
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

**BOX 8-1. Prophylaxis for Infective Endocarditis According to Cardiac Conditions and Dental Procedures[3]**

**Cardiac Conditions Associated with Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures is Recommended**

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)[a]
  - — Unrepaired cyanotic CHD including palliative shunts and conduits
  - — Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[b]
  - — Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation in which cardiac valvulopathy has developed

**Dental Procedures for which Endocarditis Prophylaxis *is* Recommended for Patients Above**

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
  - — Professional cleaning with gingival probing, biopsies, suture removal, placement of orthodontic bands

**Dental Procedures for which Endocarditis Prophylaxis *is not* Recommended even for Patients Above**

- Routine anesthetic injections through noninfected tissue
- Taking of dental radiographs
- Drilling of carious teeth
- Orthodontic/prosthodontic procedures
  - — placement or removal of appliances
  - — placement of orthodontic brackets
  - — adjustment of orthodontic appliances

[a]Except for conditions listed, antibiotic prophylaxis is no longer recommended for any other form of CHD.
[b]Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

CHAPTER 9

# Protection of Travelers

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Increasing numbers of people travel internationally each year: more than 750 million travelers crossed international borders in 2004.[1] An estimated 4% of these people are children; consequently, more than 30 million children travel internationally each year.[2] Annually up to 8% of travelers to the developing regions of the world are ill enough to seek medical healthcare while abroad or upon returning home.[3,4] Although travel may expose children to certain risks, the benefits are many. Therefore, a careful pretravel evaluation to provide appropriate guidance and preparation is critical to protect pediatric travelers and their families and allow them to enjoy their time abroad.

## PREPARATION FOR TRAVEL

### General Advice

A pretravel evaluation should be performed at least 6 to 10 weeks prior to travel. The entire itinerary for the trip should be reviewed, including destinations, time and duration of travel, types of accommodation, activities, and potential exposure to insects and animals. The evaluation should also review the medical and particularly the immunization history of the child in order to ensure that appropriate advice is given regarding preventive measures, including necessary vaccines. This evaluation can be accomplished by providing a form for the parents to complete and bring to the initial pretravel assessment visit. Particular attention should be given to children of immigrants who are returning to their home countries to visit friends and relatives because these children have been shown to be at increased risk of many infectious diseases and may be less likely to seek pretravel advice.[5,6] There are many excellent resources available that provide pretravel advice for pediatricians. The majority of these resources are accessible online (Box 9-1).

Guidance regarding travel health should be provided regarding safety issues and infectious diseases.[7–9] Motor vehicle crashes are the most common cause of death among travelers; therefore, particular attention must be given to use of seat belts and car seats as recommended according to the age and size of the child. Car seats may not be readily available at the destination and therefore should accompany the family. Other injury concerns for children include drowning, falls from unprotected balconies or windows, and electrical injuries from unprotected outlets. A parent traveling alone with children should have notarized documentation authorizing him or her to travel with the children.

Advice regarding food and water precautions and insect avoidance should be thoroughly reviewed. Skin protection is an important topic and includes both risk of serious sunburn and avoidance of infectious diseases. For sunblock, 30 is the minimum sun protection factor (SPF) recommended for children. Sunblock should be applied 30 minutes before exposure and always before insect repellent is applied where both are needed. Adolescent travelers should be counseled regarding safer sex practices and risks of body piercing and tattooing in less developed countries. Fresh water exposure of any kind should be avoided in areas that are endemic for schistosomiasis or where *Leptospira* organisms may contaminate the water. Exposure to infected stool of animals or humans can result in several types of parasitic infection either directly (e.g., hookworm) or through fecal–oral exposure (e.g., *Toxocara* spp.). Shoes provide more protection than sandals for children exposed to contaminated environments. Animal bites may result in injury, bacterial infection at the site, or rabies; therefore, children should be cautioned to avoid unknown animals, particularly dogs, while traveling. Since disposable diapers may not be available in some countries, parents should be aware that cloth diapers must be ironed after washing to kill eggs and larvae deposited on clothing by the tumbu fly, the vector of myiasis, in parts of Africa.

A travel medical kit should be assembled prior to travel and carried with the family at all times (Box 9-2). As at home, medications should be stored in childproof containers out of reach of children. A discussion of travel health insurance and what to do in the event of illness should be included in the evaluation. Written material summarizing the pretravel advice also may be helpful for families.

**BOX 9-1. Resources and Additional Information for Travelers**

- *International Travel and Health,* print version updated biannually, online version updated regularly by the World Health Organization (WHO). Available online at www.who.int/ith/
- WHO vaccine summaries: www.who.int/vaccines/globalsummary/immunization/countryprofileselect.cfm
- Centers for Disease Control and Prevention (CDC) *Health Information for International Travel,* updated approximately every 2 years by the CDC, Atlanta, USA: US Department of Health and Human Services (*The Yellow Book*). Available online at www.cdc.gov/travel/yb/index.htm
- CDC travel information section: www.cdc.gov/travel/
- CDC *Morbidity and Mortality Weekly Report* (MMWR): http://www.cdc.gov/mmwr/
- CDC *Emerging Infectious Diseases Journal:* http://www.cdc.gov/ncidod/EID/index.htm
- CDC Malaria Hotline: 770-488-7788
- CDC Travelers' Health Automated Information Line (toll-free): 1-877-FYI-TRIP
- GIDEON (Global Infectious Diseases and EpidemiOlogy Network), available online at www.gideononline.com/
- Pickering LK, Baker CJ, Long SS, et al. (eds) *Red Book: 2006 Report of the Committee on Infectious Diseases,* 27th ed. Elk Grove Village, IL, American Academy of Pediatrics. (1-888-227-1770 Publications) – a new edition is published every 3 years
- The Pan American Health Organization, the regional office of the WHO: www.paho.org/
- Immunization Action Coalition: www.immunize.org/izpractices/p5120.pdf
- United States State Department Hotline for American Travelers (202-647-5225)
- United States State Department: http://travel.state.gov/
- International Association for Medical Assistance to Travellers: www.iamat.org
- Program for Monitoring Emerging Diseases (Pro-MED-mail): www.promedmail.org
- Committee to Advise on Tropical Medicine and Travel (CATMAT): www.travelhealth.gc.ca
- Travax: www.travax.scot.nhs.uk/
- United States: American Society for Tropical Medicine and Hygiene travel health: www.astmh.org
- The International Society for Travel Medicine: www.istm.org
- United Kingdom: www.travelhealth.co.uk/diseases/travelclinics.htm
- Canada: www.travelhealth.gc.ca

