REVIEW ARTICLE

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Medical Considerations before International Travel

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In 2015, international tourist arrivals in all countries exceeded 1.2 billion persons. In 2014, the total number of arrivals in countries with emerging markets nearly surpassed the number in developed countries (www.e-unwto.org/doi/book/10.18111/9789284416899). Depending on the destination, 22 to 64% of travelers report some illness; most of these illnesses are mild and self-limited, such as diarrhea, respiratory infections, and skin disorders.[1-4] Some travelers return to their own countries with preventable life-threatening infections.[5] Yet 20 to 80% of travelers do not seek pretravel health consultation.[6] Data about the effect of pretravel advice are limited, although such advice has had a positive effect on the prevention of malaria.[7] Travelers visiting friends and relatives in their country of origin constitute the group with the highest morbidity, especially from malaria and typhoid; this group requires special approaches to illness prevention and education.[8,9]

Persons who are planning to travel to other countries often ask their health care providers for information about preventive interventions. Nonspecialists can provide information and care to healthy adults traveling to common destinations by following protocols such as those offered in this review. Advice from a specialist[10] is of benefit for persons who are planning high-risk or adventure travel, those who are immunocompromised[11-13] or have underlying chronic disease, those who are planning to live abroad for a long time, women who are pregnant[14] or plan to become pregnant soon, young children, and travelers with complicated itineraries.

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STRUCTURED APPROACH TO THE PRETRAVEL CONSULTATION

During the medical appointment that precedes international travel, a structured and sequenced approach (Fig. 1) is the most efficient way for the physician and other clinicians to address the necessary preventive and educational interventions. An individualized risk assessment that takes into consideration the exact place-by-place itinerary and factors that are particular to the prospective traveler should be performed first. Immunizations, malaria considerations, and travelers' diarrhea should be covered next. Since appropriate behavior by the traveler can substantially reduce the risk of many specific travel-related health and safety problems, the remainder of the consultation should consist of education about behavioral and self-treatment strategies (Table 1). Protection against insects and strategies for ensuring the safety of food and water are the most important. It is advisable to provide printed instructions (in lay language) because many of these measures will be initiated much later, at the traveler's destination, and time constraints may preclude detailed discussion in the office. Individual risk factors vary greatly, and not all travelers to a given country will receive the same pretravel recommendations.

VACCINATIONS

Table 2 provides data on dosing, route of administration, need for boosters, and possible accelerated regimens for vaccines administered before travel. The discussion below, which focuses on indications for each vaccine in the context of travel, should be used in conjunction with the information in the interactive graphic (available with the full text of this article at NEJM.org), which shows the geographic distribution of major travel-related diseases.

VERIFICATION AND UPDATE OF ROUTINE VACCINES

Routine vaccines are those that need to be readministered at regular intervals or series that need to be completed in a healthy adult without plans for international travel who has no medical or behavioral risk factors (Fig. 1). For many vaccine-preventable diseases, the risk of acquisition is increased in developing countries.

Importations of measles and mumps have resulted in travel-related outbreaks.[45] International travelers born in the United States after 1956 must either have received two documented doses of the measles–mumps–rubella (MMR) vaccine or have evidence of immunity. Many persons born in the United States before 1970 have never received the MMR vaccine, and many born in the 1970s have not had the second dose, a recommendation that was made in 1990. Adults who have never received the tetanus–diphtheria–acellular pertussis (Tdap) vaccine should be given a dose of Tdap, regardless of the time elapsed since the last tetanus–diphtheria vaccination. Widespread outbreaks of measles, mumps, and pertussis are currently ongoing in developed and in developing countries.[46] Persons born in the United States after 1979 must either have received two documented doses of varicella vaccine or have evidence of immunity.

Influenza is the most common vaccine-preventable disease among travelers,[47] including passengers on cruise ships. Because of year-round circulation of influenza virus in tropical and subtropical regions and an influenza season that occurs in winter in temperate regions in the southern hemisphere (which is summer in the northern hemisphere), all travelers to the tropics at any time of year and to temperate destinations where it is currently winter should have received the most current influenza vaccine available in their home country before traveling.[48] Healthy travelers who are 65 years of age or older should be up to date on pneumococcal vaccination.

