.

Pneumococcal Vaccine

Immunization of adults ≥65 years of age against invasive pneumococcal disease is routinely recommended by the ACIP. The current recommendation is for the 13-valent pneumococcal conjugate vaccine (PCV13) to be given first in a series, with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) administered 6-12 months after. However, since this recommendation is relatively recent (2014), the following regimens are also acceptable: if PPSV23 was received first, administer PCV13 after an interval of at least 1 year or more; if the first dose of PPSV23 was received prior to 65 years of age, give the first dose of PCV13 at ≥65 years of age (at least 1 year after the first PPSV23), and then give a second dose of PPSV23 at 6-12 months after the PCV13.

REQUIRED TRAVEL IMMUNIZATIONS

The immunizations for international travel identified as "required" usually refer to those covered by the WHO International Health Regulations (IHR). Historically, yellow fever, cholera, and smallpox vaccines were subject to WHO regulations. However, the requirements for cholera and smallpox vaccines for international travel were dropped several decades ago. At the present time, yellow fever vaccine is the only vaccine that may be required for

entry into member countries, according to current WHO regulations. In addition, Saudi Arabia requires evidence of immunization with meningococcal vaccine to be submitted with visa applications of inbound travelers for travel during the time of the annual Hajj.

In response to the international spread of wild polio virus (WPV) from certain countries in Africa, the WHO declared a public health emergency of international concern in May 2014 and issued temporary polio vaccine recommendations under the authority of IHR (2005) for long-term travelers and residents departing from countries with WPV in circulation. Proof of polio vaccine received between 4 weeks and 12 months before the date of departure from the polio-affected country might be *required* of such travelers. Updates on country vaccine requirements are posted on the WHO website (www.who.int) and the CDC Travelers' Health website (www.cdc.gov/travel).

The international traveler should have all current immunizations recorded in the "International Certificate of Vaccination or Prophylaxis," a document in folded booklet form printed on yellow paper and approved by the WHO. The booklet has a special page for official validation of the yellow fever vaccine and is recognized as an official document all over the world. The WHO officially removed cholera vaccination from the IHR in 1973. If given, the cholera vaccination can be recorded in the space provided for "Other Vaccinations." *Likewise, a traveler's receipt of meningococcal ACWY vaccine and/or polio vaccine should also be documented in the International Certificate of Vaccination or Prophylaxis.*

Yellow Fever Vaccine

Yellow fever is a viral infection transmitted by *Aedes aegypti* mosquitoes in equatorial South America and Africa. The endemic zones are shown in **Figure 5.1**. Immunization is required for entry into some countries within the endemic zones or may be recommended to travelers going to rural tropical areas within the endemic zones or to both rural and urban areas during yellow fever outbreaks.

Yellow Fever (YF) Vaccine

YF vaccine is a live attenuated viral vaccine prepared from the 17D strain of YF virus (YF Vax™, Sanofi). The WHO controls the production of YF vaccine, sets requirements, and approves certain laboratories for its manufacture. The vaccine leads to seroconversion rates of 95% or higher, a protection rate of over 99% in immunocompetent recipients, and a duration of immunity after one dose, which appears to be lifelong. The YF vaccine is given as a single dose for primary immunization, and the recommended booster interval is 10 years (**Table 5.3**).

YF Vaccine Booster Doses

In 2015, the ACIP recommended that routine booster doses of YF vaccine are not necessary for travelers to endemic areas because of studies showing that the primary YF vaccination elicits sustained immunity and probable lifelong protection in healthy recipients. The ACIP recommendation is in agreement with an earlier 2013 recommendation from the WHO Strategic Advisory Group of Experts on Immunization. However, since the 10-year booster dose requirement is scheduled to be removed from WHO IHR by June 2016, in the interim some travelers may find that a YF vaccine booster is still necessary for entry into certain countries. Travelers and travel health advisors can find updated country-by-country YF vaccine requirements at the WHO and CDC websites.

YF Vaccine Precautions and Contraindications

The vaccine virus is cultured in eggs and is not recommended for persons with a history of severe allergy (anaphylaxis) to eggs. A review of reports submitted to the US Vaccine Adverse Events Reporting System from 1990 through 1997 found a rate of 1/131,000 for anaphylaxis after immunization with yellow fever vaccine. The package insert contains instructions for skin-testing persons with an uncertain history of allergy to eggs. YF vaccine is contraindicated in infants <6 months of age because of the significant but rare risk of vaccine-associated neurotropic disease in such young infants after immunization (estimated

rate 1 per 8 million doses). If possible, YF immunization should be delayed until the infant is ≥9 months of age (Chapter 12). YF vaccine is generally not recommended during pregnancy except when travel to a highly endemic area cannot be avoided or postponed by the pregnant traveler, and the risk of the actual disease is thought to be greater than the theoretical risk of adverse effects from the vaccine.

Additional contraindications to receiving the YF vaccine include immune suppression caused by underlying disease (e.g., malignancy, HIV infection, congenital immune deficiency) or by medical therapy (e.g., treatment with daily corticosteroids, cancer chemotherapy, radiation therapy, organ transplant therapy). Most travel experts would consider administering YF vaccine to travelers at risk if the CD4 cell count is >400 μL in an HIV-infected person or if the corticosteroid dosage is <20 mg prednisone/day.

Fig. 5.1 (A, B) Yellow fever endemic zones. (From: Centers for Disease Control 2008. Health Information for International Travel, 2007–2008. US Government Printing Office, Washington, DC. Available at <http://wwwn.cdc.gov/travel/yellowBookCh4-YellowFever.aspx#668>.)

Fig. 5.1, cont'd

YF Vaccine-Associated Viscerotropic Disease (YEL-AVD)

YEL-AVD is likely related to the transient viremia that normally occurs after receipt of this live attenuated virus vaccine. In cases reported to the WHO and CDC, YEL-AVD occurred 2-5 days after receiving YF vaccine and is a febrile illness leading to multiple organ system failure as manifested by fever, myalgia, arthralgia, hepatitis, thrombocytopenia, disseminated intravascular coagulation, lymphopenia, rhabdomyolysis, hypotension, and oliguria. Review of the reported cases shows that the risk of YEL-AVD is very rare (13 cases reported per >100 million vaccine doses) and that the risk involved *first-time* vaccine recipients. The risk increases with age, with a rate of 3.5/100,000 vaccine recipients reported for persons 65-74 years of age, and an almost three-fold increase in rate to 9.1/100,000 among vaccine recipients aged >75 years old. Thus, careful review of the proposed itinerary with regard to risks