**BOX 9-2. Pediatric Travel Medical Kit**

**NONPRESCRIPTION ITEMS**

- Personal information card: name, birth date, chronic medical conditions, regular medications, allergies, blood type, vaccination record, emergency contact information
- First-aid supplies: bandages, adhesive tape, gauze, antiseptic cleaning solution, commercial suture/syringe kit (with letter from physician)
- Thermometer
- Analgesics/antipyretics: acetaminophen, ibuprofen
- Skin care products: barrier ointment/cream, topical corticosteroid cream, disinfectant solution (e.g., chlorhexidine)
- Antihistamine (e.g., diphenhydramine)
- Insect repellent (diethyltoluamide: DEET), insecticide (permethrin)
- Water purification system
- Oral rehydration packets
- Antimotility agent (e.g., loperamide) if older child
- Extra pair of prescription glasses

**PRESCRIPTION ITEMS**

- Currently prescribed medications
- Antimalarial prophylaxis
- Antibiotic for travelers' diarrhea (see text)
- Topical antibacterial ointment/cream
- Topical antifungal ointment/cream
- Topical ophthalmic/otic antibiotic solution

## Immunizations

Although immunization rates have been increasing over the last few years in the United States, there remain a significant number of children who are underimmunized.[10] Many countries with low immunization rates have ongoing transmission of vaccine-preventable illnesses that rarely are seen in North America. Consequently, children who travel must have up-to-date immunization coverage to minimize their risk of contracting vaccine-preventable diseases if they travel to countries where these diseases are prevalent. Country-specific vaccine-preventable disease statistics and immunization schedules can be found on the World Health Organization (WHO) website and a listing of international vaccine names also is available online.[11,12]

Travel vaccines are divided into the categories of routine, required, and recommended. *Required* travel vaccines are needed by travelers to cross international borders, according to health regulations at destination. Proof of yellow fever vaccination may be required for entry into or travel from endemic countries. Vaccination against meningococcus and polio are required for travelers to the Hajj in Saudi Arabia.[13] *Recommended* travel vaccines include vaccines that should be considered according to the risk of infection during travel.

During the pretravel evaluation, some children may need to receive vaccines in the recommended childhood and adolescent immunization schedule administered in an accelerated manner to complete their primary series, catch-up with routine vaccinations, or complete the recommended pretravel vaccine series prior to departure[13–16] (Table 9-1). The routine or catch-up schedule for immunizations should be continued when the child returns from traveling.

Two or more inactivated vaccines may be administered simultaneously or with any interval between doses, as can inactivated and live vaccines. Two parenterally administered live vaccines, if not given at the same time, should be administered at least 28 days apart.[17] Caution must be used when scheduling live vaccine administration following immune globulin (IG) administration because decreased immunogenicity of the vaccines may result.[15] This is particularly true of measles and varicella-containing vaccines. IG should not be given less than 14 days prior to administration of a live vaccine, and measles and varicella-containing vaccines should be deferred from 3 to 11 months after IG administration depending on the indication and dose of IG required (see Chapter 6, Passive Immunization). Although the effect of IG administration on the immunogenicity of varicella vaccine is unknown, the current recommendation is to use the same guidelines for varicella vaccine and IG as are used for measles-containing vaccines.[18] IG administration does not interfere with the immune response to yellow fever, oral polio virus (OPV), rotavirus vaccines or any inactivated vaccines.

## Routine Childhood Immunizations

Many vaccine-preventable diseases are endemic in most of the world; therefore, a child's routine vaccine schedule should be brought up-to-date prior to travel.[16] In particular, the primary series of vaccines, including at least 3 doses of the diphtheria and tetanus toxoids and the acellular pertussis (DTaP) vaccine, should be administered and may be given according to accelerated dosing schedules as required (see Table

**TABLE 9-1. Acceleration of Routine Vaccine Schedule for Travel**

| Vaccine | Earliest Age for First Dose | Minimum Interval Between Doses |
|---|---|---|
| Combined hepatitis A and B[a] | 1 year | 1 week, 2 weeks between 2nd and 3rd doses (booster after 1 year) |
| Hepatitis A | 1 year | 6 months[b] |
| DTaP | 6 weeks | 4 weeks, 6 months between 3rd and 4th doses |
| IPV | 6 weeks | 4 weeks |
| OPV | Birth | 4 weeks |
| Hib (conjugate) | 6 weeks | 4 weeks (booster after 12 months of age) |
| Hepatitis B | Birth | 4 weeks, 8 weeks between 2nd and 3rd doses (3rd dose should be given ≥ 16 weeks after 1st dose) |
| PCV7 | 6 weeks | 4 weeks, 8 weeks between 3rd and 4th doses (after 12 months of age) |
| Measles | 6 months followed by MMR at 12 months and at 4 to 6 years of age | 4 weeks |
| MMR | 12 months | 4 weeks |
| Varicella | 12 months | 4 weeks if ≥ 13 years of age<br>3 months if < 13 years of age |

DTaP, diphtheria, tetanus, acellular pertussis; Hib, *Haemophilus influenzae* b; IPV, inactivated polio virus; MMR, measles, mumps, rubella; OPV, oral polio virus; PCV7, pneumococcal conjugate. Regular immunization schedule should be reinstituted upon return from the endemic area.
[a]Combined hepatitis A and B accelerated schedule is an off-label use for children.
[b]Hepatitis A booster does not need to be given as an accelerated schedule as seroconversion rate following the first dose is high. The second dose can be given any time after 6 months to induce long-lasting immunity.