ROUTINE TRAVEL VACCINES

Hepatitis A vaccine is indicated for every nonimmune traveler because of foodborne transmission of the disease and an estimated incidence of 1 case per 5000 travelers per month. A single dose of hepatitis A vaccine given any time before travel, even on the way to the airport, provides more than 94% seroprotection. The current adult population in the United States generally has little to no immunity to hepatitis A virus.

Since most adults who were born in the United States have not been immunized with the hepatitis B vaccine, vaccination should be considered for all travelers, although predicting exposure to blood or body fluids during travel is difficult. In the absence of the usual risk factors for hepatitis B virus infection, long stays and close contact with residents in local communities may lead to more opportunities for injuries, the need for medical or dental care, sexual contact, and tattooing or body piercing.[49] The relative likelihood of future international travel warrants consideration of a vaccine that confers lifelong protection.[50]

South Asia has the highest risk of typhoid and paratyphoid fevers (see the interactive graphic), particularly for travelers visiting friends or relatives.[51] Vaccination against *Salmonella enterica* serovar Typhi, a foodborne bacterial pathogen with increasing rates of multidrug resistance globally, may be considered for persons traveling to other areas where typhoid and paratyphoid fevers are endemic and sanitary conditions are suboptimal. The efficacy of either available vaccine against *S.* Typhi is only 60 to 80%.[52] Adherence to the oral vaccine regimen may be as low as 70%.

TRAVEL VACCINES FOR CERTAIN DESTINATIONS

Some vaccines are indicated solely because of a specific regional itinerary (interactive graphic), regardless of whether the traveler has a specific risk behavior. Meningococcal and poliomyelitis vaccines are routine childhood vaccines that may require boosters in adult travelers with certain itineraries.

Yellow fever vaccine is necessary for personal protection during travel to some tropical coun-

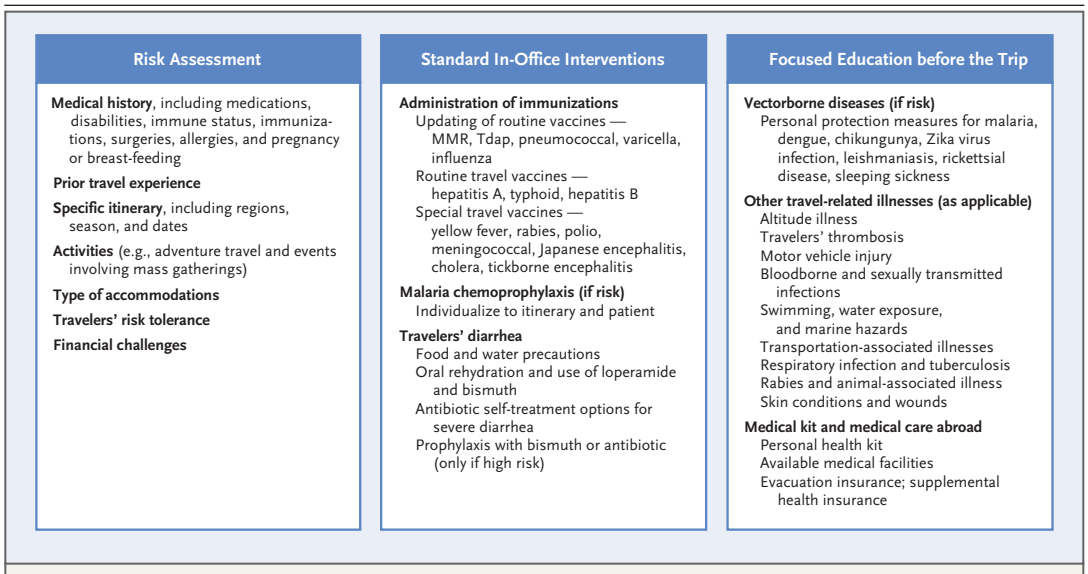


Figure 1. Structured Approach to Medical Consultation before International Travel.