TABLE 5.3 Dosage Schedules for Adult Travel Immunizations

Vaccine	Primary Series	Booster Interval
Cholera, oral inactivated whole cell recombinant B subunit (WC/rBS) (Dukoral)	Two doses[a] PO 10-14 days apart according to package directions	Booster for continued risk of exposure to cholera at approximately 6-month intervals, more frequently when the vaccine is used for protection against traveler's diarrhea due to ETEC heat-labile toxin.
Hepatitis A (Havrix)	Two doses[a] IM at 0 and 6-12 months	Protective immunity following receipt of first dose; second dose promotes long-lasting immunity.
Hepatitis A (VAQTA)	Two doses[a] IM at 0 and 6-18 months	Protective immunity following receipt of first dose; second dose promotes long-lasting immunity.
Hepatitis B (Engerix B) (standard schedule)	Three doses[a] IM at 0, 1, and 6 months	Need for booster not determined.
Hepatitis B (Recombivax) (standard schedule)	Three doses[a] IM at 0, 1, and 6 months	Need for booster not determined.
Hepatitis B (Engerix B) (accelerated schedule)	Three doses[a] IM at 0, 1, and 2 months	A 4th dose is recommended 12 months after the first dose to assure long-lasting immunity.
Hepatitis A/B (Twinrix) (standard schedule)	Three doses[a] IM at 0, 1, and 6 months	Need for booster not determined; persistence of anti-HAV and anti-HBsAg antibodies in adults for at least 10 years after primary immunization.
Hepatitis A/B (Twinrix) (accelerated schedule)	Three doses[a] IM on days 0, 7, and 21-30	A 4th dose is recommended 12 months after the first dose to assure long-lasting immunity.
Immune globulin (IG) (hepatitis A protection)	One dose[a] IM in gluteus muscle (2-mL dose for 3 months' protection; 5-mL divided dose for 5 months' protection)	Boost at 3- to 5-month intervals depending on initial dose received for continued risk of exposure.
Japanese encephalitis-purified inactivated virus (Ixiaro)	Two doses IM on days 0 and 28	Booster dose may be given 12 months after the first dose for continued risk of exposure.
Meningococcal (A/C/Y/W-135) diphtheria toxin conjugate vaccine (MCV4/MenACWY-D) (Menactra)	One dose IM	Not determined; estimated protective immunity 7 years or more.
Meningococcal (A/C/Y/W-135) CRM197 conjugate vaccine (MenACWY-CRM) (Menveo)	One dose IM	Not determined.
Meningococcus (A/C/Y/W-135) polysaccharide vaccine (MPSV4) (Menimmune)	One dose[a] SC	Estimated protective immunity 3-5 years; may boost with MenACWY-D or MenACWY-CRM vaccine.
Meningococcal B-4C (Bexsero)	Two doses at 1 month apart	Not determined.
Meningococcal B-FHbp (TruMemba)	Three doses at 0, 2, and 6 months	Not determined.

TABLE 5.3 Dosage Schedules for Adult Travel Immunizations—cont'd

Vaccine	Primary Series	Booster Interval
Rabies (HDCV) (Imovax) or Rabies (PCEC) (RabAvert)	Three doses[a] (1 mL IM in the deltoid area) on days 0, 7, and 21 or 28	Boost after 2 years for continued risk of exposure, or test serum for antibody level.
Tick-borne encephalitis (Encepur) (standard or conventional schedule)	Three doses SC on days 0, 28, and 300)	Boost 3 years after the last dose.
Tick-borne encephalitis (Encepur) (rapid schedule)	Three doses[a] SC on days 0, 7, 21	First booster dose at 15 months after the first vaccine dose; 2nd booster at 36 months after the first booster.
Tick-borne encephalitis (FSME-Immuno) (standard or conventional schedule)	Three doses[a] SC at months 0, 1-3, and 9-12 months after dose two	Boost 3 years after the last dose.
Tick-borne encephalitis (FSME-Immuno) (rapid schedule)	Three doses[a] SC on 0, 7, and 21 days	First booster dose at 15 months after the first vaccine dose; second booster at 36 months after the first booster.
Tuberculosis (BCG vaccine)[b]	One dose[a] percutaneously with multiple-puncture disk	Re-vaccinate after 2-3 months those who remain tuberculin negative to 5 TU skin test.
Typhoid, Vi capsular polysaccharide (Typhim Vi)	One dose[a] SC	Boost after 2 years for continued risk of exposure.
Typhoid, oral (Vivotif) (for persons >6 years of age)	One capsule[a] PO every 2 days for four doses	5 years; use full four-dose series for booster.
Yellow fever[b]	One dose[a] SC	10 years[c].

[a]See manufacturer's package insert for recommendations on dosage.
[b]Caution: may be contraindicated in patients with any of the following conditions: pregnancy, leukemia, lymphoma, generalized malignancy, immunosuppression from HIV infection or treatment with corticosteroids, alkylating drugs, antimetabolites, or radiation therapy.
[c]Recommendation for a booster dose is undergoing revision at the time of writing. Check the CDC Travelers' Health website for updates (http://www.cdc.gov/travel).
BCG, Bacillus Calmette-Guérin; *ETEC,* enterotoxic *Escherichia coli*; *HAV,* hepatitis A virus; *HBsAg,* Hepatitis B surface antigen; *IM,* intramuscularly; *PO,* by mouth; *SC,* subcutaneously.
Adapted from Jong, E.C., 1993. Immunizations for international travelers. In: The Travel Medicine Advisor. American Health Consultants, Atlanta, GA.

and benefits of YF vaccine is particularly important in advising senior travelers. However, the protection offered by the vaccine probably outweighs the risks in those who are traveling to regions endemic for yellow fever, regardless of age.

YF Vaccine Letter of Waiver

If a person for whom the vaccine is contraindicated must travel to a country where yellow fever vaccine is required for entry, a signed statement on letterhead stationery that states that the yellow fever vaccine could not be administered to the traveler because of medical contraindications will be accepted in lieu of the vaccination statement, according to WHO regulations. Alternately, the medical provider can complete the "Medical Contraindication to Vaccination" section of the International Certificate of Vaccination or Prophylaxis.

Meningococcal ACWY Vaccines

Due to outbreaks of meningococcal disease among Hajj pilgrims with secondary spread of meningococcal infections to family and friends after the pilgrims returned home, in 2003 Saudi Arabia implemented a *requirement* for meningococcal vaccine for all persons seeking

to travel in Saudi Arabia during the annual Hajj. Either the quadrivalent meningococcal vaccine containing capsular polysaccharides from *Neisseria meningitidis* serogroups A, C, W, Y (MCPSV4) or one of the quadrivalent meningococcal conjugate vaccines containing the same capsular polysaccharides conjugated to a protein carrier (MCV4/MenACWY-D or MenACWY-CRM) will meet the requirement. In some countries, bivalent meningococcal polysaccharide or conjugate vaccines eliciting immunity against serogroups A and C may be commonly available; however, the A/C vaccine does not protect travelers in outbreaks involving serogroup Y or W-135 disease, such as has been the case in some of the Hajj outbreaks (**Fig. 5.2**). Meningococcal vaccine is also *recommended* for travelers going to live and work in certain areas of Africa (sub-Saharan), South America (Brazil), or other parts of the world where meningococcal disease is hyperendemic or epidemic among the residents.

