REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will consider when referral to a travel medicine clinic is appropriate

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Risks of travel, benefits of a specialist consult

ABSTRACT

If patients are planning to travel to developing countries, their primary care physicians can counsel them on various medical risks, especially traveler's diarrhea, and offer to update their immunizations. However, travelers to areas where there is a risk of malaria, yellow fever, or other tropical diseases should be referred to a specialist.

KEY POINTS

Primary care physicians should be proficient in the basic pretravel consult, including advice on immunizations and travel-related health problems.

Based on the traveler's itinerary, the physician should consult current government recommendations for pretravel preparation at www.cdc.gov/travel/destinations/list.aspx.

Drug-resistant malarial strains are on the rise in many areas of the world.

To enter many African and South American countries, travelers need official certification by a specialist that they have been vaccinated against yellow fever.

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Before going abroad to areas that might pose a risk to their health, most people ought to visit their primary care physicians and many should be referred to a specialist in travel medicine.

In this article, we review the key elements of the pretravel consult as it relates to the prevention and self-treatment of the most common diseases that pose health risks for travelers. We also give guidelines for when to refer patients to a specialist.

WHY PRIMARY CARE PHYSICIANS NEED TO KNOW TRAVEL MEDICINE

International travel to exotic locations is becoming more popular. In 2008, one out of five Americans traveled abroad, and 38 million visits were to developing countries where there are significant health risks for travelers.[1]

One third to one half of travelers to developing countries experience some kind of illness while abroad, most commonly diarrhea or upper respiratory infections, which typically lead to 3 lost days during a 2-week trip.

These illnesses are often preventable and self-treatable.[2] Unfortunately, studies suggest that most travelers do not seek adequate medical advice, and that when they do they often fail to complete courses of medication.[3,4]

All these factors point to the need for primary care providers to become proficient in the pretravel consult and, if necessary, to refer patients to travel specialists and clinics.

WHY REFER TO A TRAVEL CLINIC?

In one study of travelers to areas of high risk for malaria or hepatitis A, 42% of those who

consulted only their family doctor became ill, in contrast to 22% of those who attended a travel medicine clinic.[4]

As a rule of thumb, anyone traveling to an area where malaria is endemic should be referred to a specialist, as should anyone at risk of yellow fever or typhoid fever. As many as 8 per 1,000 travelers may return from areas of risk infected with malaria.[5]

Long-term travelers and people who will spend time in urban slums or rural or remote regions have an even greater need for referral to a travel clinic, as they are at higher risk of exposure to Japanese encephalitis, cholera, epidemic meningitis, dengue fever, and rabies.[6]

THE PRETRAVEL CONSULT: ESSENTIALS

A pretravel consult ought to be scheduled 4 to 6 weeks in advance of the trip, since many vaccines require that much time to induce immunity, and some require a series of shots.

Unfortunately, many patients who think of arranging a travel consult make the appointment at the last minute, and some come with an incomplete knowledge of their travel plans. However, even without enough advance notice, a consult can be beneficial.

Travelers sometimes change their itineraries in-country or engage in unanticipated risky behaviors. A good travel medicine physician tries to anticipate even these unplanned risks and changes in itinerary.

Where is the traveler going? When? For how long?

The pretravel consult starts with a detailed discussion of the patient's itinerary. It needs to include length, dates, and location of travel, as well as anticipated activities and accommodations.

A remarkable number of travelers come to consults not knowing the names of specific countries they will visit, perhaps saying only that they are going to Africa or South America. An accurate itinerary is indispensible, as appropriate medical advice is highly specific to country and region. The incidence and geographic distribution of many travelers' diseases change over time, and this requires physicians to consult the most current information available.

TABLE 1

Indispensible resources for current travel health information

US Centers for Disease Control and Prevention: country- and province-specific health advisories (www.cdc.gov/travel)

World Health Organization, International Travel and Health, current edition (www.who.int)

US Department of State current travel warnings (travel.state.gov/travel/cis_pa_tw/tw/tw_1764.html)

Tropical countries, in general, are risky, but each pathogen has a unique distribution that may vary between urban and rural areas or by season. Detailed, up-to-date information is available from the US Centers for Disease Control and Prevention (CDC) (www.cdc.gov) for individual countries and for specific provinces and locations within those countries. Physicians should consult the CDC whenever advising a patient preparing to travel.[7]

How is the traveler's current health?