The consultation, conducted 4 to 6 weeks before departure, consists of an assessment of risk, interventions performed in the office (Tables 2 and 3), and education for the trip. MMR denotes measles–mumps–rubella, and Tdap tetanus–diphtheria–acellular pertussis.

tries in South America and sub-Saharan Africa where the acquisition of yellow fever is a risk. Separately, under the 2005 International Health Regulations (IHR), yellow fever vaccination may also be required for travelers arriving in countries where there is no local transmission of yellow fever from countries where yellow fever is endemic. That way, competent vector mosquitoes in the receiving country will be protected from acquiring and transmitting the virus. A specialized travel medicine clinic or a medical facility designated by the Centers for Disease Control and Prevention (CDC) as a yellow fever vaccination center is best situated to interpret nuanced requirements and recommendations, and referral to such a facility is recommended (wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search). Neither yellow fever vaccine nor any other vaccine is currently required for readmission to the United States. First doses of yellow fever vaccine, but not booster doses, have been associated with rare but severe or fatal adverse events (overall rate, 1 event per 250,000 doses)[40,53]; the risk is highest among persons over the age of 60 years and increases with advancing age.

Until recently, the yellow fever vaccine was uniformly considered to provide protection for 10 years.[41,54] Currently, the CDC recommends that for healthy, nonpregnant adults, 10-year boosters should be given to travelers planning a long stay in any area where there is a risk of yellow fever transmission, to all travelers spending any amount of time in high-risk areas such as West Africa, and to all persons traveling to an area with a current outbreak. On the basis of an analysis by CDC experts showing that 92% of vaccine recipients have virus-neutralizing antibody at 10 years and 80% have the antibody at 20 years, the CDC has concluded that most healthy persons can be considered to have long-term immunity.[42] For the purposes of the IHR, a single dose of yellow fever vaccine is sufficient for entry to any country. However, some countries may still consider the vaccine protective for only 10 years. Decisions about yellow fever vaccination must be based on the risk–benefit ratio for the individual traveler, with consideration of the itinerary and any specific country-entry requirements.

Because the supplies of postexposure biologic agents are unreliable in low-resource countries, administering rabies vaccine before travel simplifies any postexposure management.[55,56] A preexposure rabies series is indicated for travelers planning a long stay in areas of Latin America, Asia, or Africa where the rabies threat is constant. However, at least one study has shown

Table 1. Important Practices for Reducing Disease Risk during International Travel.

Arthropod-borne illnesses (malaria, dengue, chikungunya, Zika virus infection, Japanese encephalitis, leishmaniasis, rickettsial disease)

Wear clothing that exposes as little skin as possible.

Apply a repellent containing *N,N*-diethyl-3-meta-toluamide (DEET; concentration, 30–35%) or picaridin* (concentration, ≥20% for tropical destinations).[15,16]

Treat clothing with permethrin (or another pyrethroid) when traveling in an area of very high risk for malaria or other mosquito-borne or tickborne diseases.

Apply repellant according to the time of day and type of insects to be avoided.

- Mosquitoes that transmit malaria (anopheles mosquitoes) are generally night biters.
- Mosquitoes that transmit organisms causing dengue, chikungunya, Zika, and yellow fever (aedes mosquitoes) are generally day biters with peak biting times in the early morning and late afternoon.
- Mosquitoes that transmit West Nile virus and Japanese encephalitis (culex mosquitoes) are most active at dusk and again at dawn.

Sleep under a permethrin-impregnated bed net, if you are not sleeping in a sealed, air-conditioned room, in areas where there is a high risk of malaria or Japanese encephalitis.

Perform a full body check at least once a day in areas where tickborne disease is a risk.

Wear light-colored (not blue), heavyweight clothing in areas where African trypanosomiasis is a risk; DEET is generally ineffective.

Respiratory infection and tuberculosis

Practice hand hygiene diligently.

As much as possible, avoid crowded public transportation and crowded public places that are poorly ventilated.

Move away from anyone with a persistent or intense cough.

Screen domestic workers for tuberculosis.

If you are planning a long stay, have a tuberculosis skin test before departure, once per year thereafter, and on returning home.

Avoid excessive outdoor activity in areas of heavy air pollution during hot or humid times of the day.

Rabies and animal-associated illness

Never assume that an animal is free of rabies.

Do not handle or feed pets or unknown animals (especially dogs and monkeys).

