Immunization for Pediatric International Travelers

Appropriate immunization for pediatric international travelers is important to protect against vaccine-preventable diseases and to avoid needing medical treatment in a country where the level of care may be insufficient. The destination within a country and the nature and duration of the stay are important factors in determining pediatric immunization needs. Two excellent sources of country-specific information are the Centers for Disease Control and Prevention’s book, *Health Information for International Travel*, and the CDC’s Travel Health website, which provide updated international immunization information and disease patterns. This article details the administration of important vaccines relevant to international travel.

**HEPATITIS A VACCINES**

Hepatitis A virus exists worldwide and is one of the most prevalent vaccine-preventable diseases for travelers to consider both before and during travel. It can be acquired through exposure to contaminated water, ice, or shellfish harvested from sewage-contaminated water, or from fruits, vegetables, or other foods that are eaten raw and that were contaminated during harvesting or subsequent handling by an infected food handler.

Stools from a hepatitis A virus-infected person are most infectious from approximately 14 to 21 days before sickness is apparent to approximately 8 days after the onset of jaundice. Children can shed hepatitis A for up to 10 days after the onset of clinical illness. Hepatitis A in young children is usually asymptomatic; it is rarely fatal in children and young adults.

Children traveling to regions with high- or intermediate-incidence rates of hepatitis A such as Central and South America, Africa, and most of Asia and Eastern Europe, should be vaccinated before departure. The risk of contracting hepatitis A for those traveling to certain areas of the Caribbean is unknown, although vaccination should be considered if travel is anticipated to areas with inadequate sanitation. The US Advisory Committee on Immunization Practices (ACIP) recommends routine hepatitis-A immunization to all children between the ages of 12 and 23 months. Unvaccinated children between 2 and 18 years of age can receive catch-up vaccination. Some experts recommend that hepatitis-A vaccine can be considered in children younger than 12 months of age, when the risk of exposure to the pathogen is high.

Two monovalent hepatitis A vaccines, Havrix (GlaxoSmithKline) and VaQta (Merck), are currently licensed in the US for patients 12 months of age and older. The primary series consists of two doses given intramuscularly at least 6 months apart. Protective antibody occurs in virtually 100% of patients after the second dose for both vaccines. After completion of the primary series, anti-hepatitis A antibodies probably persist for 25 years or more; booster doses are not currently recommended. Although completion of the immunization regimen with the same product is preferable, immunization with either product is acceptable. Given the relatively long incubation period of hepatitis A (average 2 to 4 weeks), the vaccine can be administered up to the day of departure and still protect travelers, although it is best not to delay administration.

**EDUCATIONAL OBJECTIVES**

1. Describe the sources of information for country-specific, travel-related vaccination requirements.
2. Discuss the importance of the International Certificate of Vaccination or Prophylaxis.
3. Discuss the epidemiology of and vaccination against important travel-related infectious diseases.

Chokechai Rongkavilit, MD

Chokechai Rongkavilit, MD, is Associate Professor, Department of Pediatrics, Children’s Hospital of Michigan, Wayne State University School of Medicine.

Address correspondence to: Chokechai Rongkavilit, MD, 3901 Beaubien Blvd., Detroit, MI 48201; fax: 313-993-8846; email: crongkav@dmc.org.

Dr. Rongkavilit has disclosed no relevant financial relationships.

doi: 10.3928/00904481-20110615-06
The use of immune globulin (IG) may be considered for travelers who are younger than 12 months of age, are allergic to a vaccine component, or are otherwise not able to receive vaccine. Otherwise, it is considered obsolete for the purposes of travel prophylaxis. Pre-immunization testing for anti-hepatitis A antibodies generally is not recommended for children. Postimmunization testing for anti-hepatitis A antibodies is not indicated because of the high seroconversion rates in adults and children.

**JAPANESE ENCEPHALITIS VACCINE**

Japanese encephalitis (JE), a significant public health problem in South Asia, Southeast Asia, East Asia, and the Pacific, can cause irreversible neurologic damage. The JE virus is mainly transmitted by the mosquito *Culex tritaeniorhynchus*, which prefers to breed in irrigated rice paddies. Wading water birds (eg, herons and egrets) serve as virus reservoirs, but pigs, horses and humans are regularly infected. In temperate zones, such as the northern part of Asia and northern India, large epidemics occur in the summer months; in tropical areas of Asia, cases occur more sporadically and peaks are usually during the rainy season.