Next, physicians need to evaluate the traveler's current health. Some considerations:

Several immunizations cannot be given to the very young, the elderly, or those who are immunocompromised.

The greatest risk of death to travelers is not from tropical diseases but from cardiovascular disease, which according to one study is responsible for half of deaths abroad.[8] Patients with heart disease or other known health concerns need to be counseled to avoid activities that will put them at further risk. The advice applies especially in situations such as remote travel or even cruises, where prompt emergency medical care may be difficult or impossible to obtain.

A third to a half of travelers to developing countries lose 3 days of a 2-week trip due to diarrhea or other infections

People infected with human immunodeficiency virus (HIV) face discriminatory travel prohibitions in 74 countries.[9]

Foreign-born travelers who are visiting family and friends in developing countries may have lost their immunity to local pathogens and thus can be more at risk because they are not prepared to take necessary health precautions.

TABLE 2

Key elements of the pretravel consult

Obtain a detailed itinerary
Evaluate the patient's health status
Update routine immunizations
Give preventive counseling
Refer to a specialist for malaria, yellow fever, other tropical diseases
Give prescriptions and vaccinations

Also, a significant number of travelers become infected but develop illnesses only after they return, so a posttravel visit may be necessary.[6]

Prescription and even over-the-the-counter drugs may be difficult or impossible to obtain in foreign countries, and ample supplies should be brought along.

Is the traveler up to date on routine immunizations?

A number of infectious diseases that have been controlled or eradicated in North America through regular childhood immunizations are still endemic in many remote areas and developing countries. All travelers should be up to date on routine immunizations, including those for measles-mumps-rubella, tetanus, polio, meningitis, and hepatitis A and B.

Boil it, cook it, peel it, or forget it: still the rule

Polio. A one-time polio booster is recommended for adults traveling to certain countries or areas of the world.

Meningitis vaccine is now routinely given to young people, but adult patients may need it before they travel.

Hepatitis A is contracted through fecal contamination of food and water. Common sources are foods prepared in an unhygienic manner, raw fruits and vegetables, shellfish, and contaminated water.

Immunization is with two doses of an inactivated viral vaccine, either Havrix or Vaqta. The vaccine can be given to patients age 1 and older. Two doses separated by 6 to 12 months provide life-long immunity. Vaccination is recommended for all travelers except those going to Canada, Western Europe, Japan, Australia, or New Zealand.

Hepatitis B vaccine is also now routinely given to young people, but it should be offered to travelers planning to stay more than 1 month and to long-term expatriates. This vaccine is also recommended for travelers who may be exposed to blood or body fluids, who are contemplating sexual activity or tattooing in the host country, or who may require medical or dental care while traveling, as well as for adventure travelers or travelers to remote regions.

The vaccination is given in a three-dose schedule at 0, 1, and 6 months. For protection against both hepatitis A and B, the vaccine Twinrix can be used on the same schedule as for hepatitis B. An accelerated schedule of 0, 7, and 21 days with a booster at 12 months allows completion of the entire series in 4 weeks, thus putting completion of vaccination before travel in the same time frame as other vaccines in a series, such as those for rabies and Japanese encephalitis.

PREVENTIVE COUNSELING

In addition, travelers going abroad should be advised on measures to avoid diarrhea, insect-vector diseases, accidents, excessive exposure to the sun, altitude sickness, and other risks their itineraries may expose them to.

Avoiding traveler's diarrhea

Traveler's diarrhea is by far the most common health problem experienced abroad. It is prevalent in Mexico, where 20 million visits by Americans occur each year. A quarter to half of visitors to developing countries contract traveler's diarrhea and, on average, lose 2 to 3 days of their business trip or vacation.[3,10] The disease therefore imposes not only discomfort but also financial losses on travelers, especially business travelers.

Though many pathogens may be responsible, the most common one is *Escherichia coli*, usually transmitted by human fecal contamination of food or drink. Preventive measures against *E coli* are the same as for other foodborne and waterborne infections, such as hepatitis A, cholera, and typhoid fever.