9-1). The Tdap adolescent preparation with acellular pertussis vaccine should be used as the adolescent booster beginning at 11 years of age.[19] Children under 6 years of age should also receive the conjugate *Haemophilus influenzae* type b (Hib) vaccine prior to travel.

Although global polio eradication previously had been targeted for 2005, 21 previosuly polio-free countries documented polio infection between 2002 and 2005, and polio remains endemic in a few countries in Asia and Africa. (An up-to-date listing of polio cases can be found at www.polioeradication.org).[20] OPV, although widely used in the WHO Expanded Programme on Immunization – Plus (EPI-PLUS), is not available in the United States. An accelerated schedule for inactivated poliovirus vaccine (IPV) may be initiated if required, with the first dose being given at 6 weeks of age and subsequent doses being given at least 4 weeks apart.[16] If a child is traveling in the first few weeks of life and OPV is available, vaccination with OPV may be initiated at birth, with subsequent doses at 4-week intervals.[13] A booster dose of IPV should be given at 4 to 6 years of age.

More than half a million children die of measles annually, with children less than 1 year of age having the highest risk of severe disease. The risk of subacute sclerosing panencephalitis also is related to acquisition of measles virus at a young age. Maternal antibodies generally protect infants for less than 6 months. Children between 6 and 12 months of age who are traveling to countries where measles is endemic (including all countries where measles vaccination is not universal) should receive one dose of monovalent measles vaccine prior to travel. The measles, mumps, rubella (MMR) vaccine may be used if monovalent measles vaccine is unavailable; however, only doses given at or after 12 months of age count as part of the routine immunization schedule. Children older than 12 months of age should receive two doses of MMR given at least 28 days apart prior to travel.

Hepatitis B is part of the routine immunization schedule in the United States.[21] Children who have not completed their hepatitis B series should receive hepatitis B vaccine prior to travel to highly endemic areas. The hepatitis B series may be accelerated with an interval of 4 weeks after the first dose and 8 weeks between the second and third doses (with at least 16 weeks between the first and third doses). There is also an accelerated schedule with doses given at 0, 1, and 2 months, followed by a fourth dose at 12 months. A hyper-accelerated schedule of 0, 7, and 21 days with a fourth dose at 12 months can be used if necessary, but this schedule is not licensed by the Food and Drug Administration. A 2-dose schedule of adult Recombivax at 0 and 4 to 6 months is licensed in the United States for adolescents 11 to 15 years of age.[21]

Hepatitis A vaccine is universally recommended for children in the United States and should be given as a 2-dose schedule beginning at 12 to 24 months of age with the second dose 6 to 18 months later.[22] Children who have not received their hepatitis A vaccine series should be vaccinated prior to travel to developing countries. The majority of hepatitis A cases imported into the United States by travelers are related to travel to Mexico and Central America.[22] Although hepatitis A generally causes asymptomatic or mild infection in young children, such children may shed the virus for prolonged periods; consequently, vaccination of young travelers is recommended to protect both the recipient and any contacts. Children from birth to younger than 1 year of age who are at high risk of exposure to hepatitis A may be given 0.02 mL/kg of IG intramuscularly as passive hepatitis A prophylaxis.[22] For travel lasting longer than 3 months, a larger dose of 0.06 mL/kg should be used. If a child is traveling within 2 weeks of receiving the first dose of vaccine, the concomitant administration of IG may be considered; however, most travel medicine advisors do not recommend IG in this situation, even for travelers leaving the day after vaccination.

Twinrix (GlaxoSmithKline) is a combined hepatitis A and B vaccine that is licensed for individuals 18 years of age and older.[13,21] Twinrix-Junior is not licensed in the United States but is widely available in Europe and Canada for children between 1 and 15 years of age. These vaccines are given in a 3-dose schedule at 0, 1, and 6 months. For last-minute travel they can be accelerated in a schedule of 0, 7, and 21 days with a booster given at 1 year.[23] Recently, in Canada and parts of Europe, two *adult* doses of the vaccine 6 months apart have been approved for children 1 to 15 years of age.[24]

Varicella vaccine is recommended for all susceptible children and is given in the United States 2 as doses to children from 12 months through 12 years of age. For children less than 13 years of age, the second dose should be given 3 months after the first. For adolescents 13 years of age and older, 2 doses are required with an interval of at least 4 weeks between doses.[16] For children with unknown varicella status, a cost analysis suggests that serotesting before immunization is cost-effective for children 5 years of age and older if follow-up for immunization is assured, whereas immunization without assessing antibody status is cost-effective up to 4 years of age.[25]

The conjugate pneumococcal vaccine is part of the routine childhood immunization schedule and should be given as a 4-dose series at 2, 4, 6, and 12 to 15 months of age, although it also can be accelerated as needed (see Chapter 123, *Streptococcus pneumoniae*).

A quadrivalent conjugate meningococcal vaccine for serogroups A/C/Y/W-135 was licensed in 2005 in the United States for children 11 years and older. It is recommended for use in all children 11 to 12 years of age and unvaccinated adolescents at high-school entry (15 years) (see Chapter 125, *Neisseria meningitidis*).[26,27] This vaccine has been shown to be safe and to produce an excellent immune response in children between 2 and 10 years of age, although it is not yet approved for use in this age group.[28] Guillain–Barré syndrome (GBS) was reported in adolescents vaccinated with the quadrivalent conjugate meningococcal vaccine;[29] rate of GBS among vaccine

recipients is slightly higher than that seen in unvaccinated people. Surveillance for additional cases is ongoing.