Fig. 5.2 Areas with frequent epidemics of meningococcal meningitis. (From: Centers for Disease Control 2008. Health Information for International Travel, 2007–2008. US Government Printing Office, Washington, DC. Available at <http://wwwn.cdc.gov/travel/yellowBookCh4-Menin.aspx#651>.)

The ACIP recommends *routine* immunization against meningococcal disease with ACWY quadrivalent vaccine for young people 11-18 years old and for incoming college freshmen who will live in large residence halls on campus (some institutions *require* immunization for matriculation because of the increased risk of meningococcal transmission in such student populations). Meningococcal vaccination is also recommended for persons at increased risk of disease, such as microbiologists who may be routinely exposed to strains of *N. meningitidis*, military recruits, persons with complement component deficiencies, and persons with anatomic or functional asplenia. Meningococcal B vaccine is discussed under "Recommended Travel Vaccines" below.

The meningococcal conjugate vaccines promote eradication of the nasopharyngeal carrier state due to the high levels of mucosal antibodies elicited, and there is a strong antibody response to subsequent booster doses of the vaccine. Use of a meningococcal conjugate vaccine is preferred for those persons who need imminent as well as possible future protection against meningococcal disease because immunity can be effectively boosted by additional conjugate vaccine doses, although the meningococcal polysaccharide vaccine is sufficiently protective for use in travelers and others anticipating limited exposure to meningococcal disease.

The duration of immunity following immunization with a conjugate vaccine is estimated to be 7 years, although no formal booster interval has been recommended at this time. Persons who received the MPSV4 vaccine in the past and who remain at risk of exposure to meningococcal disease may be boosted with a conjugate vaccine.

Meningococcal ACWY-Diphtheria Toxin Protein Conjugate (MenACWY-D) Vaccine

MenACWY-D vaccine (Menactra®, Sanofi) is a quadrivalent vaccine derived from serogroups A/C/W-135/Y capsular polysaccharides conjugated to diphtheria toxin protein, which enables enhanced immunogenicity through activation of a strong T-cell immune response in vaccine recipients. The vaccine is licensed for use among persons 9 months through 55 years of age and given as a single dose administered by IM injection.

Meningococcal ACWY-CRM Conjugate (MenACWY-CRM) Vaccine

MenACWY-CRM vaccine (Menveo®, Novartis) is a quadrivalent vaccine derived from serogroups A/C/W-135/Y capsular polysaccharides conjugated to diphtheria toxin mutant CRM197. The vaccine is licensed for use among persons 2 months through 55 years of age and given as a single dose administered by IM injection.

Meningococcal Polysaccharide A/C/Y/W-135 Vaccine (MPSV4)

MPSV4 vaccine (Menimmune®, Sanofi) is a quadrivalent capsular polysaccharide vaccine inducing immunity against serogroups A/C/Y/W-135. A single dose administered by subcutaneous (SC) injection provides immunity for approximately 3-5 years among healthy recipients, although vaccine efficacy is variable in young children. A second dose of vaccine after 2 or 3 years is recommended for children living in high-risk areas who received the first vaccine dose at <4 years of age.

Polio Vaccine

Polio vaccine is given as part of the routine immunization series to infants and children in the United States. A four-dose series of inactivated poliovirus vaccine (IPV) administered by IM or SC injection is given at 2, 4, and 6-18 months of age, and at 4-6 years old (Chapter 12). IPV (Ipol®, Sanofi) is the only polio vaccine used in the United States since 2000, when a policy decision to discontinue the use of oral polio vaccine was made in order to avoid the rare occurrence of vaccine-associated paralytic poliomyelitis from the attenuated live virus vaccine. Oral polio vaccine is still in use in countries outside the United States.

A single lifetime IPV booster dose is recommended for adult travelers 18 years and older who are traveling to countries with recognized circulation of WPV or to countries that border countries that have areas with WPV in circulation. WPV circulation has been

reported in Afghanistan, Pakistan, Middle Eastern countries, Egypt, Nigeria, and other countries located in a belt across sub-Saharan Africa. Outbound long-term (≥4 weeks) travelers and residents of WPV-affected countries may be *required* to show proof of polio vaccination between 4 weeks and 12 months before departure under WHO IHR in order to prevent importation of polio into polio-free countries by infected travelers. The CDC regularly updates its website regarding which countries have ongoing transmission of polio and which countries may require proof of polio vaccination from exiting travelers.

Cholera Vaccine

There is no WHO regulation requiring cholera vaccine for entry into any country. Currently available cholera vaccines are discussed under "Recommended Travel Vaccines" below.

Smallpox Vaccine

The smallpox vaccine (vaccinia virus vaccine) is no longer available commercially. Limited supplies are released on a case-by-case basis from the CDC based on individual review. Research scientists and healthcare workers who work with the smallpox virus and closely related viruses are candidates for immunization. The last case of smallpox acquired through natural transmission was reported in 1977, and the requirement for smallpox vaccine for international travel was removed from the WHO regulations in 1982.

RECOMMENDED TRAVEL VACCINES

Recommended travel vaccines are those that are given to travelers based on the anticipated level of risk of exposure. Vaccines in this category may include hepatitis A, immune globulin (for hepatitis A), hepatitis B, typhoid fever, cholera, meningococcal disease, rabies, Japanese encephalitis, and tick-borne encephalitis vaccines. Immunization against tuberculosis or a tuberculosis skin test may also be recommended for some travelers. Brief descriptions of each vaccine are given below. Table 5.3 lists dosage schedules for adult travel immunizations.

Hepatitis A Vaccine

Hepatitis A is a serious viral infection with an oral-fecal transmission pattern similar to polio, cholera, typhoid, hepatitis E, and traveler's diarrhea. Hepatitis A infections are reported to be the leading cause of vaccine-preventable illness occurring among non-immune international travelers, where the incidence rate can be as high as 20 cases/1000 travelers per month among travelers during rural or adventure travel in developing countries. A lower rate, 3-6 cases/1000 travelers per month, has been observed among travelers going to tourist areas or hotels and resorts in developing countries.