The rule for avoiding traveler's diarrhea may be summarized by the CDC-coined phrase, "boil it, cook it, peel it, or forget it." Simple, written advice is most likely to be followed.[6] Thorough boiling or cooking kills bac-

teria in contaminated food, and food should be served steaming hot. Travelers should only eat foods they know have been well cooked, declining cold dishes like salsa or casseroles. They should avoid tap water for brushing teeth or in the form of ice cubes and should stick to drinking bottled beverages, preferably carbonated ones. No matter how appetizing a salad looks, travelers should avoid eating fresh fruits and vegetables unless they are sure that they were peeled under sanitary conditions. Simply eating at a high-priced restaurant is not a guarantee of uncontaminated food. Before meals or any hand-to-mouth contact, hands should be washed in soap and water or with sanitizers.

Travelers to remote areas may wish to acquire filtering devices, chlorine, or iodine for treating water. A combination of filtering and iodine treatment is most effective.

While this advice is undoubtedly wise, the evidence shows that, in practice, most travelers fail to take all precautions, and the benefits of this counseling have been difficult to demonstrate.[11] Therefore, physicians should prescribe drugs for prophylaxis and self-treatment of traveler's diarrhea during travel.

Bismuth subsalicylate (Pepto-Bismol) taken as two tablets or 2 oz of liquid 4 times a day while traveling may reduce the risk of diarrhea by one half, though it should be avoided by patients with contraindications to aspirin.[3,6]

Self-treating traveler's diarrhea

Proper hydration is crucial, since dehydration can worsen and prolong symptoms.

Ciprofloxacin (Cipro) 500 mg orally two times daily for 3 to 5 days is effective.

Azithromycin (Zithromax) 500 mg daily for 3 to 5 days may be better in some areas of Southeast Asia, where fluoroquinolone-resistant bacteria are prevalent.

Rifaximin (Xifaxan), a nonsystemic antibiotic, is another option. The dosage is 200 mg three times a day for 3 days.

Avoiding insect bites

Malaria, yellow fever, tickborne encephalitis, and dengue fever are all transmitted by insect bites. Often the best protection is to avoid being bitten.

Bites can be avoided by using insect repellants containing diethyltoluamide (DEET) or picardin. If the traveler is going to be out in the sun, he or she should apply sunscreen first, then DEET on top of that. *Anopheles*, which transmits malaria, is a night-biting mosquito and may be avoided by staying in screened areas at dusk and dawn and by using bed netting. Permethrin, an insecticide, can be applied to clothing and mosquito netting.

Other things to avoid

Accidents are the second most common cause of death in travelers (after cardiovascular disease), accounting for as many as one-third of deaths.[9] Several studies indicate road accidents are the major cause of accidental death, but also significant are drowning and air crashes. Travelers should be advised that transportation in developing countries is often more dangerous than at home. Seaside vacationers should be aware of the dangers of riptides and other threats to swimmers and should obey warnings posted at beaches.

Sexually transmitted diseases. When appropriate, physicians should warn travelers about the dangers of contracting HIV and other sexually transmitted diseases, especially in sub-Saharan Africa.

Sunburn, dehydration. Travelers should regularly use sunscreen and should remain hydrated.

Crimes against and involving tourists are a serious threat in many places, including some popular destinations. All of the 100,000 young people traveling to Mexico each year for spring break should read the US Department of State warnings against crime and possible arrest in that country.[12] Travelers who are victims of crimes in foreign countries should contact their national consulate as soon as possible. The US Department of State issues advisories on countries where there is danger to travelers because of political turmoil, crime, or other causes.[13]

Motion sickness and jet lag can be ameliorated by proper hydration, avoiding caffeine, and using a scopolamine patch or dimenhydrinate (Dramamine).[1]

Causes of death in travelers, in order of frequency:
- **Cardiovascular disease**
- **Accidents**
- **Tropical diseases**

When traveling to wilderness areas

Wilderness and expedition medicine is a complex subset of travel medicine.[14] All travelers

TABLE 3

How to find a travel clinic locally and internationally

International Association for Medical Assistance to Travelers, http://www.iamat.org

International Society of Travel Medicine, http://www.istm.org

US Centers for Disease Control and Prevention "find-a-clinic," http://www.cdc.gov/travel/content/find-clinic.aspx

need to understand the risks of whatever activities they undertake.

