As tourism grows, an increasing number of people are traveling to higher-risk destinations; thus, clinicians must become familiar with recommendations for travel health safety. Each year, 30 to 40 million Americans travel outside the United States. Although the most popular destinations are Europe, Central America, and the Caribbean, travel to Africa and Asia is increasing substantially. International travel, particularly to developing countries, can be associated with the risk of infectious and noninfectious diseases. These risks can be decreased, eliminated, or modified with vaccinations, prophylactic medications, and education. Optimally, pretravel advice must be individualized to a person’s medical history, itinerary, and risk behavior. In addition to risk assessment-based immunizations, issues such as traveler’s diarrhea, malaria prophylaxis, sexually transmitted diseases, and management of underlying medical problems must form a part of pretravel management. Adventure or prolonged travel or persons with underlying medical diseases such as insulin-dependent diabetes mellitus, transplantation, immunodeficiencies, and dialysis warrant additional preventive measures. This review primarily updates pretravel management of adults.


AIDS = acquired immunodeficiency syndrome; DVT = deep venous thrombosis; FDA = Food and Drug Administration; HIV = human immunodeficiency virus; TD = traveler’s diarrhea

PRETRAVEL SCREENING

Pretravel screening helps to stratify risk of the traveler. Risk stratification involves reviewing the itinerary, behavior patterns (such as eating habits), underlying medical history, and vaccine or medication contraindications. Details of the itinerary, lodging, budget, duration, and time to departure are extremely helpful in preparing the traveler for the trip. Prolonged travel, backpacking, low-budget travel, foreign-born individuals returning to visit friends and family, and imminent travel are associated with a higher incidence of travel-related complications. Medical problems or issues such as diabetes, transplantation, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), coronary artery disease, chronic obstructive pulmonary disease, and end-stage renal failure may substantially affect the immunogenicity of vaccines and implications for health while traveling. Live vaccines are contraindicated in immunocompromised or pregnant persons; thus, travel to a particular risk area is not possible. For example, patients who cannot receive the yellow fever vaccine should not travel to the Amazon. Allergies to vaccine components such as thimerosal or aluminum or to medications such as sulfonamides may preclude use of certain vaccines or medications. Contact allergy to thimerosal is not a contraindication to thimerosal-containing vaccines.

GENERAL ADVICE

Elderly persons or those with chronic medical diseases may benefit from a pretravel physical examination. Travelers should carry a letter stating medical diagnosis, list of medications with doses, and needles or syringes. Some medications, such as methylphenidate hydrochloride, are prohibited in certain countries. Carrying a letter from a physician may prevent problems at airports. Travelers should carry

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A question-and-answer section appears at the end of this article.

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enough essential medications to last the duration of the trip, and the supply should be divided between carry-on and check-in baggage. Medications should be in original bottles with appropriate labels. Because dental problems can occur, patients with ongoing dental illnesses should have a dental examination before they travel to avoid invasive procedures in other countries. Most health insurance companies do not cover medical expenses that occur outside the United States. Travelers should consider additional travel health and air evacuation insurance, irrespective of their age, medical history, or type of travel.

Studies have shown that 25% to 50% of travelers engage in sexual relations with new partners abroad, including other tourists, locals, or commercial sex workers. Discussing alcohol consumption and safe sex with patients may help in preventing sexually transmitted diseases while traveling; this is especially relevant in light of increasing worldwide HIV prevalence. Patients should be advised to bring condoms from the United States because of poor availability or quality of condoms in some developing countries.

Because accidents are the most common preventable cause of mortality during travel, patients must be reminded to avoid high-risk situations, such as driving in a foreign country, riding 2-wheelers (motorcycles, scooters), or riding in overcrowded buses, particularly in adverse weather conditions or under the influence of alcohol. Travelers should follow basic traffic laws. Seat belt use should be encouraged, but the availability of functional seat belts may be severely limited in some developing countries.

Illnesses related to air travel include motion sickness, barotrauma, hypoxemia in select patients, and possibly deep venous thrombosis (DVT). Motion sickness is common with flying. Patients can be advised to take either meclizine or dimenhydrinate for prophylaxis. Although airplanes are pressurized, expansion of air can occur and cause barotrauma in air- or gas-containing organs, particularly the ears, sinuses, and gastrointestinal tract. Swallowing or chewing during take-off and descent may decrease ear barotrauma. Ear barotrauma is more likely to occur in a traveler with a cold or an eustachian tube dysfunction. Occasionally, a serous otitis or tympanic membrane perforation can occur but usually resolves spontaneously. Because of air expansion, air travel is a relative contraindication for patients who have recently undergone abdominal surgery (previous 2 weeks). Patients with severe anemia (hemoglobin level <7 g/dL), sickle cell trait or disease, underlying chronic pulmonary obstructive disease and chronic hypoxia, or recent cerebrovascular accident may experience exacerbation of symptoms. Such patients may need to have oxygen on board, which must be arranged ahead of time with the airlines. Also, most airlines require a physician to verify the patient’s ability to fly safely and to provide a certification called the Medical Fitness for Air Travel form.