Influenza vaccine is recommended for children 6 months of age and older who are at risk of developing complications, such as children with chronic diseases. Influenza vaccine also is recommended for healthy infants and children from 6 to 59 months of age and close contacts of infants and children from 0 to 59 months of age.[30] It is noteworthy for children who are traveling that the influenza season occurs from April to September in the southern hemisphere and year-round in the tropics.[31] Influenza outbreaks have occurred on cruise ships and on organized group tours in any latitude and season.[30]

## Required and Recommended Vaccines for Travel

Table 9-2 provides details regarding travel vaccines recommended for children.

### Cholera Vaccine

The risk of cholera is low for travelers. Cholera vaccines are not available in the United States. Cholera vaccines are licensed in some countries: WC/rBS (inactivated), variant WC/rBS (inactivated), and CVD 103-HgR (live attenuated).[32] Cholera vaccine is not required for entry into any country. The WHO recommends use of cholera vaccine only for travelers who plan to work in refugee camps or as healthcare providers in endemic areas.[33]

### Typhoid Vaccine

Typhoid vaccine is recommended for pediatric travelers to the Indian subcontinent and other developing countries in Central and South America, the Caribbean, Africa, and Asia.[34] Children are particularly at risk of developing the disease and of becoming chronic carriers. Two vaccines are available for prevention of typhoid: a live attenuated oral vaccine (Ty21a), which can be used in children 6 years of age and older, and a purified Vi capsular polysaccharide vaccine that is delivered intramuscularly to children 2 years of age and older. The efficacy of both vaccines is approximately 70%; therefore, receipt of the vaccine does not eliminate the need for food and water precautions.[35] If exposure continues, revaccination is recommended every 2 years for the polysaccharide vaccine and every 5 years for the oral Ty21a vaccine.

The Ty21a vaccine is only available in capsules in the United States, which limits usefulness in younger children. The Ty21a vaccine must be refrigerated and taken with cool liquids approximately 1 hour before eating. The Ty21a vaccine should not be taken concurrently with the antimalarial proguanil, and antibiotics should not be used from the day before the first capsule until 7 days after completing the vaccine course. Clinical trials of a Vi conjugate vaccine demonstrating safety, efficacy, and immunogenicity in children 2 years of age and older are ongoing.[36,37]

### Yellow Fever Vaccine

Yellow fever vaccine is a live attenuated vaccine that may be required or recommended for travel to central South America and sub-Saharan Africa. Some countries in Africa require an international certificate of vaccination (or physician waiver letter) against yellow fever of all entering travelers; other countries may require evidence of vaccination from travelers coming from or traveling through endemic or infected areas. The vaccine is recommended for all children 9 children of age and older traveling to endemic areas. Yellow fever vaccine is effective 10 days after administration of the first dose and a booster is required every 10 years for travelers at ongoing risk. Risks and benefits of yellow fever vaccination and likelihood of infection must be considered carefully in pregnant women and people who are immunocompromised.[38] Yellow fever vaccine contains egg protein; therefore, people with previous anaphylaxis to eggs should not receive the vaccine. The vaccine is only available in the United States from providers certified by state health departments.[39]

A vaccine-associated encephalitis syndrome has been reported in young infants at a rate of 0.5 to 4 per 1000 infants vaccinated.[13] Neurologic symptoms occur 7 to 21 days after immunization; disease is related to reversion of vaccine virus to wild-type neurotropic virus. Consequently, the vaccine is contraindicated in infants less than 6 months of age. For infants 6 to 9 months of age who cannot avoid travel to a yellow fever-endemic area, consultation with an expert in the field is recommended. Yellow fever vaccine-associated viscerotropic disease, a severe systemic illness that can result in fatal organ failure, rarely has been reported.

**TABLE 9-2. Schedule and Dosing for Travel Vaccines**

| Vaccine | Schedule | Minimum age | Dose (mL) | Route | Booster Dose |
|---|---|---|---|---|---|
| BCG (live attenuated) | 1 dose | Birth | < 30 days: 0.3 mL (dilute to half concentration)<br>> 30 days: 0.3 mL | Intradermal preferred but subcutaneous acceptable | None |
| Hepatitis A/B, combined (inactivated/recombinant) | 3 doses: 0, 1, and 6 months | 1 year | 0.5 mL | Intramuscular | None |
| Japanese encephalitis (inactivated) | 3 doses: 0, 7, and 14 or 30 days | 1 year | 1–3 year: 0.5 mL<br>> 3 years: 1.0 mL | Subcutaneous | 3 years |
| Meningococcal – A/C/Y/W-135 (polysaccharide) | 1 dose | 3 months (see text) | 0.5 mL | Subcutaneous | < 4 years: 2–3 years<br>≥ 4 years: 3–5 years |
| Meningococcal – A/C/Y/W-135 (conjugated polysaccharide) | 1 dose | 11 years | 0.5 mL | Intramuscular | Unknown |
| Rabies (inactivated cell culture) | 3 doses: 0, 7, 21, or 28 days | Birth | 1.0 mL | Intramuscular | Consider at 2 years if high-risk |
| Typhoid, Ty21a (live attenuated) | 4 doses: alternate days | 6 years | 1 capsule | Oral | 5 years |
| Typhoid, Vi (capsular polysaccharide) | 1 dose | 2 years | 0.5 mL | Intramuscular | 2 years |
| Yellow fever (live attenuated) | 1 dose | 9 months | 0.5 mL | Subcutaneous | 10 years |

BCG, bacille Calmette-Guérin.