Mountain climbers and skiers have to contend with altitude sickness and frostbite. Scuba divers have the risks of decompression sickness, barotrauma, and hazardous marine life. Travelers on expeditions may have to deal with predatory animals, exotic parasites, and ethnic or political violence. People who participate in these activities should do so only when they are properly certified and educated in the associated health risks.

Ordinary tourists should enjoy safe adventures with well-established tour agencies and venues and should be cautioned against activities that expose them to dangers they may not be prepared to confront.

A remarkable number of travelers do not know which countries they will visit

Insurance, evacuation, and emergency care

Health insurance often does not pay for preventive travel medicine. Unfortunately, cost can be a factor in immunizations and other health care. The cost of most travelers' medications and vaccinations is generally comparable to that of other immunizations. The exceptions are two specialized vaccines—ie, for Japanese encephalitis ($1,000 or more for a full course) and for rabies, which can cost considerably more. Pricing by different providers can vary widely.

Travelers, especially those who are pregnant, elderly, disabled, or immunocompromised or who have preexisting diseases, need to review their insurance policies to make certain that care in foreign countries is covered. If not, evacuation insurance can be purchased at a relatively modest cost.

Pretravel counseling and immunization are legitimate expenses for business travelers. Visitors to developing countries and other remote areas should research which emergency medical facilities are available (TABLE 3).

TRAVEL TO AREAS OF MALARIA

While many travelers can confidently consult their primary care provider, those traveling to places where malaria is prevalent should be referred to a physician with a thorough and current knowledge of the incidence of drug-resistant strains of the disease and other complex issues in travel medicine. Short-term and long-term travelers are often approached differently, but a travel medicine consult should be obtained for any patient traveling to a region with malaria risk.

Geographically, the areas where most of the other diseases described below pose a risk overlap with the areas where malaria is endemic, and specialists at a travel clinic will know, based on the traveler's itinerary, what additional immunizations are recommended or required. Malaria is endemic in much of South America, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, parts of the Middle East, the west coast of Mexico, and southern China (FIGURE 1).

Malaria kills up to 3 million each year

Malaria, caused by the *Plasmodium* parasite, transmitted by the night-biting *Anopheles* mosquito, is responsible worldwide for between 1 and 3 million deaths annually, mostly of children in sub-Saharan Africa.[15] Every year about 1,500 Americans are diagnosed with malaria and, on average, 10 die.[6]

Nearly all cases of malaria and deaths from it are preventable. Prophylaxis is imperative for travelers to affected areas, as is preventive counseling. Based on the patient's itinerary, the physician needs to thoroughly research potential exposure to drug-resistant strains before choosing which antimalarial regimen to prescribe.

Malaria causes symptoms of anemia, fever, or nausea and, without treatment, can lead to coma and death. Because two of the five strains, *P vivax* and *P ovale*, can remain dormant in an infected person's liver for up to 1 year and, in rare cases, up to 4 years after travel, it is imperative that a returned traveler who