An inactivated mouse brain-derived JE vaccine (JE-MB) has been licensed since 1992 for use in those aged 1 year or older who are traveling to JE-endemic countries. The recommended series for JE-MB is three doses administered subcutaneously on days 0, 7, and 30. An abbreviated schedule (days 0, 7, and 14) can be used when the longer schedule is impractical. Although JE-MB is the only JE vaccine licensed in the US for use in children aged 1 to 16 years, it is no longer available in the US. If a child is judged to be at risk for JE while traveling to an endemic area, available options for JE vaccination include:

1. Administer an inactivated Vero cell culture-derived JE vaccine (JE-VC) off-label, because JE-VC is currently approved in the US for patients 18 years of age and older;
2. Enroll the child in the ongoing JE-VC vaccine trial at a clinical trial site listed at: www.cdc.gov/ncidod/dvbid/jencephalitis/resources/UpdtJEVaccChildren_Web_Table1.pdf; or
3. Refer the child to receive the vaccine at an international travelers’ health clinic in Asian countries.9

The vaccine should be offered to pediatric travelers spending a month or longer in endemic areas during the transmission season, especially if travel will include rural areas. The vaccine also should be considered for children spending less than 30 days in areas experiencing epidemic transmission and those whose activities, such as extensive outdoor activities in rural areas, place them at high risk for exposure. In all instances, travelers should be advised to take personal precautions (eg, reduce exposure to mosquitoes and use insect repellent).

Rates of serious allergic reactions (generalized urticaria or angioedema) to JE-MB vaccine are low (1 to 104 per 10,000). No serious hypersensitivity reactions or neurologic adverse events were identified among JE-VC recipients in clinical trials; post-licensure surveillance as well as pediatric studies are ongoing to evaluate the safety of JE-VC in a larger population.

**MENINGOCOCCAL VACCINES**

Meningococcal disease is characterized by sudden onset of fever, intense headache, nausea, vomiting, stiff neck, and a rash with pink macules that becomes petechiae. The case-fatality ratio may approach 50%. Long-term sequelae among survivors includes hearing loss, neurologic disability, or limb loss.10 Up to 10% of populations in endemic countries carry *Neisseria meningitidis* asymptptomatically in the nose and throat.

Five major meningococcal serogroups associated with the disease are A, B, C, Y, and W-135. Meningococci serogroups
B and C are responsible for most disease in the Americas and Europe. Serogroups A and C meningococci account for most meningococcal disease cases in Africa and Asia; serogroup W-135 has been associated with epidemics in Saudi Arabia and Burkina Faso.

In the sub-Saharan African “meningitis belt,” which stretches from Senegal to Ethiopia, outbreaks of serogroup A meningococcal disease occur regularly during the dry season (December through June). In addition, major epidemics occur every 8 to 12 years. Travelers to the meningitis belt during the dry season should be advised to receive meningococcal vaccine, especially if they expect to have prolonged contact with local populations. A serogroup W-135 epidemic has occurred in Saudi Arabia in association with the Hajj pilgrimage. Saudi Arabia requires that visitors have a certificate of vaccination before entering the country.

There are three meningococcal vaccines currently available: a tetravalent meningococcal polysaccharide vaccine (MPV4) and two tetravalent meningococcal polysaccharide-protein conjugate vaccines (MCV4). The latter is preferred because it is efficacious in young children, confers long-term protection, and provides herd immunity by reducing nasopharyngeal carriage and transmission. MCV4 is recommended as routine vaccination for adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years. If the first dose was given at age 13 to 15 years, the booster dose should be given at age 16 to 18 years. If the first dose was given at or after age 16 years, no booster dose is needed.

In addition, the two-dose primary series administered 2 months apart followed by a booster dose every 5 years should be given for those aged 2 to 55 years with persistent complement component deficiency (eg, C5-C9, properdin, factor H, or factor D) and functional or anatomic asplenia. The vaccine is recommended for children 2 years of age and older who are traveling to countries in which meningococcal disease is hyperendemic or epidemic. Children who continue to be at risk for meningococcal infection, despite having been vaccinated with MPV4 3 or more years earlier, are also candidates for revaccination with MCV4. The FDA has not approved either MCV4 or MPV4 for children younger than 2 years of age.