### Rabies Vaccine

Rabies is highly endemic in Africa, Asia (particularly India), and parts of Latin America, but the risk to travelers is low. Pre-exposure rabies immunization is recommended for travelers with an occupational risk of exposure, for people planning extended stays in endemic areas where medical care is limited, and for outdoor travelers.[40] Given that children are more likely to interact with animals and not report an animal bite, rabies pre-exposure vaccination should be considered for children traveling to endemic countries for at least 1 month. The pre-exposure vaccine series involves 3 doses of 1.0 mL given intramuscularly at 0, 7, and 21 or 28 days.[40] The series can be administered using either of the two licensed vaccines in the United States: human diploid cell vaccine (HDCV), and purified chick embryo cell (PCEC) vaccine. If a child is bitten or sustains a skin-penetrating scratch by a potentially rabid animal, 2 additional doses must be completed as soon as possible, but rabies IG is not required. Without pre-exposure immunization, treatment requires rabies IG and 5 doses over 28 days of an approved vaccine. (Note: rabies IG is often not available in many developing countries.)

### Japanese Encephalitis Virus Vaccine

Japanese encephalitis, an arboviral infection transmitted by *Culex* mosquitoes, is endemic in rural areas of Asia although occasional epidemics occur in periurban areas. In temperate regions, transmission occurs from April to November, but disease occurs year-round in tropical and subtropical areas. The disease is uncommon in travelers.[41] Although the majority of cases are subclinical, half of patients with clinical disease have persistent neurologic abnormalities and the case fatality rate is close to 25%.[42] Vaccine is recommended for all travelers older than 12 months of age who are traveling in rural endemic areas for at least 1 month. Three doses of the inactivated vaccine that is available in the United States are given over 2 to 4 weeks. The vaccine has been associated with both immediate and delayed hypersensitivity reactions; therefore, travelers should receive their last dose of vaccine at least 10 days prior to travel and be observed for 30 minutes after vaccine administration. The duration of immunity is unknown. A booster can be administered after 36 months.

### Meningococcal Vaccine

Five serogroups of *Neisseria meningitidis* (A, B, C, Y, and W135) are responsible for the vast majority of meningococcal disease. The epidemiology of serogroups responsible for disease is changing worldwide; B, C, and Y are most prevalent in the United States, whereas A, C, and more recently W135 cause the majority of epidemic disease in sub-Saharan Africa where the incidence of meningococcal disease can be as high as 30 cases per 100,000 annually.[26,27]

Meningococcal vaccine is required for travelers to the Hajj and is also recommended for people traveling to the "meningitis belt" in equatorial Africa during the dry season from December to June. The quadrivalent conjugate vaccine for serogroups A/C/Y/W-135 should be given to children 11 years of age and older. For children 2 years of age and older who are traveling to areas where epidemics are occurring, the polysaccharide quadrivalent A/C/Y/W-135 vaccine is recommended. Although there is little response to polysaccharide vaccines in children less than 2 years of age, some short-term protection to serogroup A may be provided by two doses of the vaccine given 3 months apart; consequently, this is advised for infants from 3 to 24 months of age who are traveling to high-risk areas. Children who received the polysaccharide meningococcal vaccine before 4 years of age should be revaccinated within 2 to 3 years if they remain at risk.[27]

Conjugate vaccines for serogroups A, C, and A/C are available in a number of countries other than the United States for use in infants and older children. Seventeen cases of GBS have been reported in adolescents who received conjugated A/C/Y/W-135 meningococcal vaccine in the United States during 2005 and 2006; an association between the two events has been shown, with an excess risk of 1.25/million doses.[29] A vaccine for group B meningococcus has proven elusive, although development is ongoing and an epidemic strain-specific vaccine (MeNZB) has been licensed in New Zealand and is undergoing postlicensure evaluation.[43,44]

### Tickborne Encephalitis Virus Vaccine

Tickborne encephalitis is transmitted by *Ixodes rincinus* ticks in the forests of central and eastern Europe during the summer months.[42] Although 2 vaccines are licensed in some countries, including Canada, for use in children, neither is available in the United States.

### BCG

Bacille Calmette-Guérin (BCG) vaccine is part of the routine vaccination schedule in many developing countries where tuberculosis (TB) is highly endemic. BCG does not prevent TB infection but has been shown to decrease the incidence of severe TB disease such as miliary TB and TB meningitis. Vaccination with BCG can be considered for a young human immunodeficiency virus (HIV)-negative traveler (under 5 years of age) who will be spending a substantial period of time in a country that is highly endemic for TB when contact with people with active TB is likely.[13,45] In addition, children who do not receive BCG and who have traveled to a country with a high TB burden should have a tuberculin skin test prior to and 3 months following their travel.[31]

## Malaria Prophylaxis

Malaria is caused by infection with *Plasmodium* species, most commonly through the bite of an infected female *Anopheles* mosquito. Malaria is one of the leading causes of death among children under 5 years of age worldwide, causing more than half a billion infections and 1 million deaths each year. Young children, pregnant women, and people who previously or recently have not been exposed to malaria have the highest risk of severe disease. Although malaria is endemic throughout the tropics, the highest risk for malaria infection in travelers occurs in sub-Saharan Africa, Papua New Guinea, the Solomon Islands, and Vanuatu.[46] There is no vaccine available for prevention of malaria infection; therefore, families traveling with children must be given advice regarding personal protective measures and malaria chemoprophylaxis if they are traveling to endemic areas.

## Chemoprophylaxis

The type of chemoprophylaxis recommended depends on the likelihood of drug resistance, potential adverse reactions, cost, and convenience. In addition, characteristics of the individual traveler, including age, ability to swallow tablets, and any specific contraindications, are relevant.[47] Breastfeeding infants require prophylaxis since antimalarial drugs do not reach high enough levels in human milk. Several medications are recommended for prevention of malaria in children: chloroquine, mefloquine, doxycycline, and atovaquone/proguanil (AP, Malarone). Primaquine, a second-line drug for prophylaxis, may be useful when other antimalarial drugs cannot be used (see Chapter 271, *Plasmodium* Species (Malaria)). Chloroquine and mefloquine should be initiated 1 to 2 weeks prior to travel although doxycycline, AP, and primaquine may be started 1 day before exposure. All chemoprophylaxic agents must be continued for 4 weeks after departure from malaria-endemic areas, except for AP and primaquine which need be continued for only 1 week after exposure.