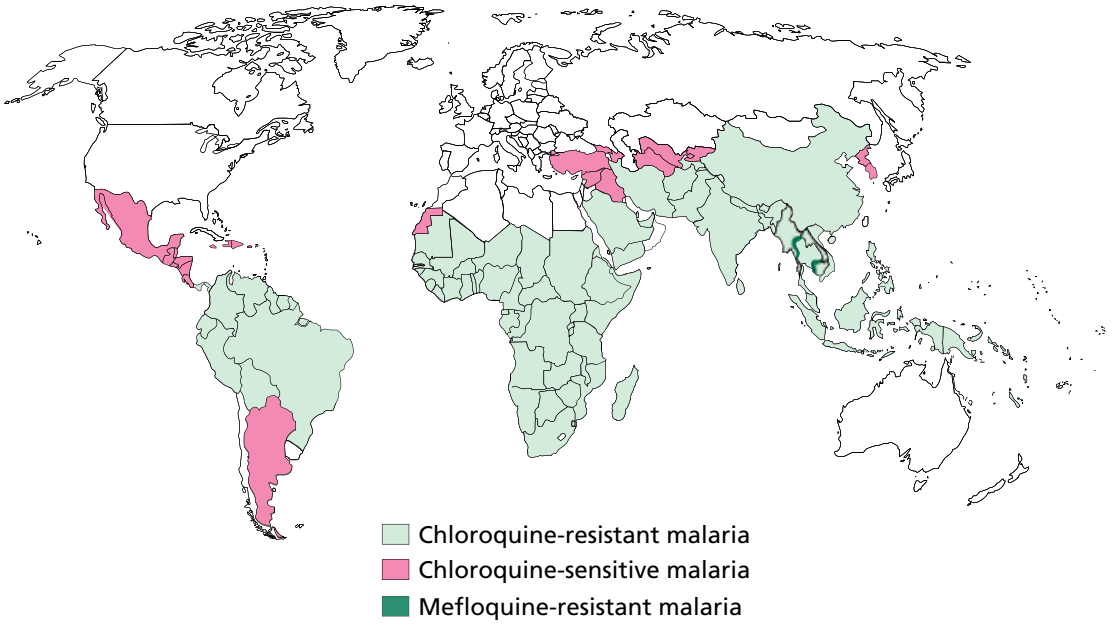

FIGURE 1. Global distribution of malaria, and reported areas of drug resistance.

BASED ON DATA FROM THE US CENTERS FOR DISEASE CONTROL AND PREVENTION

experiences flu-like symptoms seek medical attention and inform the treating physician of the need to screen for malarial infection. The primary means of diagnosis is through microscopic examination of the blood.

No malaria vaccine, but prophylactic drugs are available

Unlike many of the illnesses discussed below for which vaccines are available, malaria prophylaxis requires the active participation of the patient in completing a course of medication, so noncompliance becomes a risk.

A number of prophylactic drugs are available. The choice depends on the locally resistant strains.[16]

Chloroquine (Aralen), the traditional malarial prophylactic drug, is still effective against many strains, primarily in Central America and some areas of the Middle East. The dosage is 500 mg once a week, started 1 week before travel and continued for 4 weeks after return to the United States.

Mefloquine (Lariam) is dosed at 250 mg weekly. The patient should be carefully screened for depression, anxiety, and other mood disorders. Even the report of bad dreams or nightmares should make a patient be considered a poor candidate for this medication. The patient should start taking this drug 3 weeks before travel to provide time to assess for adverse effects and, if necessary, to change the antimalarial regimen. Mefloquine is taken weekly while traveling and is continued for 4 weeks after return.

Doxycycline (Vibramycin) is an antibiotic. As an antimalarial prophylactic, it is taken as 100 mg daily beginning 2 days prior to travel and continuing while travelling and for 4 weeks after return.

Atovaquone-proguanil (Malarone) prevents infection at the blood stage and in the liver. It is well tolerated and is begun 2 days before travel. It is taken daily while traveling and daily for 1 week after return.

Those traveling to where malaria is prevalent should be referred to a specialist

Yellow fever

Yellow fever is spread by the day-biting *Aedes aegypti* mosquito. It is prevalent in equatorial Africa and South America (FIGURE 2).

Immunization is required for entry to more than 20 African nations and is recommended for those traveling to most of South America. The only physicians who can give this vaccine are those who have approval from their state health department and have been issued an official stamp, used on the World Health Organization (WHO) yellow