Pre-exposure prophylaxis is recommended for pediatric travelers at increased risk of exposure to rabies. Any of the three cell culture vaccines mentioned can be given intramuscularly on days 0, 7 and 28 (or 21 if time is limited). Prophylaxis might offer partial immunity and protection if post-exposure prophylaxis is delayed, and it can simplify post-exposure management by eliminating the need for RIG and decreasing the number of vaccine doses. Children who receive pre-exposure prophylaxis should have a neutralization antibody test every 6 months to 2 years depending on the risk of exposure. Children who have had rabies exposure but have been immunized are considered immunologically primed against rabies and simply require post-exposure prophylaxis on days 0 and 3.

Prophylaxis after exposure to rabies virus should not await the results of laboratory diagnosis of the animal unless the animal is considered unlikely to be infected with rabies and the test result can be obtained within 48 hours. Prophylaxis can be postponed if the animal can be observed for at least 10 days and rabies is not suspected clinically. Prophylaxis should include prompt and thorough wound cleansing, passive immunization with RIG (20 IU/kg of HRIG or 40 IU/kg of ERIG), with the full dose infiltrated around the wounds and any remaining dose given intramuscularly distant from the vaccination site), and administration of a cell culture rabies vaccine on day 0, 3, 7, and 14. The fifth dose on day 28 is no longer required.

Bite exposure carries more risk for rabies than non-bite exposure, and therefore requires post-exposure prophylaxis. Prophylaxis is not indicated for non-bite exposure unless saliva or other potentially infected animal material is introduced into fresh, open cuts in skin or onto mucous membranes. An unprovoked attack might be more likely than a provoked attack to indicate that the animal is rabid. Bites as a result of feeding or handling a healthy animal should generally be regarded as provoked. In addition, the prophylaxis should be based on the local epidemiology of animal rabies. The neutralizing antibody testing 2 to 4 weeks after completing the post-exposure series should be considered
in immunocompromised hosts. If the antibody response is not adequate, a specialist or public health official should be consulted. Immunosuppressive agents should not be given during post-exposure prophylaxis unless essential.

Although rare, human cases of rabies as a result of airborne transmission of the rabies virus have been reported. This might be clinically important in view of bat cave exposures. Other situations that might qualify for prophylaxis include finding a bat in the same room with a person who might be unaware that a contact occurred. However, prophylaxis is not needed in those situations if the bat is tested negative for rabies. In unusual exposure situations, public health officials should be consulted for post-exposure management.

**TYPHOID FEVER VACCINES**

Most cases of enteric (typhoid or paratyphoid) fever are confined to the Indian subcontinent and Southeast Asia. Pediatric travelers visiting friends and relatives in endemic areas appear to be at increased risk compared to other travelers, as they tend to have less control over their diets, being served untreated water and uncooked foods.

The available vaccines, including the parenteral Vi-capsular polysaccharide vaccine and the live-attenuated oral Ty21a vaccine, are effective only against *S. typhi*. None seem to provide any protection against *S. paratyphi*, particularly *S. paratyphi A*, which is increasing in the Indian subcontinent. The Vi-polysaccharide vaccine is given intramuscularly as a single dose. It is recommended for children 2 years or older and should be given at least 2 weeks before departure. Currently, there are no available vaccines for children younger than 2 years.

The oral vaccine, which is recommended for children aged 6 years or older, should be given as one capsule every other day for four doses. The capsule should be kept in the refrigerator and be taken with cool liquid 1 hour before a meal. Concurrent use of antibiotics or antimalarials may interfere with antibody response.

A contraindication to typhoid vaccination includes a history of a severe local or systemic reaction after a previous dose. The parenteral vaccine should not be given during an acute febrile illness. The oral vaccine should not be given to immunocompromised patients; the parenteral Vi-polysaccharide vaccine may be an alternative. The oral vaccine should not be given during gastrointestinal illness. Antimalarial agents should be avoided for at least 24 hours before the first dose and 7 days after the last dose of oral typhoid vaccine. Proguanil should be delayed until 10 days after the last dose of the oral vaccine. A unique phenomenon of typhoid vaccine immunity is that it can be overcome by a large number of the organisms ingested. Thus, other protective measures, including drinking boiled or bottled water, eating thoroughly cooked food, and peeling fruits must be followed despite vaccination.