## Protective Measures

Because no malaria chemoprophylaxis is 100% effective, personal protective measures, such as barrier and chemical protection and

exposure avoidance, should be used to minimize risk of contact with mosquitoes. These protective measures also can decrease risk of other insectborne diseases, such as dengue and other arboviruses.

Since *Anopheles* mosquitoes that transmit malaria bite from dusk to dawn children must have adequate protection during these hours. The *Aedes* mosquito that transmits yellow fever, chikungunya, and dengue virus bites primarily in the early morning and late afternoon. The vector of Japanese encephalitis, the *Culex* mosquito, bites between dusk and dawn. When there is a risk of insect exposure, children should be dressed in light-colored clothing that covers their arms and legs. Other measures to avoid insect bites include staying in air-conditioned or well-screened accommodation or using insecticide-treated bed nets.

Chemical protection provides additional defense against insectborne diseases. The safest and best studied is *N,N*-diethyl-meta-toluamide (DEET).[47] Although adverse reactions, such as encephalopathy and rashes, have been described with use of high concentrations of DEET in children, this compound is considered safe when used appropriately according to product label instructions[46, 48] (Box 9-3). The concentration of DEET correlates with duration of protection; therefore, products with lower concentrations need to be reapplied. DEET is approved by the Environmental Protection Agency and the American Academy of Pediatrics in a concentration of 30% down to 2 months of age; in standard preparations, this concentration will provide 4 to 6 hours of protection. Picaridin (7%), recently approved as Bayrepel and Cutter Advanced in the United States, appears to be a safe and well-tolerated repellent that provides protection for only 2 to 3 hours. Citronella oil is impractical since its duration of action is less than 1 hour.[49]

Permethrin (a safe chrysanthemum derivative) is a contact insecticide that may be used for treatment of bed nets and clothing.[50] Permethrin-treated fabric has a duration of efficacy between 2 weeks and 6 months depending on the method of treatment. The best chemical protection against mosquito bites is the use of a combination of permethrin-treated clothing and DEET on exposed skin.

## TRAVELERS' DIARRHEA

### Risk

Travelers' diarrhea is one of the most common illnesses among travelers, affecting 9% to 40% of children who travel.[50] Both the incidence and severity of travelers' diarrhea are age-dependent, with the highest rates, longest duration, and greatest severity occurring in infants and children under 3 years of age.[51] Children's stools may normally be quite variable; consequently, travelers' diarrhea is defined as a twofold or greater increase in the frequency of unformed stools lasting at least 2 to 3 days. The infectious causes of travelers' diarrhea in children and adults are predominantly bacterial and include enterotoxigenic *Escherichia coli* (ETEC), which is the most common cause, enteroaggregative *Escherichia coli* (EAEC), *Salmonella, Campylobacter, Shigella,* enteropathogenic *Escherichia coli* (EPEC), and, rarely, enterohemorrhagic *Escherichia coli* (EHEC). Viral and parasitic infections are less common causes of pediatric travelers' diarrhea, although rotavirus, *Cryptosporidium parvum, Giardia lamblia,* and *Entamoeba histolytica* also account for a small proportion of diarrhea in young travelers.

The risk of developing travelers' diarrhea depends on the travel destination, with rates as high as 73% among children traveling to North Africa and 61% among children visiting India.[51] Travel to Southeast Asia, Latin America, and other African countries has been associated with rates of approximately 40%.

Although travelers' diarrhea is generally a self-limited infection, it can cause significant morbidity, particularly if it results in moderate to severe dehydration. Parents must be counseled regarding the symptoms and signs of dehydration as well as the approach to oral rehydration and when to seek medical attention.

**BOX 9-3. Precautions for Use of Diethyltoluamide (DEET)**

- Use repellents containing ≥ 30% DEET only
- Apply sparingly to exposed skin
- Apply only to intact skin
- Apply to face by wiping; avoid eyes and mouth; do not spray directly on face
- Wash off with soap and water when coming indoors
- Do not inhale or ingest repellent
- Do not apply on hands or other areas that are likely to come in contact with the eyes or mouth
- Do not allow children under 10 years to apply DEET themselves. Apply to your own hands then apply to the child
- Do not use on children less than 2 months of age

### Preventive Measures

Because there are no vaccines licensed in the United States for prevention of travelers' diarrhea in children, counseling regarding food and water precautions is the most important preventive measure. Vaccines are in development in preclinical and clinical phases against ETEC, *Shigella* spp., and *Campylobacter jejuni*; a combined cholera and ETEC oral vaccine is licensed in Canada for children 2 years of age and older.[52]

General rules regarding food and water precautions when traveling apply to both children and adults; however, young children are more likely to explore the environment with their hands and mouths, thus creating opportunities for infection. Frequent handwashing with soap and water is critical, particularly before eating, although alcohol-based handwashes may be used no water is not available.

Children must be reminded to use safe water sources for all drinking, toothbrushing, and food preparation. Safe water sources include bottled water from a trusted source or water that has been boiled, chemically treated, or filtered. Combination chemical and filter pumps may provide the best protection in filtered water as filters vary in the size of microbes which are removed.[2] Water should be boiled for at least 1 minute at altitudes less than 2000 meters and 3 minutes at greater than 2000 meters.[31] Carbonated drinks also are considered safe for drinking, but water used to make ice may be contaminated. For infants, breastfeeding is the safest form of nutrition. In addition to its many health benefits, breastfeeding does not require a source of clean water, unlike the use of formula, both in its preparation and the cleaning of bottles.

The selection and preparation of foods are important during travel to minimize the risk of travelers' diarrhea. Although the advice to "boil it, cook it, peel it, or forget it" frequently is given, it is often not practical to follow. If possible, only steaming-hot freshly made food should be consumed. Families traveling with children should have a ready supply of snacks and avoid buying food from street vendors (Box 9-4).