The available data suggest that an association, although small, exists between air travel and DVT. All patients, particularly those with risk factors such as a history of DVT, recent surgery or trauma, malignancy, obesity, pregnancy, or genetic prothrombotic predisposition and women taking oral contraceptives or hormone replacement therapy, should be advised to exercise their legs during the flight. The role of aspirin in the prevention of DVT is controversial. Compression stockings may be reasonable for patients at risk for DVT, and prophylactic anticoagulation should be considered for very high-risk patients.

Jet lag and fatigue occur commonly in international travelers. Jet lag, typically worse when flying eastward, results from desynchronization of the sleep-wake cycle and other internal circadian rhythms, such as hormonal or temperature rhythms. For short and/or a series of short international flights (<72 hours), the patient should be advised to take brief naps at the corresponding home afternoon time or at late nighttime. Napping for less than 40 minutes avoids reverting to the home sleep cycle. For longer eastward trips, activities should be adjusted to correspond with time on the plane and on arrival. A mild bedtime sedative for 3 to 4 days after arrival at the destination or after return to the United States may help adjust the sleep cycle. Potential adverse effects, such as daytime drowsiness, that may interfere with planned activities or driving should be discussed. Patients could try the medication once before leaving home to ensure no adverse effects. Use of melatonin for jet lag is controversial and has not been clearly shown to be effective.

**IMMUNIZATIONS**

An important part of advice to travelers is vaccination against common and travel-related vaccine-preventable diseases. A review of immunization against diseases such as diphtheria, measles, and polio is advised because some of these diseases are prevalent in many developing countries. Although specific travel-related vaccinations may not be cost-effective, they are beneficial and may be required or recommended depending on travel history. Vaccine recommendations are best individualized to each traveler’s itinerary, activities, time before departure (for completion of schedules or to mount an adequate immune response), previous immunizations, and medical history.

Travel vaccine schedules, boosters, common contraindications, and adverse effects are listed in Table 1.

**Cholera**

*Vibrio cholerae* causes outbreaks in many countries where sanitation and food and water hygiene are inad-
Table 1. Common Vaccines for International Travelers*

<table>
<thead>
<tr>
<th>Vaccine (efficacy)</th>
<th>Primary course</th>
<th>Booster</th>
<th>Accelerated schedule</th>
<th>Specific contraindications†</th>
<th>Adverse effects‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera (oral)§ (60%-100%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hepatitis A (about 70%-80% at 2 wk; 95% at 4 wk)</td>
<td>Adults ≥18 y: 1.0 mL IM in deltoid at 0 and 6 mo</td>
<td>None</td>
<td>1.0 mL IM in deltoid at 0, 1, 4 mo or 0, 2, 4 mo (second dose at least 1 mo after first dose, third dose should be at least 4 mo after first dose and at least 2 mo after second dose); schedule of 0, 1, 2, 12 mo is FDA approved for Engerix-B vaccine only</td>
<td>Age &lt;2 y; allergy to aluminum, aluminum hydroxide, or other vaccine components depending on vaccine used; pregnancy is relative contraindication</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Adults ≥20 y: 1.0 mL IM (20 µg) at 0, 1, 6 mo</td>
<td>None unless anti-HBs antibody is &lt;10 mIU/mL</td>
<td>1.0 mL IM in deltoid on days 0, 7, 21 with a 12-mo booster</td>
<td>Age &lt;20 y; allergy to thimerosal (mercury) or other components depending on vaccine used; hypersensitivity to yeast; pregnancy is relative contraindication</td>
<td>Headache, nausea; rarely, anaphylaxis or other systemic effects</td>
</tr>
<tr>
<td></td>
<td>Adults ≥18 y: Havrix, 720 EL U/mL, and Engerix-B, 1.0 mL (with 20 µg of HBsAg) IM in deltoid at 0, 1, 6 mo</td>
<td>Unknown</td>
<td>1.0 mL IM in deltoid on days 0, 7, 21 with a 12-mo booster</td>
<td>Age &lt;18 y; allergy to aluminum, aluminum phosphate, aluminum hydroxide, 2-phenoxylethanol, formalin, thimerosal, neomycin, or yeast protein; pregnancy is relative contraindication</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td></td>
<td>Adults and children: IM deep into gluteus; trip duration: &lt;3 mo, 0.02 mL/kg; ≥3 mo, 0.06 mL/kg; maximal dose for small children, 3 mL; maximal volume in 1 site, 5 mL for adults, 1-3 mL for children</td>
<td>Every 3-5 mo depending on dose; repeated doses required with continued exposure</td>
<td>None</td>
<td>Allergy to thimerosal; isolated IgA deficiency; severe thrombocytopenia or coagulation disorder contraindicates IM injection; concurrent administration with MMR and varicella vaccines</td>
<td>Soreness and swelling at the injection site; urticaria; serious adverse effects are rare</td>
</tr>
<tr>
<td></td>
<td>Adults and children &gt;2 y: 1.0 mL SQ on days 0, 7, 30; children 1-2 y: 0.5 mL SQ on days 0, 7, 30</td>
<td>Same dose at least every 3 y</td>
<td>Adults and children &gt;2 y: 1.0 mL SQ on days 0, 7, 14; children 1-2 y: 0.5 mL SQ on days 0, 7, 14</td>
<td>Age &lt;1 y; allergy to thimerosal or gelatin; history of urticaria and allergies implies greater risk of allergic reactions to vaccine; last dose should not be given &lt;10 d before travel; history of rash, hives, or generalized itching after bee stings or medications; pregnancy</td>
<td>Urticaria, angioedema; 16 to 64 cases per 10,000 vaccines; systemic effects (fever, headache, aching, chills, dizziness, nausea, vomiting, abdominal pain, malaise) in 10% of recipients</td>
</tr>
<tr>
<td></td>
<td>Adults and children, none; 2 doses, 80%; 3 doses, 99%</td>
<td>Adults: same dose every 3-5 y</td>
<td>None</td>
<td>Age &lt;2 y; allergy to thimerosal; pregnancy</td>
<td>Transient fever in 2% of children</td>
</tr>
</tbody>
</table>