The hepatitis A case fatality rate associated with acute infections is <0.1% in childhood from <1 to 14 years of age. There is an age-related rise in the disease mortality rate: 0.4% from 15 to 39 years of age, 1.1% in persons >40 years of age, and 2.7% in persons >50 years of age. Although up to 60% of adults >40 years of age from industrialized countries may have immunity to hepatitis A through clinical or subclinical infection, most travelers <40 years old are susceptible. If time allows, a serum test for hepatitis A antibody could be performed in people who are of foreign birth, resided overseas, travel frequently in non-industrialized countries, have a history of a previous illness with jaundice, or were born before 1945; unnecessary immunization may be avoided if a person has protective antibodies from hepatitis A infection in the past.

Hepatitis A Virus (HAV) Vaccine

Several safe and highly efficacious inactivated HAV vaccines have become available commercially since the 1994 release of Havrix® (GlaxoSmithKline). Havrix is an inactivated HAV vaccine derived from the HM-175 viral strain and given by injection. The others include VAQTA® (Merck), an inactivated parenteral HAV vaccine derived from the CR-326F strain; Avaxim® (Sanofi), an inactivated parenteral HAV vaccine derived from the

GBM viral strain; and Epaxal® (Crucell), an inactivated parenteral virosomal HAV vaccine derived from the RG-SB viral strain. Havrix and VAQTA are available worldwide. The other inactivated HAV vaccines are distributed mostly in Western Europe, and a live-attenuated hepatitis A vaccine Biovac-A (Pukang) approved by the WHO is available in Asia and South America. The immunization schedules for the inactivated HAV vaccines listed above consist of a single primary dose given by IM injection into the deltoid muscle, resulting in protective antibody titers within 2-4 weeks (98-100% seropositivity rate). The first vaccine dose is followed by a booster dose 6-12 months later, producing levels of antibody predicted to give protection for ≥10 years. After the primary series of two doses, additional boosters are not currently advised.

Delayed Hepatitis A Vaccine Booster Dose

In some cases, travelers return for their booster dose of inactivated hepatitis A vaccine later than the recommended time of 6-12 months after the primary dose. Based on the results of clinical studies, delaying the booster dose up to 66 months after primary vaccination did not seem to influence the anamnestic immune response to the booster dose. These findings suggest that a booster dose given later than the recommended 6-12 months will still be highly effective.

Hepatitis A Vaccine Interchangeability

Using one of the inactivated hepatitis A vaccines for the primary dose and then using a hepatitis A vaccine made by a different manufacturer for the booster dose is not a recommended or officially approved practice. However, it appears from the preliminary results of clinical studies that Havrix and VAQTA may be used interchangeably without significant loss of protective antibody levels elicited (data from Merck Vaccine Division).

Immune Globulin (IG)

Immune globulin (purified human immune globulin) may be used to provide temporary protection against hepatitis A virus infection through the passive transfer of pre-formed antibodies against hepatitis A present in the IG (at least 100 IU/mL) and is given to travelers who are unable to receive hepatitis A vaccine. Duration of protection is dependent on dose, with a dose of 0.06 mL/kg (10 mg IgG/kg) administered as a deep IM injection into the gluteus maximus muscle providing up to 3-4 months' protection (**Table 5.3**).

Concurrent Administration of Hepatitis A Vaccine with Immune Globulin

Updated recommendations no longer call for concurrent administration of IG when hepatitis A vaccine is given <2 weeks before trip departure. The vaccine induces a vigorous antibody response in normal hosts that may not totally protect the recipient against infection but will most likely protect the recipient from developing severe disease, in the case the vaccine recipient is exposed to hepatitis A virus before the vaccine-induced antibodies are at a level (>20 mIU/mL) sufficient to prevent infection. Using this rationale, hepatitis A vaccine has been successfully used for post-exposure immunization of susceptible persons during hepatitis A outbreaks.

Hepatitis B Virus (HBV) Vaccine

In many parts of Asia and Africa, up to 15% of the general population may be asymptomatic carriers of hepatitis B virus. Travelers going to Asia and Africa who will live and work among the residents, such as missionaries, healthcare personnel, volunteer relief workers, teachers, students, adventure travelers, and other travelers who might have intimate or sexual contact with the residents, should consider immunization against hepatitis B. In addition, inadvertent exposures to hepatitis B among travelers can occur during medical procedures (emergency or elective) and personal grooming/esthetic activities (shaving, manicures/pedicures, tattoos, piercings, etc.). Although hepatitis B vaccine has been recommended for routine immunization of children in the United States since the early 1990s, many adult travelers at potential risk of infection would not have received hepatitis B vaccine as a routine immunization.

Two recombinant hepatitis B virus vaccines are available: Recombivax HB® (Merck) and Engerix-B® (GlaxoSmithKline). The standard dosage schedule for both vaccines consists of doses administered by IM injection into the deltoid muscle at 0, 1, and 6 months.

Hepatitis B Vaccine Low-Responders or Nonresponders

Among travelers who are at high risk of hepatitis B exposure, such as healthcare workers, volunteer relief workers, missionaries, long-term travelers and expatriates, the possibility of vaccine recipients who do not seroconvert with protective levels of antibody after immunization should be considered. Known risk factors are increasing age (>30 years old), chronic medical conditions, obesity, smoking, male gender, and vaccine administration into the buttock.

Immune protection against Hepatitis B virus is measured by serum levels of antibodies to Hepatitis B surface antigen (Anti-HBs). Anti-HBs testing should be performed 1-6 months after the last dose of vaccine. If there is no seroconversion (≥10 mIU/mL), one additional dose of HBV should be given, and the anti-HBs titer re-checked 4-12 weeks later. If there is still no measurable antibody response, the second series is completed with two additional doses given at monthly intervals after that. Limited data from clinical studies have shown that anti-HBs titers and protection do not always correlate closely, such that even those with low or undetectable titers may still be protected after immunization due to cellular immunity, with an amnestic antibody response following a subsequent exposure to hepatitis B virus or the hepatitis B vaccine years afterward.

Accelerated Hepatitis B Vaccine Schedules

Engerix B vaccine has a Food and Drug Administration (FDA)-approved accelerated dosage schedule of 0, 1, and 2 months. This may allow full immunization of a traveler with limited time before departure; however, a booster dose at 12 months is recommended to assure long-lasting immunity. Another accelerated schedule approved for adolescents and adults calls for the first two doses of either hepatitis B vaccine to be given 1 or 2 months apart, and for the third dose to be given at least 4 months after the first dose; in this case, a booster dose at 12 months is not required.

Hepatitis A/B Combination Vaccine

A hepatitis A/B combination vaccine (Twinrix®, GlaxoSmithKline Biologicals) was released in 2001 in the United States and is approved for use in persons 18 years of age or older. The vaccine contains 720 ELISA (enzyme-linked immunosorbent assay) units of hepatitis A antigen and 20 μg of hepatitis B antigen, and the standard immunization series consists of three doses given at 0, 1, and 6 months. Clinical studies have shown that the combination hepatitis A/B vaccine is highly efficacious and safe, with long-term protection demonstrated up to 10 years after primary immunization. The use of this combination vaccine will be convenient for travelers and other persons who need protection against both diseases, and decreases the total number of vaccine injections required (3 vs. 5). A pediatric formulation of the hepatitis A/B vaccine is not licensed in the United States but is available in other countries.