Additional food and water precautions can decrease risk of other infectious diseases while traveling. These include avoidance of unpasteurized dairy products to eliminate risk of brucellosis and other bacterial infections. Raw or undercooked meat and fish should not be consumed due to risk of parasitic infections. Avoiding undercooked seafood can decrease risk of hepatitis A. In developing countries raw vegetables and fruit that cannot be self-peeled should be avoided.

Chemoprophylaxis for travelers' diarrhea generally is not advised in children.[51] However, short-term prophylaxis (< 3 weeks) could be considered for children with increased susceptibility to travelers' diarrhea, such as children with achlorhydria, or children in whom travelers' diarrhea might have significant medical consequences (e.g., children with chronic renal failure, congestive heart failure, diabetes mellitus, or inflammatory bowel disease).[53]

**BOX 9-4. Prevention of Travelers' Diarrhea in Children**

**DO**
- Eat only thoroughly cooked food served hot
- Peel fruit
- Drink only bottled, carbonated, boiled, chemically treated, or filtered water
- Prepare all beverages and icecubes with boiled or bottled water
- Wash hands before eating or preparing foods
- Continue breastfeeding throughout travel period

**DON'T**
- Eat raw vegetables or unpeeled fruit
- Eat raw seafood or shellfish or undercooked meat
- Eat food from street vendors
- Drink tap water
- Consume milk or dairy products unless labeled as pasteurized or irradiated

## Treatment

Treatment of travelers' diarrhea in children must include close attention to hydration status, and parents should be counseled regarding early signs of dehydration. Oral rehydration therapy (ORT) using a homemade or commercially prepared oral rehydration solution (ORS) can be used to prevent dehydration associated with diarrheal disease. Commercial ORS should be used to treat mild to moderate dehydration; severe dehydration may require intravenous fluid resuscitation.[54,55] ORS packets should be part of a family's travel medical kit. Locally made preparations can be used early in therapy, although they differ in composition from the reduced-osmolarity ORS recommended by WHO (Table 9-3).[54,55] Breastfeeding should be continued in infants, and solid food intake should be maintained along with rehydration with ORT throughout the diarrheal episode, although foods high in simple sugars should be avoided because the increased osmotic load may worsen fluid losses.

Loperamide generally is used in combination with antibiotics for treatment of travelers' diarrhea in adults; however, the role of loperamide in pediatric travelers' diarrhea remains controversial, despite being licensed for use in children 2 years of age and older. Although loperamide has been shown to decrease duration and severity of acute diarrhea in children, this drug has been associated with significant side effects in children and is not recommended for younger children.[54,56] Racecadotril is an enkephalinase inhibitor that has been associated with decreased stool output in clinical trials; however, further studies are required. Zinc supplementation has been associated with improved outcomes in diarrheal disease in children in developing countries, but zinc supplementation is not recommended in treatment of travelers' diarrhea.[54]

There is little evidence for use of antimicrobial agents in pediatric travelers' diarrhea.[51] Fluoroquinolones for 1 to 3 days are the drug of choice for adults with travelers' diarrhea that is moderate to severe, persistent (>3 days), or associated with fever or bloody stools. Although there are concerns regarding the potential for development of arthropathy and antimicrobial resistance with fluoroquinolone use in children, the Food and Drug Administration has approved ciprofloxacin for anthrax and as a second-line agent for the treatment of urinary tract infections in children from 1 to 17 years of age.[57,58] Therefore, fluoroquinolones could be considered safe in children for the short course required for travelers' diarrhea. A 3-day course of ciprofloxacin at a dose of 20 to 30 mg/kg per day divided twice daily with a maximum dose of 500 mg bid is recommended for children with moderate to severe or bloody diarrhea.[51]

Azithromycin is often used as the first choice for treatment of pediatric travelers' diarrhea, especially in areas with a high prevalence of fluoroquinolone-resistant *Campylobacter* species such as India and Thailand because it is given once a day and has a known safety profile in children. A dose of 10 mg/kg once daily for 3 days (maximum dose of 500 mg) is appropriate.[51] In adults a single dose of antibiotic has been shown to be as effective as 3 days' treatment; therefore, in children a full 3-day course may not be necessary.[59,60] Rifaximin (Xifaxan), a nonabsorbed rifamycin derivative, has been approved in the United States for treatment and prevention of travelers' diarrhea for people 12 years of age and older.[61] A liquid preparation is available in some countries for pediatric use.

If travelers' diarrhea does not respond to a course of antimicrobial therapy, medical attention should be sought to investigate other possible causes of the diarrhea.

**TABLE 9-3. Formulation of Oral Rehydration Solution (ORS)**

| World Health Organization | Home Formula |
|---|---|
| • Sodium chloride 2.6 g/L (75 mmol/L sodium) | • 3.5 g NaCl ($^3/_4$-teaspoon table salt) |
| • Potassium chloride 1.5 g/L (20 mmol/L potassium) | • 1.5 g KCl (1 cup orange juice) |
| • Trisodium citrate, dihydrate 2.9 g/L (10 mmol/L citrate) | • 2.5 g $NaHCO_3$ (1 teaspoon baking soda) |
| • Glucose, anhydrous 13.5 g/L (75 mmol/L glucose) | • 20 g glucose (4 tablespoons sugar) Water to final volume of 1 L (33 oz) |

## EMERGING INFECTIOUS DISEASES

Over the past few years, several infectious agents, such as severe acute respiratory syndrome (SARS) coronavirus, and the H5N1 strain of avian influenza, have emerged as potentially widespread health threats. Although the SARS coronavirus does not appear currently to be of concern, pediatricians who are advising families regarding travel health must keep informed of the current status of emerging infectious diseases that may pose a threat to the traveler. Several websites provide up-to-date information regarding such infections, including that of the WHO and the Centers for Disease Control and Prevention (see Box 9-1).