(continued on page 834)
### Table 1. Continued

<table>
<thead>
<tr>
<th>Vaccine (efficacy)</th>
<th>Primary course</th>
<th>Booster</th>
<th>Accelerated schedule</th>
<th>Specific contraindications†</th>
<th>Adverse effects‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliovirus (injectable)</td>
<td>Adults ≥18 y: 0.5 mL SQ at 0, 2, 8-14 mo</td>
<td>Same dose repeated once if primary series completed at least 5 y previously</td>
<td>Primary series: 3 doses at 0, 1, 2 mo (minimum 4 wk apart); give as many doses as time allows and remaining doses can be completed either in endemic country (expatriates) or in United States</td>
<td>Allergy to neomycin, polymyxin B, or streptomycin; pregnancy</td>
<td>Rarely, anaphylaxis or other systemic effects</td>
</tr>
<tr>
<td>Rabies</td>
<td>1.0 mL IM in deltoid on days 0, 7, and 21 or 28</td>
<td>Unknown, possibly 5 y; check serology before giving booster</td>
<td>Days 0, 7, 21</td>
<td>Allergy to vaccine component depending on vaccine used; pregnancy; mefloquine, chloroquine can interfere with immune response to intradermal vaccine</td>
<td>Localized lymphadenopathy, headache, myalgia, malaise, dizziness</td>
</tr>
<tr>
<td>Typhoid (injectable) (64%-72%)</td>
<td>Adults and children ≥2 y: 0.5 mL IM in deltoid in adults, vastus lateralis in children</td>
<td>Same dose every 2 y</td>
<td>None</td>
<td>Age &lt;2 y; &lt;2 wk before exposure; allergy to phenol; pregnancy</td>
<td>Headache, tremor, abdominal pain, vomiting, diarrhea, cervical pain</td>
</tr>
<tr>
<td>Typhoid (oral)§¶ (50%-80%)</td>
<td>Adults and children ≥6 y: 4 capsules orally every other day on days 0, 2, 4, 6</td>
<td>Same dose every 5 y</td>
<td>None</td>
<td>Age &lt;6 y; acute vomiting or diarrhea; immunocompromised#: unable to complete 1 wk before exposure; use of antibiotics 24 h before initiation of vaccine or 72 h after completion of doses; mefloquine and chloroquine should be started at least 3 d after completion of oral typhoid vaccine; pregnancy</td>
<td>Rarely, nausea, abdominal pain, cramps, vomiting, fever, headache, rash</td>
</tr>
<tr>
<td>Yellow fever (&gt;95%)</td>
<td>Adults and children ≥9 mo: single dose of 0.5 mL SQ</td>
<td>Same dose every 10 y</td>
<td>None</td>
<td>Age &lt;9 mo; immunocompromised#: off immunosuppressants &lt;3 mo; &lt;8 wk since blood or plasma transfusion; received other live-antigen vaccines within past 4 wk (MMR, oral typhoid, varicella, or OPV); &lt;10 d before arrival in area where yellow fever vaccine is indicated; allergy to eggs, chicken, gelatin, or egg protein; pregnancy or likelihood of pregnancy 3 mo after vaccine</td>
<td>Generally mild fever, headache, muscle ache 5 to 14 d after immunization; vaccine strain encephalitis or disease occurs rarely in infants or elderly persons</td>
</tr>
</tbody>
</table>