Accelerated Hepatitis A/B Vaccine Schedule

Hepatitis A/B vaccine (Twinrix) given on 0, 7, and 21-30 days elicits a high level of protective antibody against both hepatitis A and hepatitis B, 1 month following the third dose. A fourth dose at 12 months is recommended to boost the longevity of the immune response to the accelerated schedule. The accelerated hepatitis A/B Twinrix schedule was FDA approved in the United States in 2006. The accelerated hepatitis A/B vaccine schedule should be considered for last-minute travelers at risk whose departure date is 21-30 days from the date of the travel clinic appointment. If the departure date is <21 days from the clinic encounter, the traveler should be immunized with one dose of monovalent hepatitis A vaccine, concurrently with monovalent hepatitis B vaccine on a standard schedule, or consideration should be given to an accelerated hepatitis B vaccine schedule.

Typhoid Vaccine

The incidence of typhoid fever among US travelers is relatively low (58-174 cases per 1 million travelers), but among reported cases in the United States, 62% were acquired during international travel. Mexico, Peru, India, Pakistan, and Chile are countries where the risk of transmission appears particularly high. Sub-Saharan Africa and Southeast Asia are also regarded as areas of increased risk for typhoid fever. The risk of typhoid fever infections to the traveler is further heightened by the multidrug-resistance patterns emerging in *Salmonella typhi* strains around the world to antibiotics commonly used in the treatment of gastrointestinal infections, including the widely used fluoroquinolones.

Avoidance of potentially contaminated food and drink during travel is important, even if the typhoid vaccine is received. The protection against typhoid fever afforded by immunization may be overwhelmed by ingestion of highly contaminated food: protection rates of 43-96% were reported in field trials with the oral live-attenuated typhoid vaccine among residents of endemic areas. However, only limited data are available to predict actual protection rates in people who travel from non-endemic areas to endemic areas for typhoid. There are two typhoid vaccines available in the United States: the oral Ty21A typhoid vaccine and the parenteral Vi capsular polysaccharide typhoid vaccine. Neither typhoid vaccine will give protection against paratyphoid fever, caused by strains of *Salmonella paratyphi*.

Ty21A Oral Typhoid Vaccine

The oral typhoid vaccine (Vivotif®, Crucell) contains a live attenuated strain of *Salmonella typhi* bacteria (Ty21A). The vaccine is in capsule form and is recommended for people 6 years of age and older. A primary (or booster) series consists of four capsules, one taken every other day on an empty stomach over the course of 1 week. The booster interval is 5 years, and another four-capsule regimen is used to renew immunity. A liquid suspension form of this vaccine is available in Europe, and this facilitates administration of the vaccine to children and others who have difficulty in swallowing capsules. Persons who were previously immunized with one of the parenteral typhoid vaccines and who now desire immunization with the oral vaccine should receive the full four-capsule series. Safety of the live oral Ty21a typhoid vaccine in immune-compromised persons has not yet been demonstrated, and this vaccine should not be administered to these persons. The vaccine is not recommended for pregnant women because of lack of data regarding its safety (Category C).

Ty21A Typhoid Vaccine and Concomitant Drugs

Any conditions interfering with multiplication of the vaccine strain bacteria in vivo may result in an insufficient bacterial antigen stimulus to induce a protective response. The live oral typhoid vaccine should not be administered during an acute gastrointestinal illness nor if the individual is receiving treatment with sulfonamides, doxycycline, or other antibiotics. The antimalarial drugs chloroquine and mefloquine may be administered concomitantly with the oral typhoid vaccine without decreasing the immune response rate. However, proguanil, one component of the atovaquone/proguanil (Malarone) fixed-dose combination drug used for prevention and treatment of chloroquine-resistant malaria, does significantly decrease the immune response to oral typhoid vaccine. Therefore, proguanil and atovaquone/proguanil should be administered ≥10 days after the final dose of the vaccine.

Ty21A Oral Typhoid Vaccine and Other Vaccines

Concomitant administration of oral polio vaccine, oral cholera vaccine, or yellow fever vaccine does not appear to suppress the immune response of the oral typhoid vaccine.

Vi Capsular Polysaccharide (ViCPS) Typhoid Vaccine

A highly purified Vi capsular polysaccharide typhoid vaccine (Typhim Vi®, Sanofi) elicits immunity 10 days following receipt of a single primary dose by IM injection. The ViCPS typhoid vaccine is usually very well tolerated, has a low rate of adverse effects, and is safe for use in children >2 years old, pregnant women, and travelers with a compromised

immune system. The protection elicited by the Vi polysaccharide typhoid vaccine is similar to that seen following immunization with the live oral Ty21A typhoid vaccine. The booster interval for the ViCPS typhoid vaccine is 2 years.

ViCPS Typhoid Vaccine Combined with Hepatitis A Vaccine

Typhoid fever and hepatitis A viral infections are both transmitted through oral-fecal contamination of food and beverages, thus protection against both diseases is indicated for many international travelers. Several studies have shown that simultaneous administration of the Vi polysaccharide typhoid vaccine (Typhim Vi™) and hepatitis A vaccine (Havrix or VAQTA) at different injection sites results in no significant increase in adverse side effects nor in impaired efficacy of either vaccine.

Cholera Vaccine

Travelers going to cholera-endemic or cholera-epidemic areas are encouraged to follow food and water precautions as recommended for prevention of all forms of travel-associated diarrhea (see Chapter 8). Travelers going to such areas who have underlying gastric conditions, such as achlorhydria or partial gastric resection, or who take medications that block gastric acid production (e.g., H2 blockers, proton pump inhibitors) may have increased susceptibility to cholera infection and should be considered as priority candidates for cholera immunization. Other prime candidates for cholera vaccine are healthcare workers who plan work in areas of high endemicity for cholera, for example, India or sub-Saharan Africa, or in refugee camps and/or communities during a known outbreak of cholera. There are two oral cholera vaccines (OCV) that are WHO-prequalified for use in areas at risk for cholera. Both are whole-cell killed vaccines of *Vibrio cholerae* O1.