A highly pathogenic strain of avian influenza (H5N1) has caused outbreaks in poultry in several countries in Asia, Africa, the middle East, and eastern Europe. Human cases of H5N1 also have been documented in Cambodia, China, Indonesia, Iran, Thailand, Turkey, and Vietnam. Although there have been rare confirmed human-to-human transmissions of H5N1, which have high case-fatality rates have also been documented in a number of these countries. (An up-to-date listing of confirmed human cases can be found. Although there have been rare confirmed human-to-human transmission of H5N1 in these outbreaks, there is concern that further mutations in the virus may result in a pandemic strain of influenza. A number of recommendations for travelers have been made to decrease their risk of acquiring H5N1 infection[62] (Box 9-5). Although oseltamivir has been used in treatment of and prophylaxis against H5N1, it is not recommended that a prescription for oseltamivir be given to travelers.

## THE IMMUNOCOMPROMISED TRAVELER

Children with immunodeficiencies require special consideration at their pretravel evaluation because of increased risk of travel-related illness.[63] Most patients with altered immune systems, particularly those with decreased T-lymphocyte immunity, should not receive live vaccines because of risk of developing clinical illness from the vaccine strain.[64] IPV should be given instead of OPV to all members in the family of an immunocompromised person, and vi typhoid vaccine should be administered instead of the Ty21a vaccine to an immunocompromised child, although there is no risk to the patient if family members receive the live oral vaccine.[15,21] However, MMR, varicella, and yellow fever vaccines should be considered for HIV-seropositive

**BOX 9-5. Precautions to Decrease Risk of H5N1 Infection**

- Avoid all direct contact with poultry and ducks, including poultry farms and bird markets
- Wash hands frequently with soap and water (alcohol-based handwashes can be used if hands are not visibly soiled)
- Cook all poultry-based foods, including eggs, thoroughly

children who are not severely immunocompromised (see Chapter 227, Rubeola Virus (Measles and Subacute Sclerosing Panencephalitis); Chapter 205, Varicella-Zoster Virus). Killed or subunit vaccines may be administered to children with altered immunity, although responses to the vaccines may be diminished.[64] Asplenic patients may respond poorly to polysaccharide vaccines in particular. Patients with certain B-lymphocyte deficiencies, such as X-linked and common variable agammaglobulinemia, should avoid OPV, vaccinia, and live bacterial vaccines, although other patients with humoral deficiencies, including selective immunoglobulin A (IgA) and IgG subclass deficiency, need only avoid OPV; other live vaccines can be considered.

Some travel-associated illnesses may be more severe in immunocompromised travelers. Asplenic travelers are at greater risk of severe babesiosis and malaria, and organ and stem cell transplant recipients are more likely to develop bacteremia associated with gastroenteritis due to *Salmonella* or *Campylobacter* spp.[65] HIV-seropositive travelers with low CD4 lymphocyte counts must be particularly conscious of risk factors associated with opportunistic infections such as *Toxoplasma gondii, Isospora belli, Salmonella* spp. and *Cryptosporidium parvum,*[65] and, therefore, must be particularly cautious regarding food, water, and animal exposures.

## RETURN FROM TRAVEL

Routine posttravel screening generally is not required for asymptomatic, short-term travelers, although screening may be considered for long-term travelers, expatriates, adventure travelers, and people who have experienced significant illness while traveling.[4,66] If posttravel screening is indicated, the tests required should be determined by the potential exposures associated with the travel itinerary and any symptoms, if present.

Children who develop symptoms after travel should seek immediate medical attention, and parents must inform the physicians caring for them of their travel itinerary. This is particularly critical if the itinerary has included a malaria-endemic area, since chemoprophylaxis cannot prevent all cases of malaria. Because malaria can present with nonspecific symptoms in children, any symptoms of fever, rigors, headache, malaise, abdominal pain, vomiting, diarrhea, poor feeding, or cough following travel to an endemic country should be evaluated promptly by a physician.[67]

Travel-relatetd illness has been shown to be highly dependent on itinerary. In a report of disease and relationship to place of exposure among ill returned travelers, significant regional differences in proportionate morbidity were reported.[4] Typhoid fever was seen most frequently in travellers returning from South Asia. Malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, especially sub-Saharan Africa, although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria. Rickettsial infection, primarily tickborne spotted fever, occurred more frequently than malaria or dengue among travelers returning from southern Africa.[4]

SECTION C

# Host Defenses Against Infectious Diseases

CHAPTER 10

## Immunologic Development and Susceptibility to Infection

Maite de la Morena

The human immune system has evolved to protect the individual from infectious microbes. It does this by utilizing a complex interactive network of cells, proteins, and organs. This response is both innate and adaptive, each with unique characteristics. The innate response to a pathogen occurs immediately (within hours), lacks clonal specificity for a particular pathogen, and does not confer long-lasting protection, i.e., immunologic memory. The adaptive immune response, although triggered by components of the innate immune response, takes days to evolve, requires processing and presentation of antigens derived from the pathogen, is specific to the particular pathogen and most importantly confers immunologic memory, i.e., the organism "remembers" the signature of a pathogen upon subsequent encounter. Experiments of nature in humans, such as those recognized as the inherited disorders of immune function,[1] have taught us that despite the apparent redundancy of the system, quantitative and qualitative defects in individual components and/or pathways result in abnormal function and susceptibility to particular infections.

This chapter provides a general overview of the development of innate and adaptive immune responses, addresses some of the immunologic developmental characteristics unique to the fetus and newborn, and addresses pathogen susceptibility in general terms, which can serve as an introduction to Sections M, N, and R of this textbook.

## THE INNATE IMMUNE RESPONSE

The innate immune system offers a first line of defense against invading pathogens. Both cellular and humoral factors constitute its major components. These include: (1) antimicrobial products and phy-