* AIDS = acquired immunodeficiency syndrome; FDA = Food and Drug Administration; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IM = intramuscular; MMR = measles-mumps-rubella; NA = not available; OPV = oral polio vaccine; SQ = subcutaneous.
†Severe reaction to previous dose or moderate to severe ongoing illness precludes use of any vaccination.
‡Pain at injection site, redness, swelling, occasional fever, and flu-like symptoms can occur with any vaccine and are not contraindications to subsequent doses.
§Not available in the United States.
¶Can be given at the same time as inactivated vaccines: OPV, yellow fever and oral typhoid vaccines; OPV should be repeated in 3 mo.
#Refrigerate. Should be taken on an empty stomach (1 h before meals) with cool or lukewarm liquid.
#Immunocompromised state: HIV or AIDS, leukemia, lymphoma, generalized malignancy, undergoing long-term chemotherapy, radiation therapy, or taking large doses of corticosteroids (more than 2 mg/kg per day or more than 20 mg/d); status posttransplant, or fewer than 3 mo since completing therapy for any of these disorders.
equate. Incidence of cholera is highest in Africa, accounting for 72% of global cholera. At present, an epidemic of *V. cholerae* biotype *el tor*, is ongoing in South Africa. Peru, Ecuador, Guatemala, Nicaragua, and countries in the Middle East and Asia have ongoing seventh pandemic cases. Because the risk of cholera to an average traveler is low (0.01%-0.001% per month of stay in a developing country), a cholera vaccine is rarely indicated. However, vaccination is advised for persons working with refugee populations, those living in endemic-epidemic areas, and military personnel. Currently, cholera vaccine is not required for entry into any country. The parenteral vaccine has been discontinued in the United States because of its frequent adverse effects and brief and unreliable immunogenicity. Newer oral cholera vaccines (an inactivated whole cell--B subunit vaccine and a live attenuated CVD 103-HgR *V. cholerae* 01 serogroup vaccine) provide better immunity (85%-90% and 60%-100%, respectively) with fewer adverse effects. Both of these vaccines are licensed in countries other than the United States. Therefore, the current best advice for travelers going to cholera-endemic areas is to adhere to strict food and water precautions and to learn self-management of severe watery diarrhea.

**Hepatitis A and Immunoglobulin**

Hepatitis A is a predominantly food-borne viral hepatitis that occurs worldwide. Risk is low in Australia, Japan, Korea, North America, and Europe including southern Europe. Hepatitis A is the most frequently occurring vaccine-preventable disease among travelers. Ingestion of fecally contaminated water or food, such as raw seafood, is the source of infection. The risk increases with indiscriminate eating habits, person-to-person contact, and prolonged travel duration. The risk of acquisition of hepatitis A among nonimmune travelers is 3 to 20 cases per 1000 nonimmune persons who stay in a developing country for at least a month. Approximately 10% of 1- to 14-year-old and 20% of 15- to 40-year-old patients with hepatitis A require hospitalization. Mortality increases with age, being greater than 2% in persons older than 40 years. The inactivated hepatitis A vaccines (Vaqta [Merck] and Havrix [SmithKline Beecham]), available in the United States since the mid-1990s, are extremely efficacious and safe. Both vaccines provide protective antibody levels in 94% to 100% of patients within 4 weeks of vaccination, and both can be used interchangeably. Immunity among children younger than 2 years is limited because of poor immunogenicity. Maternal antibody interferes with immunity in children younger than 12 months. Immune response may be limited in immunocompromised hosts. US immigrants from countries with a high prevalence of hepatitis A who visit their home countries should be vaccinated according to hepatitis A serostatus because most are likely to be immune. Coadministration of passive immunity (85%-90% protection) with γ-globulin should be reserved for high-risk patients traveling imminently (<2 weeks), such as elderly persons, children younger than 2 years, those with underlying medical problems, or immunocompromised persons. Concurrent administration of most vaccines is not contraindicated with γ-globulin except the measles-mumps-rubella vaccine and varicella vaccine. Because of the long incubation period of hepatitis A virus and the rapid onset of protection with the vaccine, the vaccine alone may be adequate in most healthy persons for whom travel is imminent.

**Hepatitis B Vaccine**

Areas with a high prevalence of hepatitis B include Asia, Africa, parts of South America, the Middle East, southern and western Pacific islands, Haiti, and the Dominican Republic. Risk of hepatitis B for travelers is mainly associated with medical or dental care abroad, potential blood transfusion for an accident or illness, and sexual or needle exposures. Expatriation and frequent or prolonged international travel to developing countries are indications for initiating inactivated recombinant hepatitis B vaccination (Recombivax HB [Merck]; Engerix-B [SmithKline Beecham]). Health care workers, volunteers, or missionaries in developing countries require the hepatitis B vaccine series. For patients leaving imminently, an accelerated schedule can be used to achieve protective immunity. Currently, only Engerix-B has received approval from the Food and Drug Administration (FDA) for an accelerated schedule of 0, 1, and 2 months with a 12-month booster.

**Combined Hepatitis A and B Vaccine**

A new combined hepatitis A (Havrix [720 EL U/mL]) and hepatitis B (Engerix-B [20 µg of recombinant hepatitis B surface antigen]) vaccine called Twinrix (SmithKline Beecham) was approved by the FDA in 2001 for use in adults older than 18 years. Twinrix is given on a 0-, 1-, and 6-month schedule. Studies have shown that Twinrix is as efficacious as the monovalent vaccines of Havrix (99% of the vaccinees are seropositive at 2 months) and for hepatitis B (84% of the vaccinees are seropositive at 2 months). This vaccine is convenient for long-term travelers and for those who need rapid protection. An accelerated schedule of 0, 7, and 21 days with a 12-month booster is as efficacious as a standard schedule. Indications for this vaccine are similar to those for hepatitis B vaccine in travelers.