Killed Whole-Cell B Subunit Oral Cholera Vaccine (WC/rBS OCV)

WC/rBS oral cholera vaccine (Dukoral®, Crucell) is approved for use in persons 2 years of age and older. In addition to stimulating immunoprotection against cholera, the vaccine has been shown to offer some protection against traveler's diarrhea due to antibodies elicited against the recombinant cholera B subunit toxin component cross-reacting with the heat-labile toxin secreted by enterotoxic *Escherichia coli* (ETEC) (see Chapter 8). Two doses are taken orally at least 1 week apart (up to 6 weeks), and the vaccine provides protection against cholera for 2 years and short-term (3 months) protection against traveler's diarrhea caused by ETEC. Children 2-6 years old should take 3 doses 1 week apart. Protection starts 1 week after the last dose of the vaccine is taken, with a protective efficacy range of 50-86%. Adverse side effects consist of gastrointestinal symptoms rarely reported. Dukoral is not licensed in the United States but is available in Canada and some countries in Western Europe, South America, and Asia. In Canada Dukoral is available without prescription for prevention of traveler's diarrhea, but a prescription is required for the vaccine to be used for prevention of cholera.

Killed Whole-Cell Bivalent (O1 and O139 Serogroups) Oral Cholera Vaccine (BivWC OCV)

BivWC OCV (Shanchol™, Shantha Biotechnics-Sanofi Company) is not currently available in the United States but has been used in vaccine programs to prevent cholera in endemic areas, mainly in Asia, and BivWC OCV also was used to control disease spread during the cholera outbreak in Haiti in 2010 after the earthquake. The vaccine can be used in persons 1 year of age and up; two doses are given orally 2 weeks apart. Onset of protection is from 7 to 10 days after the second dose, and the vaccine is estimated to provide 65% protection lasting at least 5 years.

Meningococcal Serogroup B Vaccine

Quadrivalent meningococcal vaccines against serogroups A, C, Y, and W-135 are discussed above in "Required Travel Vaccines." At the time of writing, there is no WHO IHR for meningococcal serogroup B (MenB) vaccine, although sporadic and sustained outbreaks of serogroup B disease have been reported throughout the world. The ACIP *recommends* MenB

vaccine for certain high-risk groups, including persons with complement deficiency or functional asplenia (status post-splenectomy, sickle cell anemia), microbiologists with routine exposure to *N. meningitidis* isolates, and persons identified at increased risk because of ongoing serogroup B meningococcal outbreaks in the community. International travelers such as healthcare providers, teachers, students, and missionaries going to live and work in areas with ongoing serogroup B meningococcal outbreaks may also wish to avail themselves of MenB vaccine protection; they need to plan ahead to allow completion of the given vaccine series before departure. There is currently no ACIP recommendation for universal MenB immunization of incoming US college freshman who will live in campus housing; however, in 2015, ACIP did vote to follow the recommendation of ACIP's meningococcal working group, which stated that the serogroup B meningococcal vaccine series "may be administered to adolescents and young adults 16 through 23 years of age," further specifying that 16-18 years is the preferred age for vaccination.

Two meningococcal B (MenB) vaccines are FDA licensed and available in the United States at the time of writing, both approved for use in persons 10-25 years old. Once started, the MenB vaccine series should be completed with the same product.

Meningococcal B-4C Vaccine (MenB-4C)

MenB-4C vaccine (Bexsero, Novartis Vaccines) contains three recombinant proteins: *Neisseria* adhesin A, factor H binding protein (FHbp) fusion protein, and *Neisseria* heparin binding antigen, plus outer membrane protein PorA serosubtype P1.4. It is administered by injection of two doses at least 1 month apart.

Meningococcal B-FHbp Vaccine (MenB-FHbp)

MenB-FHbp vaccine (TruMemba, Wyeth Pharmaceuticals) consists of two purified recombinant FHbp antigens and is licensed to be given as a series of three doses, with the second dose at 2 months and the third dose at 6 months after the first.

Rabies Vaccine

Animal bites, especially dog bites, present a potential rabies hazard to international travelers who travel to rural areas in Central and South America, the Middle East, Africa, and Asia. Pre-exposure rabies immunization is recommended for rural travelers, especially adventure travelers who go to remote areas, and for expatriate workers, missionaries, and their families living in countries where rabies is a recognized risk. Veterinarians, animal handlers, cavers, field biologists, and laboratory workers are also considered at high risk of rabies exposure.

Pre-exposure rabies immunization with the three-dose primary vaccine series simplifies the post-bite medical care of a person following an animal bite. Without pre-exposure immunization, the bitten person needs treatment with both rabies immune globulin (RIG) and a series of four doses of a modern tissue culture-derived vaccine administered as soon as possible after the incident. Both RIG and high-quality rabies vaccine doses may be difficult for the international traveler to access in the areas of greatest rabies risk. More detailed recommendations for post-bite treatment are discussed below.

Pre-Exposure Rabies Vaccines

There are two inactivated rabies virus vaccines available, both derived from viruses grown in tissue culture cells: human diploid cell vaccine (HDCV, Imovax™, Sanofi) and purified chick embryo cell vaccine (PCEC, Rabavert™, Novartis). These vaccine products may be used interchangeably in the pre-exposure rabies immunization: a total of three doses (1.0 mL each) of rabies vaccine are administered by IM injection on days 0, 7, and 21 or 28. Mild local reactions to rabies vaccine are common and consist of erythema, pain, and swelling at the injection site. Mild systemic symptoms including headache, dizziness, nausea, abdominal pain, and myalgias may develop in some recipients. In approximately 5% of people receiving booster doses of HDCV for pre-exposure prophylaxis and in a few receiving post-exposure immunization, a serum sickness-like illness characterized by urticaria, fever, malaise, arthralgias, arthritis, nausea, and vomiting may develop 2-21 days after a vaccine dose is received.

Rabies Vaccine Booster Doses

Whether or not a traveler requires boosters of rabies vaccine depends on that traveler's risk of exposure to rabies. For low-risk itineraries, no booster is recommended. For those with "frequent" risk (e.g., spelunkers, veterinarians, and staff in rabies-epizootic areas) serologic testing is advised every 2 years, with booster vaccination if the antibody titer is below protection levels. For those with "continuous" exposure (e.g., rabies research lab workers), serological testing is advised every 6 months with booster vaccination if the antibody titer is below a protective level.

Rabies Post-Exposure Vaccine and Rabies Immune Globulin (RIG)

Receipt of pre-exposure rabies immunization simplifies the care of a person if a high-risk bite is sustained. In addition to immediate wound care (vigorous cleansing, debridement, loose approximation of skin edges, and antibiotics to prevent wound infection), two additional 1-mL IM doses of rabies vaccine on days 0 and 3 are recommended for optimal protection.

If a person who has not received pre-exposure rabies vaccine is bitten while in a rabies-endemic area, post-exposure care for the bite includes a dose (20 IU/kg) of RIG, with one-half the dose infiltrated at the wound site if possible and the remainder given by IM injection. In addition, four doses (1 mL) of rabies vaccine should be given by IM injection on days 0, 3, 7, and 14. A fifth dose of rabies vaccine on day 28 after the bite injury is recommended for patients with immune compromise.