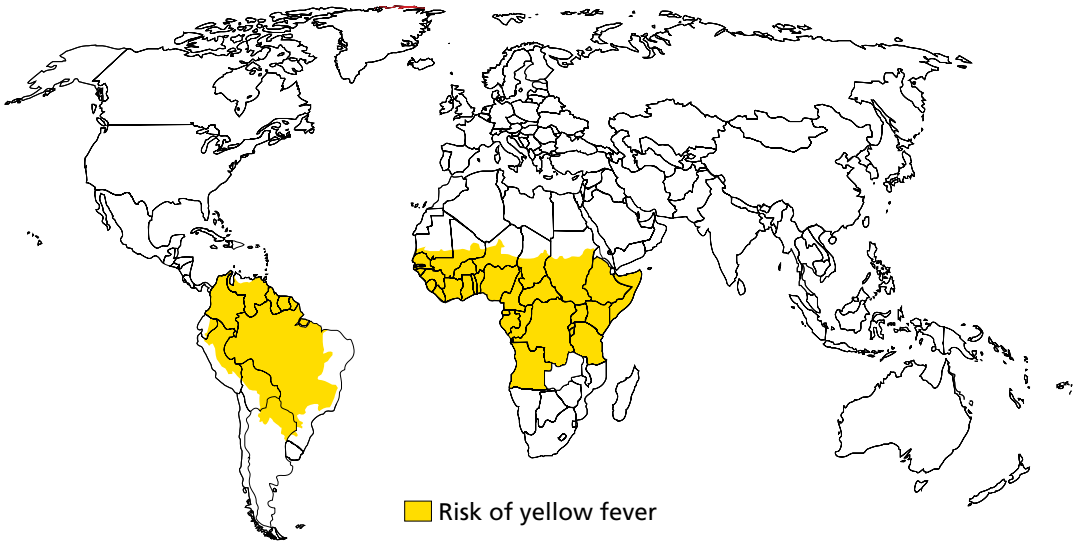

FIGURE 2. Approximate global distribution of yellow fever (2007 data).

FROM THE US CENTERS FOR DISEASE CONTROL AND PREVENTION

fever vaccination card. Several countries require the card for entry from places where yellow fever is present. For any multicountry travel involving at least one area where yellow fever is endemic, the entire itinerary needs to be reviewed to make sure all legal entry requirements are met. The WHO maintains a current list of these requirements.[17] If there is any doubt, it is generally best to refer and certify the traveler.

Yellow fever vaccine is live-attenuated and should not be given to immunocompromised patients

Referral should be timely. The vaccine must be given 10 days prior to entry into a country where yellow fever is endemic; it is valid for 10 years.

The yellow fever vaccine is a live-attenuated vaccine and should not be given to infants younger than 9 months old, adults over age 60 who are not properly screened and informed, or pregnant women. Immunocompromised patients are excluded from receiving this vaccine, as are patients taking immunosuppressant drugs and patients with thymus disorders such as myasthenia gravis. Patients who have had chemotherapy must wait 3 months before being vaccinated. Those on steroids (eg, prednisone 20 mg or more daily) must wait until 2 weeks after cessation of steroids to receive this vaccine. Patients who cannot be vaccinated should be advised not to travel to areas with a high risk of yellow fever.

Women contemplating pregnancy should use contraception for 28 days after yellow fever vaccination. Children younger than 9 months and the elderly are at higher risk of adverse reactions from the vaccine, either neurotropic or viscerotropic disease that mimics yellow fever infection. It is possible for physicians to write a medical waiver of contraindication to vaccination for patients who should not be immunized.

Typhoid fever

Typhoid fever can occur anywhere in the world, but it is endemic in the tropics. Worldwide, an estimated 200,000 deaths occur each year from typhoid fever, and 400 cases are reported annually in the United States, most commonly acquired by travelers to the Indian subcontinent.[18] One study indicates that 95% of infected travelers had not been vaccinated, and a significant number returned with drug-resistant strains.[19]

Typhoid fever is caused by ingestion of *Salmonella typhi* bacteria. It causes a febrile illness with infection of the digestive tract and reticuloendothelial system.

Prevention is the same as for traveler's diarrhea: drink no local water and eat nothing raw. Vaccination can be provided in an intramuscular shot or a series of oral capsules. The shot is well tolerated and is valid for 3 years. The capsule provides 5 years of immunity. Vaccination is recommended for people going to areas with a high prevalence of typhoid fever,

such as India, and for people planning to spend more than 2 weeks in an area where typhoid is endemic, as well as for adventurous eaters.

SOME TRAVELERS NEED MORE PROTECTION

Some travelers need more preventive measures than typical tourists or other short-term visitors. Long-term visitors or travelers to remote or other high-risk areas (eg, adventure travelers, relief workers, mission workers) may need, in addition to the measures described above, measures against Japanese encephalitis, rabies, cholera, epidemic meningitis, and dengue fever.

Japanese encephalitis

Japanese encephalitis virus is transmitted by mosquito bite. The major regions where it is endemic are rural India and Southeast Asia, most typically in areas with rice paddies and pig farms. Travelers at risk are expatriates to these areas, those planning a long stay, and remote-adventure travelers.

The vaccine JE-VAX is given as a series of three shots, on days 0, 7, and 28. Another vaccine, Ixiaro, is given in a series of two shots, on days 0 and 28.