**Japanese B Encephalitis Vaccine**

Japanese B encephalitis is a mosquito-borne viral encephalitis that occurs in rural parts of Asia, especially near
pig farms. It is prevalent in China, the Indian subcontinent, Japan, eastern Russia, and other Southeast Asian countries. It has seasonal variation (more in summer, rainy months). Japanese B encephalitis has a 30% case fatality rate in patients with overt infections, with high neuropsychiatric sequelae. Risk of acquisition is mainly associated with extensive (>24 weeks) rural travel, backpacking, or rain forest travel in endemic countries. The full course of the inactivated Japanese B encephalitis vaccine (Biken) results in seroconversion in 100% of recipients, and neutralizing antibodies remain for at least 3 years. Common adverse effects like myalgias, headache, or fever occur in 20% of vaccine recipients, and hypersensitivity reactions (generalized urticaria, angioedema, respiratory distress, and anaphylaxis) occur in 0.6% of recipients. Hypersensitivity reactions can be immediate or delayed up to 10 days and are more likely in persons with a history of urticaria or other allergies. Patients with Japanese B encephalitis must defer international travel and remain in areas with ready access to medical care for 10 days after receiving a dose of the vaccine.

**Meningococcal Vaccine**

Certain areas of the world, especially central Africa, have seasonal epidemics caused by *Neisseria meningitidis*, mostly serogroups A or C, during the dry seasons (December through June). *N meningitidis* is also an important cause of disease among travelers taking the Haj pilgrimage in Saudi Arabia, and vaccination is required for entry into Saudi Arabia. The currently available vaccine in the United States (Menomune [Aventis]) is effective only against serogroups A, C, Y, and W-135 and does not cover serogroup B. Since October 1999, meningococcal vaccine has been recommended for college students living in US dormitories. Requirements are similar for students traveling abroad to study in other countries, such as the United Kingdom.

**Poliomyelitis Vaccine**

Although poliomyelitis is reaching near eradication worldwide, pockets with ongoing wild strain transmission still exist, such as in African countries and in Asia. Poliomyelitis was declared eradicated from the Western Hemisphere until a recent outbreak of vaccine-strain polio in Haiti and the Dominican Republic. Currently, all travelers to Haiti, the Dominican Republic, eastern Europe, Africa, and Asia are advised to receive a 1-time adult parenteral inactivated trivalent polio vaccine booster if the primary series has been completed.

**Rabies**

Unlike the United States where the principal vectors for rabies are wild animals or bats, in many parts of the world, particularly India, Nepal, Mexico, Colombia, Ecuador, El Salvador, Guatemala, Peru, Philippines, Sri Lanka, Thailand, and Vietnam, rabies is transmitted by dogs, cats, and other animals. A rabies preexposure vaccination with the inactivated viral rabies vaccine (HDCV [Imovax]) is recommended for expatriates, especially children, adventure travelers, and animal handlers. Preexposure prophylaxis precludes the need for rabies immunoglobulin if a bite occurs. Scarcity and safety of the rabies immunoglobulin worldwide highlights preexposure prophylaxis for select populations. If bitten, persons with preexposure vaccination still require 2 additional rabies vaccine doses (on the day of the bite and on day 3, instead of a full 5-dose course). All animals that bite, especially unprovoked, outside of the United States should be considered rabid unless proved otherwise, particularly in highly endemic countries. Patients should be advised to wash the wound immediately and seek medical care as soon as possible.

**Typhoid Fever**

Typhoid vaccine is recommended for travel to regions highly endemic for *Salmonella typhi*, such as the Indian subcontinent, parts of South America, and Africa. Travel to Mexico, Haiti, North Africa, and Iran is considered intermediate risk. Protective efficacy of the typhoid vaccines ranges from 46% to 96%. The oral typhoid vaccine is not currently available in the United States. The older parenteral vaccine (Wyeth-Ayerst) had pronounced local and systemic adverse effects and has not been available in the United States since December 1999. The available typhoid vaccine (injectable Typhim Vi [Pasteur Merieux Connaught]) is better tolerated and has a protective efficacy of 64% to 72%. A new combined vaccine against typhoid fever and hepatitis A is being studied, and thus far it has been found to be safe and efficacious.