Human-derived RIG and tissue culture-derived rabies vaccine are difficult to obtain in many rabies-endemic areas. The supply of RIG in developing countries is likely to be derived from horse serum, and administration of horse-derived RIG is accompanied by a significant risk of serum sickness. The rabies vaccines available in developing countries could be Semple-type vaccines, derived from infected brain tissue of laboratory animals. Such preparations have a potential for serious adverse side effects and decreased protective efficacy compared with the modern tissue culture-derived rabies vaccines.

Japanese Encephalitis Virus Vaccine

Japanese encephalitis (JE) is a viral infection primarily transmitted by *Culex* mosquitoes in Asia, Southeast Asia, and the western Pacific (**Fig. 5.3**). Transmission is year round in the tropical and subtropical zones and during the late spring, summer, and early fall in the temperate climate zones. Pigs and some species of aquatic birds are natural reservoirs of the virus, while the mosquito vectors breed extensively in flooded rice fields and irrigation projects. JE virus infections may cause an asymptomatic infection or a nonspecific febrile illness that is not recognized or diagnosed. Residents living in JE transmission areas appear to acquire immunity through natural infections over the years, thus reported cases of symptomatic disease and serious neurologic sequelae are seen most often in children younger than 15 years of age and in the elderly. There is no specific treatment, and care is supportive: up to one-third of diagnosed cases survive with permanent cognitive and neurologic impairments, and approximately one-third of patients die.

JE virus is considered the most common cause of vaccine-preventable encephalitis in Asia. Approximately 68,000 cases are reported annually among residents in the countries and areas at risk. The incidence of JE cases is decreasing in endemic countries and areas where immunization against JE has been incorporated into standard childhood vaccine programs or where targeted community vaccine programs against JE have been implemented. However, factors such as climate change, land use patterns, and human migration within the endemic areas are contributing to the emergence of JE in new geographic areas and among new populations, thus resulting in negligible net change in JE incidence statistics in some countries despite vaccine prevention efforts.

JE is not usually considered a risk for short-term travelers visiting only well-developed urban destinations and resorts within JE endemic areas. However, even in countries with long-standing JE vaccine programs and no reported human infections, the JE virus continues

Fig. 5.3 Geographic distribution of Japanese encephalitis. (From: Centers for Disease Control 2008. Health Information for International Travel, 2007–2008. US Government Printing Office, Washington, DC. Available at <http://wwwn.cdc.gov/travel/yellowBookCh4-Japaneseencephalitis.aspx#638>.)

to be present in the environment and can be detected in sentinel animals and in birds. Thus, JE transmission from natural reservoirs to non-immune humans is an ever-present risk to travelers in countries where JE transmission appears to be "under control" based on numbers of reported cases.

Since JE has been acquired by short-term travelers as well as long-stay travelers, all travelers going on trips of any length to endemic areas during JE transmission season (when biting mosquitoes are present), especially to rural agricultural areas where pig farming is present, should be educated about the risk of JE and the availability of a safe, effective vaccine to prevent the disease. Furthermore, since urban development encroaching on agricultural lands is typical in many parts of Asia and can bring infected mosquitoes into the proximity of susceptible urban dwellers, and backyard piggeries may serve as local JE reservoirs, even travelers planning strictly urban stays in Asia and Southeast Asia should be educated about the risk of JE transmission. Personal protective measures to prevent mosquito bites such as wearing protective clothing, using insect repellents, and sleeping under

permethrin-treated bed nets (see Chapter 1) are also important toward decreasing the traveler's risk of JE infection and other mosquito-borne infections (e.g., malaria, dengue fever).

Japanese Encephalitis Purified Inactivated Virus Vaccine (JE-PIV)

The JE-PIV vaccine Ixiaro™ (Valneva) derived from the SA 14-14-2 JE virus strain cultured in Vero cell tissue cultures was licensed by the FDA in 2009 for use in adults 17 years of age and older, and in 2013 for use in children 2 months through 16 years. Two doses of JE-PIV vaccine administered 28 days apart by IM injection will elicit protective levels of antibodies for up to 12 months after the first vaccine dose. The dose is 0.5 mL for adults and children 3 years of age and up. For children 2 months through 2 years, the vaccine dose is 0.25 mL (one-half the adult dose). A booster dose is recommended 1 year after primary immunization for continued risk of exposure in adults; there are limited data about booster doses in children. Local pain and tenderness at the injection site are the most commonly reported adverse side effects, with up to 10% of adult vaccine recipients reporting headache, myalgia, fatigue, and an influenza-like illness. In children, fever was the most commonly reported systemic symptom following a vaccine dose. Clinical studies suggest that a single dose of JE-PIV may effectively boost protective antibodies in persons who were immunized in the past with the previously available mouse brain-derived JE vaccine. A recently published randomized controlled trial showed that strong short-term immunity could be elicited in healthy adults by administering JE-PIV vaccine on an accelerated regimen with the two-dose primary series administered 1 week apart (off-label at the time of writing).

Tick-Borne Encephalitis Vaccine

Tick-borne encephalitis (TBE) is caused by infection with either of two closely related viruses: Central European encephalitis virus (CEEV) in Europe (Austria, Czechoslovakia, Germany, Hungary, Poland, Switzerland, Northern Yugoslavia) and Russian Spring Summer encephalitis virus (RSSEV) in the Commonwealth of Independent States (the former Soviet Union) during the months of April through August. There is overlap of the areas of transmission in Eastern Europe (**Fig. 5.4**). TBE is transmitted to humans by bites from infected *Ixodes ricinus* ticks usually found in forested areas of endemic regions (**Fig. 5.5**). However, systemic infection after ingestion of unpasteurized dairy products from infected cows, goats, or sheep can also occur.

Disease caused by this infection can lead to serious neurological sequelae or even fatal outcomes. Medical care consists of symptomatic treatment, as there is no specific cure. Immunization against TBE is the primary mode of prevention for populations living in endemic areas and travelers to those areas. The availability of TBE vaccines in mostly endemic areas and the multiple-dose immunization schedule mean that most travelers from North America who anticipate a need for protection against TBE will not be able to obtain pre-travel immunization. Travelers planning outdoor activities (hiking, biking, camping) in areas where TBE is a risk need to rely on personal protection measures to prevent tick bites. Travelers to such areas should be also advised to avoid ingestion of unpasteurized dairy products.

FSME-Immuno TBE Vaccine

Vaccination against TBE is currently not available in the United States. FSME-Immuno TBE vaccine (Immuno, Vienna) is available in Canada and Europe. The vaccine is produced in chick embryo cell cultures, and primary immunization consists of three doses given by SC injection. Another TBE vaccine called Encepur TBE Vaccine is manufactured by Chiron (Behring) and is distributed in European and Asian countries. Clinical studies have shown that the two vaccines are interchangeable and that administration using the rapid schedule of 0, 7, and 21 days with a booster dose of vaccine given at 15 months after the last vaccine dose yields rapid onset of protection and sustained high antibody titers over a 300-day observation period.