Patients who are allergic to bee or wasp stings should not be vaccinated. The patient should remain in the office for 30 minutes after each dose to permit observation for mild anaphylactic reactions such as angioedema and urticaria, and should complete the series 10 days before travel to allow for observation for delayed reactions. Patients must weigh the risk of contracting the disease against the high cost of the vaccine.

Rabies

Rabies is a potential risk anywhere in the world except in Western Europe and Australia. Because the vaccine is costly, it is generally not given for prophylaxis except for travelers certain to have contact with animals, especially the major vectors, ie, dogs, cats, bats, and monkeys.[20] Counseling about vigilance in avoiding animal contact and not promoting interaction through feeding wild animals should be part of any pretravel consult. Rabies, once acquired, is fatal.

The patient should be instructed on proper care of a bite from a potential rabies source and told to halt travel and seek medical attention. The wound should be cleaned with soap and water for 15 minutes to remove any saliva and virus from the soft tissue; this has proven to be effective in animal experiments. A virucidal such as benzalkonium chloride (Zephiran) or aqueous iodine should then be put in the wound.

Preexposure vaccination is done in a three-dose series (given on days 0, 7, and 21–28). The patient should complete the series and adhere to the dosing schedule as closely as possible. It may be necessary to find a source of vaccine for the patient once he or she has arrived in the destination country.

If bitten, travelers without preexposure vaccination must find a source of vaccine and human rabies immune globulin (HRIG) before continuing on their trip. Postexposure treatment is 20 IU/kg of HRIG infiltrated around the wound to wall off the virus inoculation site. If the wound is in a digit or small area and not all of the HRIG can be given, then the remaining HRIG is given intramuscularly at a site distant from the vaccine site. If the patient has multiple bites, the HRIG should be diluted so it can be infiltrated around all wounds. The HRIG should be given immediately or within 7 days of beginning the vaccine series once a source is located. Later treatment than this can interfere with the patient's ability to mount an immune reaction.

Rabies vaccine is initiated at the same time as HRIG and is given on days 0, 3, 7, 14, and 28. The CDC may soon change the schedule to allow for only four postexposure shots, but this has not yet been done as of this writing.

The patient vaccinated before exposure requires only booster doses of rabies vaccine at days 0 and 3.

Long-term travel to high-risk areas requires protection against Japanese encephalitis, rabies, cholera, epidemic meningitis, dengue fever

Cholera

Cholera is an epidemic gastrointestinal disease historically responsible for millions of deaths. It is endemic in most tropical countries, especially in Africa and southern and southeastern Asia.[21]

High-risk patients, most often those working with refugees and disaster victims in endemic areas, should receive the traveler's diarrhea and cholera vaccine Dukoral, which immunizes against *Vibrio cholera* and enterotoxogenic *E coli*.

The vaccine, which is not available in the United States but is available abroad, is given as two oral doses 1 week apart for adults and three oral doses for children ages 2 to 6, and the second dose must be given 7 days before travel; this provides protection for 6 months.

At various times, the above vaccines have been in short supply. Travel medicine consults should be obtained for proper identification of the at-risk traveler for efficient use of any possibly limited vaccine.

Epidemic meningitis

The vaccine against epidemic meningitis is now routinely given in the United States to adolescents at the age of 12 or upon entry to college or the military. The fatality rate from the disease is 10%.

Meningococcal disease transmission peaks in the sub-Saharan "meningitis belt" in the dry season of December through June. Travelers to these areas at these times should be immunized. Travelers planning close contact with the local population (eg, health care workers) should be immunized. Patients traveling to Saudi Arabia for Hajj in Mecca must be immunized for meningitis for entry to the country during this time. The vaccine must be given within 3 years of entering the country and not less than 10 days before.

Dengue fever

Dengue fever is a flavivirus transmitted through the *Aedes aegypti* mosquito. No vaccine is available for dengue fever, so for now the only advice is to avoid insect vectors.

There are four closely related but serologically different dengue viruses that provide only weak cross-protection. In fact, previous infection with one serotype in a traveler then infected with another poses a risk of dengue hemorrhagic fever.

Because of inattention to public sanitation, this virus and its mosquito vector have reemerged in areas where they were once eliminated. The viral infection is a risk for the traveler to both urban and rural areas in the Americas, Southeast Asia, and Africa. The Pan American Health Organization has seen the number of reported dengue cases increase from 66,000 in 1980 to 700,000 in 2003.[22]

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