**Yellow Fever**

Yellow fever is a mosquito-borne viral illness characterized by fever, upper gastrointestinal bleeding, hepatitis, and encephalitis. The yellow fever vaccine must be administered at least 10 days before travel to endemic areas, such as equatorial parts of South America and Africa. It is a required vaccine for entry into some countries with ongoing epidemics. In other uninfected countries, a person must show proof of vaccination if traveling directly from an endemic or infected country in order to prevent introduction of the disease into the local vector. Since the yellow fever vaccine is a live-attenuated viral vaccine, it is contraindicated in immunocompromised patients, pregnant or lactating women, and infants younger than 6 months. Among immunocompromised persons, the risk of the actual disease vs the disease from the vaccine must be as-
sessed. Persons with HIV or AIDS who have minimal immunosuppression (CD4 count >200 cells µL) can receive the vaccine. However, the immune response may be lower among these people compared with immunocompetent persons. Recently, vaccine strain disease was reported among elderly (>75 years) persons receiving the yellow fever vaccine.19

**Routine Vaccines**

Routine childhood vaccinations should be reviewed for all persons and boosters administered as necessary. In addition, pneumococcal and influenza vaccine recommendations should be reviewed. An influenza vaccine is advised for persons at high risk of influenza complications, such as those taking a cruise, traveling to the Southern Hemisphere during April through September, or traveling to tropical countries any time because influenza is nonseasonal in such areas, and for persons older than 50 years with or without underlying medical problems. Persons with no previous history of primary varicella should be tested and vaccinated if nonimmune.

**MALARIA PREVENTION**

Annually, 300 to 500 million cases of malaria occur in more than 100 countries, and the numbers are increasing because of climate and other factors. Malaria among travelers is also increasing. *Plasmodium falciparum* contributes to most malaria-related deaths. Approximately 30,000 travelers from industrialized countries contract malaria annually.19 In the United States, about 1000 cases are reported annually to the Centers for Disease Control and Prevention; however, some may be unreported.20 The risk of acquiring malaria depends on the duration of stay, geographic areas visited, risk behavior (extensive exposure to outdoors and rural areas and inadequate personal protective measures), and the type of prophylaxis taken. Among American travelers, the risk of *P falciparum* malaria is highest among those traveling to Africa. Imported *P falciparum* malaria has an overall mortality rate of 4% and is considerably higher in patients with severe disease. The mortality rate also increases with age (30% in persons >70 years). Fatal imported malaria is associated with nonadherence with or inappropriate chemoprophylaxis, delay in seeking medical attention, or delayed diagnosis or treatment.21 Thus, travelers must seek appropriate pretravel advice for this preventable condition.

The choice of malaria chemoprophylaxis depends on area of travel, activities planned, and the individual’s factors. Chloroquine-resistant *P falciparum* malaria now dominates most endemic regions except Mexico, the Caribbean, Central America, and parts of the Middle East. *P falciparum* malaria resistant to chloroquine and mefloquine has emerged along the borders of Thailand, Cambodia, and Myanmar (Burma). Resistance to sulfadoxine-pyrimethamine is common among *P falciparum* in the Amazon basin, Southeast Asia, and in parts of Africa. Over the past decade, chloroquine-resistant *P vivax* malaria has been identified in Myanmar, Guyana, Papua New Guinea, and other areas of Southeast Asia.

Chemoprophylaxis is recommended for all urban and rural travelers to sub-Saharan Africa (except most areas of South Africa), the Indian subcontinent, areas of Oceania (Far Southeast Asia including Papua New Guinea, Irian Jaya, and Vanuata), and Haiti, as well as for rural and nonresort exposures in Southeast Asia, Central and South America, and parts of Mexico, North Africa, and the Dominican Republic. Antimalarial prophylactic drug options based on drug-resistance patterns are listed in Table 2.

Chloroquine-susceptible *P falciparum* malaria is now limited to Central America. Chloroquine is well tolerated, has minimal adverse effects (gastrointestinal upset being most common), and is safe for infants and pregnant women. Retinal toxicity is rare, even with long-term (years) weekly administration of chloroquine.

Mefloquine is the most widely used antimalarial prophylactic agent and is more than 90% efficacious.22 It is given weekly as 250-mg salt, starting 1 to 2 weeks before travel, weekly while in the endemic area, and for 4 weeks after return. Mefloquine is recommended for chloroquine-resistant malaria (both *P falciparum* and *P vivax*). Adverse

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### Table 2. Malaria Prophylaxis

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Chloroquine-susceptible areas*</th>
<th>Chloroquine-resistant areas*</th>
<th>Chloroquine- and mefloquine-resistant areas*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First choice</td>
<td>Chloroquine</td>
<td>Mefloquine</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>First alternative</td>
<td>Mefloquine</td>
<td>Doxycycline</td>
<td>Atovaquone plus proguanil</td>
</tr>
<tr>
<td>Other alternatives</td>
<td>Sulfadoxine-pyrimethamine, doxycycline</td>
<td>Atovaquone plus proguanil</td>
<td>...</td>
</tr>
</tbody>
</table>

*See text for areas of distribution.
effects of mefloquine are mostly dose related. At prophylactic doses, most adverse effects are mild and self-limited, including nausea, diarrhea, strange dreams, dizziness, insomnia, and headache. Nightmares, anxiety, and depression can occur, but drug discontinuation is necessary in less than 1% of prophylactic mefloquine users. Severe neuropsychiatric reactions (psychosis, seizures) are reported to occur infrequently (approximately 1 in 10,000 to 1 in 13,000 persons) with prophylactic doses. Contraindications to its use include history of seizures, arrhythmias, psychiatric illness, and a previous reaction to mefloquine. Mefloquine is safe for pregnant women in the second and third trimester and for children who weigh more than 5 kg.