Fig. 5.4 **Areas of tick-borne encephalitis (TBE) transmission in Eastern Europe.**

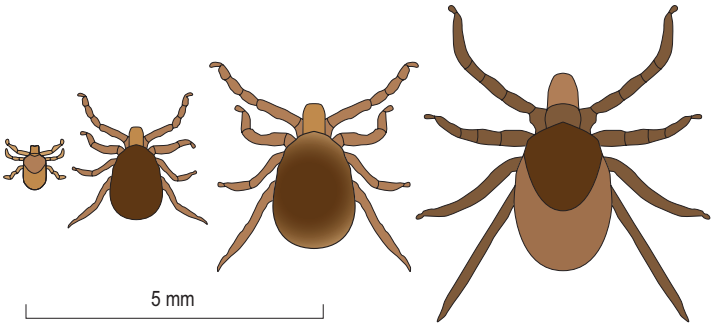

Fig. 5.5 Tick vector (transmitter) of tick-borne encephalitis. *Ixodes ricinus*, from left to right: larva, nymph, adult female, adult male. (Courtesy of Fedor Gassner, Wageningen University.)

Tuberculosis (BCG) Vaccine

People going on short trips for tourism or business to countries where tuberculosis (TB) is much more common among the general population than in the United States are not considered to be at great risk of contracting TB. Travelers who will live among foreign residents or who will work in foreign orphanages, schools, hospitals, or other facilities may be at significant risk of exposure to infection with TB, which is commonly spread from person to person by inhalation of infected respiratory droplets in closed environments. Such travelers should be skin tested with tuberculin purified protein derivative (PPD) and control antigens (such as *Candida* and *Trichophyton*) or an interferon-gamma release assay (IGRA), such as QuantiFERON-TB Gold In-Tube test (QFT-GIT) or SPOT TB test (T-Spot), before and after the trip. Persons who convert to a skin test–positive status or from a negative to a positive IGRA following international travel need further evaluation and are candidates for consideration of prophylactic treatment with isoniazid or other drugs to prevent TB disease.

Occasionally, children in families going abroad for extended residence are requested by the receiving country to provide proof of bacillus Calmette-Guérin (BCG) vaccine receipt to qualify for a visa. A BCG vaccine is commercially available in the United States and is approved by the American Academy of Pediatrics Committee on the Control of Infectious Diseases for use in children going to live in areas where TB is prevalent or where there is a likelihood of exposure to adults with active or recently arrested TB. The BCG vaccine also might be considered appropriate in the case of uninfected (PPD skin test–negative) healthcare workers who are going to work in areas where there is a high endemic prevalence of tuberculosis in the population and who will have limited access to medical diagnosis and treatment.

Bacillus Calmette-Guérin Vaccine (BCG)

BCG vaccine is widely used all over the world for childhood immunization against TB, although this has never been a public health policy in the United States. There is no consensus on the protective efficacy of BCG vaccines, and estimates of protection have varied from study to study. Epidemiologic data suggest that the vaccine may be more useful in protecting children from disseminated extrapulmonary complications of tuberculosis, including TB meningitis, than in protecting adults from primary pulmonary infection.

Persons immunized with BCG vaccine become PPD skin test–positive for several years afterward, regardless of the degree of protection conferred by the vaccine. As a general rule, the longer the duration since BCG administration and the larger the PPD skin reaction, the more likely it is that the PPD skin reaction represents a true positive. In those who have

received BCG vaccine, the IGRA is preferred over a PPD for diagnosis of latent TB infection.

Like other live attenuated vaccines, BCG vaccine is contraindicated in people with immunosuppression caused by congenital conditions, chemotherapy, radiation therapy, HIV infection, or another condition resulting in impaired immune responses. Pregnancy also is considered a relative contraindication.

CONCLUSION

Despite the availability of safe, highly efficacious vaccines against many of the diseases that are health risks to international travelers, there are several factors that influence travelers' acceptance of immunization recommendations. Practical concerns include the time available before trip departure, past history of allergies to or intolerance of specific vaccines, avoidance of multiple vaccine doses administered by injection, and the traveler's overall budget for pre-travel health preparations. Other factors influencing the traveler's choice of travel immunizations include his or her cultural perceptions of the health risks presented by a given itinerary, whether or not adventure travel away from normal tourist routes is planned, and anticipated access to organized medical care and/or medical evacuation in case of medical illness while traveling abroad.

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The rapid vaccination schedule makes it feasible for some travelers going to TBE transmission areas to obtain protection before exposure to this vaccine-preventable disease.

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This report shows that despite continuing efforts to improve vaccine awareness among US healthcare providers, pharmacists, and the public, adult vaccination coverage remains low for most routinely recommended vaccines. This highlights the importance of using the travel clinic visit as an opportunity to review the traveler's status with regard to routine immunizations and to advise on the required and recommended travel vaccines.

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Gershman, M.D., Staples, J.E., 2013. World Health Organization reports that 10-year yellow fever vaccine booster is not necessary. CID: 57 (October 1) Available at <http://cid.oxfordjournals.org> (accessed February 1, 2014).

Report on a new recommendation from the WHO Strategic Advisory Group of Experts that a single dose of yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection.

Jellinek, T., Burchard, G.D., Dieckmann, S., et al., 2015. Short-term immunogenicity and safety of an accelerated pre-exposure prophylaxis regimen with Japanese encephalitis vaccine in combination with a rabies vaccine: a phase III, multicenter, observer-blind study. J. Travel Med. 22, 225–231.

Clinical trial demonstrating that the immunogenicity of an accelerated 1-week JE vaccine regimen was non-inferior to that of the standard JE vaccine regimen and had no impact on concomitant rabies vaccination. This accelerated regimen would be useful for travelers departing for JE-endemic areas on short notice but is not licensed at the time of writing.

World Health Organization, 2010. Cholera vaccines WHO position paper. Wkly Epidemiol Rec. No13 85, 117–128. Available at <http://www.who.int/wer/2010/wer8513.pdf> (accessed July 14, 2015).

World Health Organization, 2014. Use of oral cholera vaccine in humanitarian emergencies. Available at <http://www.who.int/cholera/vaccines/OCV_in_humanitarian_emergencies-_15Jan2014_pdf> (accessed July 14, 2015).

These two documents from the WHO provide detailed information on cholera vaccines, manufacturers, supplies, and use in cholera outbreaks and provide essential information for relief workers, disaster response teams, and program planners involved in cholera outbreak areas.