**YELLOW FEVER VACCINE**

Yellow fever is a viral hemorrhagic fever that remains endemic in many countries in tropical Africa and South America, principally in the Amazon region and contiguous grasslands. Several species of mosquitoes transmit the virus. Yellow fever has a wide spectrum of illness, from mild nonspecific febrile symptoms to severe multiorgan failure and death.

Children aged 9 months and older who are traveling to or living in areas of tropical Africa and South America where the disease is endemic should be vaccinated. Some countries require that travelers, even if only in transit through these areas, have a valid International Certificate of Vaccination or Prophylaxis (ICVP) completed, signed and validated with the official stamp from a travel clinic designated by the US Health Department. The ICVP is valid from 10 days after vaccination and for the subsequent 10 years. Travelers arriving without a completed ICVP may be quarantined or refused entry unless they submit to onsite vaccination. ICVP is not required by some countries for infants younger than 6 months or younger than 9 months, depending on the country.

Because yellow fever vaccination is a regulated international immunization, such requirements may be enforced strictly for those traveling from Africa or South America to Asia, where yellow fever does not exist but *Aedes* mosquito vectors are present. Some countries in Africa require evidence of vaccination from all entering travelers. Although this vaccine is not recommended for infants younger than 9 months, vaccination for infants 6 to 8 months of age should be considered if exposure to yellow fever is unavoidable. Because of the risk of vaccine-associated encephalitis, infants younger than 6 months of age should not receive yellow fever vaccine. A live-attenuated (17D) vaccine was developed by means of serial passage of the wild-type virus in chicken-embryo tissue. The 17D vaccine induces long-lasting neutralizing antibodies in about 99% of those who are vaccinated.

Yellow fever vaccine is given subcutaneously at the dose of 0.5 mL. The International Health Regulations require revaccination every 10 years; however, yellow fever immunity may persist up to 35 years and probably for life.

Side effects to 17D yellow fever vaccine are usually mild, including headache, myalgia, low-grade fevers, or other minor symptoms for 5 to 10 days. Rare hypersensitivity reactions, characterized by urticaria or wheezing, occur principally among those with a history of egg allergy. If vaccination is essential, an intradermal test dose can be administered under medical supervision for those with a questionable history of egg hypersensitivity. Yellow fever vaccine-associated neurotropic disease among children younger than 6 months of age is the most common serious adverse event, and presents similarly to viral encephalitis.
In 2001, yellow fever vaccine-associated viscerotropic disease was described among vaccine recipients.²⁷,²⁸ It manifests with fever, hypotension, respiratory failure, elevated hepatocellular enzymes, hyperbilirubinemia, lymphocytopenia, thrombocytopenia, and death. Vaccination of nursing mothers should be avoided due to the theoretical risk for transmitting the vaccine virus to the breast-fed infant. Nursing mothers can be vaccinated when travel to endemic areas cannot be avoided.

Infection with yellow fever vaccine virus poses a theoretical risk for encephalitis in patients with symptomatic HIV infection, malignancy, and those whose immunologic responses are suppressed by corticosteroids, chemotherapy, or radiation; these patients should not be vaccinated. If travel to an endemic area is necessary, patients should be instructed in methods for avoiding mosquitoes. In addition, their physician should provide them with vaccination waiver letters. Asymptomatic HIV-infected patients who have laboratory evidence of adequate immune system function and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination. No data exist regarding possible interference between yellow fever vaccine and other vaccines. Since yellow fever vaccine is live, it should be given simultaneously with or at least 1 month apart from other live vaccines. Although chloroquine inhibits replication of yellow fever virus in vitro, it does not adversely affect antibody responses to the vaccine among humans receiving antimalarial prophylaxis.²⁹

CONCLUSION

The serious and sometimes deadly diseases described in this article are often preventable by visiting a physician for proper immunizations. Patients who seek the necessary destination-specific vaccinations before they travel can safeguard themselves and their children against preventable diseases, even in the presence of insufficient local medical care.

REFERENCES