Doxycycline (100 mg/d) is the alternative to mefloquine and is an equally efficacious prophylactic agent against mefloquine-resistant \textit{P falciparum}. Major drawbacks of doxycycline are daily administration (leading to rapid loss of antimalarial prophylaxis with missed doses), nausea, vomiting, occasional esophageal ulceration, photosensitivity, yeast superinfections, and inability to use in pregnant women and in children younger than 8 years. Advantages of doxycycline include quick onset of antimalarial activity, allowing administration for imminent entry into an endemic area, and some antibacterial effect against traveler’s diarrhea (TD).

In 2000, the FDA approved atovaquone plus proguanil (250 mg/100 mg) (Malarone) for malaria prophylaxis and treatment in children and adults. Overall efficacy of Malarone for prophylaxis of \textit{P falciparum} malaria is 95% to 100% compared with placebo in semi-immune populations. In nonimmune persons, the protection is 96% (68%-99%) for \textit{P falciparum} malaria and 81% (45%-94%) for \textit{P vivax} malaria. It is well tolerated, with mild gastrointestinal side effects being the most common adverse events. The main drawbacks are daily administration and cost, currently about $5 a day. For prophylaxis, Malarone is taken daily: initiated 2 days before the traveler enters an endemic area, taken daily while there, and taken for 7 days after return. It has some causal activity, ie, it is effective against the liver phase of the plasmodium life cycle. The prophylactic use of Malarone is best limited to travelers to chloroquine-resistant malaria areas who have contraindications to mefloquine and doxycycline or to travelers going to endemic areas for brief (2-7 days) trips. Malarone is also used for self-treatment of suspected malaria if a person develops malaria while in a foreign country and prophylaxis was inadequate, as long as the prophylaxis taken was not Malarone. It is the drug of choice for self-treatment in areas where sulfadoxine-pyrimethamine resistance is common.

In some countries, another alternative to mefloquine or doxycycline is a combination of chloroquine with proguanil. However, it is not recommended because it is not as efficacious as the previously mentioned drugs. Proguanil is not available in the United States.

New antimalarials being studied for prophylaxis include tafenoquine, primaquine, etaquine, and azithromycin.

Use of personal protection measures, such as insect repellents, mosquito bed nets, and long-sleeved clothing and pants, should be reinforced to persons traveling to tropical countries not only for malaria protection but also for other insect-borne diseases. Formulations with 30% to 35% of DEET \((N,N\text{-diethyl-3-methylbenzamide})\) are recommended for adequate protection and minimal toxic adverse effects. Of importance, patients should be reminded that sunscreen is applied first and then the insect repellent because insect repellents can decrease the efficacy of the sunscreen by 20% to 30%. Plant-based insect repellents are not as effective as those containing DEET. Persons traveling into highly endemic areas or forests or those planning extensive outdoor exposure may be advised to use a clothing insecticide called permethrin. Permethrin impregnation of clothes is effective for 2 weeks despite laundering. Combined use of skin insect repellent and permethrin can decrease insect bites substantially.

**TRAVELER’S DIARRHEA**

Traveler’s diarrhea is common during international travel, especially travel to developing countries. It accounts for 64% of all illnesses affecting tourists, and the most common cause is bacterial. Enterotoxigenic \textit{Escherichia coli}, \textit{Campylobacter}, \textit{Salmonella}, and \textit{Shigella} account for most cases. Enterotoxigenic \textit{E coli} occurs in 17% to 70% of TD in South America. Rotavirus, \textit{Campylobacter}, and \textit{Salmonella} occur more often in the winter. Parasitic etiology is not common in short-term travelers. \textit{Cyclospora} is commonly noted in Nepal. A pathogen is not identified in 40% of TD cases. In a study of 17,000 travelers, the incidence of TD was 26% to 50% in Central and South American countries, 40% in Africa, 50% in Nepal, and 10% in Europe. The highest incidence of diarrhea occurs among children 2 years of age and younger and among adults 20 to 30 years of age. Although TD does not result in mortality, approximately one third of travelers are confined to bed, 40% have to change their itinerary, and less than 1% are hospitalized. Host factors predisposing to TD include immunosuppression, hypochlorhydria, inflammatory bowel disease such as ulcerative colitis and Crohn disease, and young age.

Prevention of TD includes education regarding risk factors and food and water hygiene. Risk factors include drinking tap water, iced drinks, or fresh juices; eating food in small restaurants or from vendors; eating locally made ice cream or flavored ices; and eating fruit not personally peeled by the traveler.
Patients with immunosuppression such as transplant recipients, those taking corticosteroids, and those with chronic medical problems such as inflammatory bowel disease may require prophylactic antibiotics to prevent TD. Prophylactic medications for TD include bismuth subsalicylate, antibiotics, or probiotic agents. Bismuth subsalicylate is effective in preventing 65% of cases of TD.29 However, the disadvantages of bismuth subsalicylate include the number of doses needed, problems among patients taking aspirin or an anticoagulant, and black discoloration of the tongue and stool. Additionally, bismuth subsalicylate can decrease bioavailability of doxycycline by 30% to 50%, an important fact to remember in patients taking doxycycline for malaria prophylaxis. Use of antibiotics for TD prophylaxis is reserved for a select population, as described previously. Prophylactic ciprofloxacin has been shown to prevent 90% of cases of TD.29 Other antibiotics used for prophylaxis include trimethoprim-sulfamethoxazole and doxycycline. However, both have limited efficacy because of increasing resistance of diarrheal pathogens worldwide.

Self-treatment of TD consists of fluid replacement, with or without use of an antibiotic, and an antimotility agent if needed. Fluid replacement is important, especially if the person has frequent episodes of diarrhea, is in hot climates, or has a fever. For mild diarrhea, drinking any fluids may be sufficient. However, for watery TD, fluids containing electrolytes and glucose are required. This can be accomplished by drinking water reconstituted with widely available oral rehydration salts approved by the World Health Organization. Proper use of loperamide should be explained to minimize the risk of complications developing with its use. Loperamide is effective for symptomatic relief of TD. For travelers with moderate diarrhea (4 to 5 stools a day, inability to participate in the planned activity), self-treatment using an antibiotic with loperamide is advised. However, those with severe diarrhea, ie, diarrhea associated with fever (temperature >38.3°C) or bloody stools, should be advised to take an antibiotic for 3 to 5 days without loperamide. Bloody diarrhea may represent shigellosis-producing E coli 0157 or shigellosis. In such situations, antimotility agents can be potentially harmful and are best avoided. Travelers with severe, persistent, or bloody diarrhea should seek care at a local medical facility for appropriate evaluation.

Fluoroquinolones are the most commonly used empirical self-treatment of TD. Antibiotics reduce the duration of diarrhea from 3 to 5 days to fewer than 1 to 2 days.30 Studies have shown that ciprofloxacin with loperamide is more effective than a 3-day course of ciprofloxacin alone and much more effective than a single dose of ciprofloxacin.30 A single 750-mg dose of ciprofloxacin can be used for mild to moderate diarrhea. However, if TD continues, a 3- to 5-day course should be completed. Other fluoroquinolones, such as levofloxacin, norfloxacin, or ofloxacin, can be used. Worldwide fluoroquinolone resistance among Campylobacter, Salmonella, and Shigella may result in the failure of empirical treatment. The best alternative to the fluoroquinolones for self-treatment of TD is azithromycin. In 2 clinical trials, azithromycin had 82% cure rates for multidrug-resistant Shigella compared with 89% with ciprofloxacin.31 For TD from other pathogens, azithromycin had a cure rate of 86% compared with 100% with ciprofloxacin. Azithromycin was more effective against Campylobacter TD than ciprofloxacin (62% vs 48%).32 Trimethoprim-sulfamethoxazole, doxycycline, or oral cephalosporins have limited activity due to increasing antimicrobial resistance.

CONCLUSIONS
Although it has associated risks, travel to any part of the world can be safe with adequate pretravel preparation. The key to appropriate pretravel advice is to obtain details of the itinerary, review the medical history, and be aware of current recommendations. Special risk groups, such as pregnant women, immunocompromised hosts, small children, and elderly persons with medical problems, may require additional preparation.

REFERENCES
Questions About Medical Advice for International Travelers

1. Which one of the following viral vaccines is contraindicated in organ or bone marrow transplant recipients?
   a. Japanese encephalitis vaccine
   b. Hepatitis A vaccine
   c. Hepatitis B vaccine
   d. Yellow fever vaccine
   e. Meningococcal vaccine

2. Which one of the following is the most common preventable cause of mortality while traveling?
   a. TD
   b. Malaria
   c. Yellow fever
   d. Cardiovascular diseases
   e. Accidents

3. Which one of the following is contraindicated for concurrent administration with γ-globulin?
   a. Measles-mumps-rubella vaccine
   b. Japanese encephalitis vaccine
   c. Hepatitis A vaccine
   d. Hepatitis B vaccine
   e. Inactivated poliomyelitis vaccine

4. In which one of the following areas of the world is doxycycline the drug of choice for malaria prophylaxis?
   a. Borders of Thailand, Cambodia, and Myanmar
   b. Borders of Panama and Costa Rica
   c. South Africa
   d. Venezuela
   e. Borders of Brazil and Argentina

5. Which one of the following vaccines is contraindicated in a person with a history of urticaria who is traveling to rural Cambodia for 3 months?
   a. Measles-mumps-rubella vaccine
   b. Japanese encephalitis vaccine
   c. Hepatitis A vaccine
   d. Hepatitis B vaccine
   e. Yellow fever vaccine

Correct answers:
   1. d, 2. e, 3. a, 4. a, 5. b