If bitten, scratched, or licked on broken skin, clean the wound immediately with soapy water and seek postexposure treatment for rabies (even if rabies vaccination was completed before exposure) or herpes B virus (transmitted by monkey bites).

Consider minimizing going running or bicycling in high-risk rabies areas.

Travelers' diarrhea

Eat well-cooked, hot foods.

Always wash hands before eating and after using the toilet.

Avoid eating food from market stalls and street vendors.

Avoid tap water and drinks or ice made from tap water, unless advised of their safety by a reliable source.

Avoid buffets where food covers or fly controls are not used and where food has been sitting out for many hours.

Avoid high-risk food such as shellfish, raw or undercooked foods, unpasteurized dairy products, mayonnaise, cold sauces or salsas, fruits you haven't peeled yourself, and salads.

Swimming, water exposure, and marine hazards

Heed posted warnings and avoid beaches that are not patrolled.

Do not swim alone or after dark and do not walk on any beach after dark.

Avoid use of alcohol or mind-altering drugs while engaging in water sports.

Avoid water where there is sewage contamination or algae are present.

Avoid any exposure (e.g., rafting, swimming, or wading) to water known to be infected with schistosomiasis (bilharzia).[17]

SCUBA dive only with personnel certified by the Professional Association of Diving Instructors (PADI) or the National Association of Underwater Instructors (NAUI) and use equipment only from PADI- or NAUI-certified dive operators.

Follow established timetables for air travel after diving.†

In tropical waters, watch for jellyfish, sea urchins, and corals.

Decline water transportation in vessels without personal flotation devices or life jackets.

Wear appropriate footwear when walking, wading, or swimming to avoid injury and exposure to parasites and poisonous plants and animals.

Hikers, bikers, and adventure travelers with exposure to water or wet environments may consider prophylaxis with 200 mg of doxycycline once per week (or 100 mg daily if used for concomitant malaria prophylaxis) in developing countries where there is a substantial risk of leptospirosis.[18]

Since sand may be contaminated in areas frequented by animals, sit on a towel, blanket, or piece of clothing if a chair or hammock is not available. Shake out all fabrics thoroughly after use.

Eating predatory reef fish (barracuda, jackfish, grouper, or snapper), even if well cooked, may cause ciguatera poisoning.

Eating mackerel, tuna, bonito, mahi-mahi, or amberjack may cause scombroid poisoning.

Transportation-associated illnesses

To prevent barotrauma, chew or swallow during ascents and descents; feed young children or provide them with a pacifier during ascents and descents.

To prevent motion sickness, move to the center of the vehicle; fix your gaze on still, distant objects; and increase airflow across your face.

Treatment with scopolamine patches or tablets or with meclizine, initiated before departure, may minimize symptoms of motion sickness during a cruise or travel on rough roads. Ondansetron has not been shown to prevent nausea due to motion sickness.

If you are traveling east across more than three time zones, you can expose yourself to light early in the day, advancing the body clock so that it will be synchronized with the new time zone. Conversely, if you are traveling west, you can expose yourself to light at dusk and in the early part of the evening, delaying the body clock so that it will be synchronized with the new time zone. Crossing more than eight times zones in either direction reverses the time for morning or evening light.

Zolpidem and possibly melatonin offer some benefit in adapting to local sleeping cycles.

Medical kit and medical care abroad

Carry a compact medical kit that includes the following:

- Simple first-aid supplies, such as bandages, gauze, hemostatic gauze, antiseptic, antibiotic ointment, butterfly bandages, skin glue, and splinter forceps.
- A thermometer and antipyretic agents.
- Antifungal creams, cough and cold remedies, antacids, hydrocortisone cream, and blister pads.
- Condoms.
- Sunscreen and insect repellent.

Adequate medical and evacuation insurance should be arranged, even for short trips.

Contact information for hometown medical providers, health insurance carriers, and a medical assistance company should be accessible at all times.

If you are planning a long stay, integrate into the local expatriate medical infrastructure (i.e., become familiar with the doctors, hospitals, pharmacies, and ambulance services that cater to foreigners) immediately after arrival so that you can seek competent care for any illness early in its course.

If you have cardiac disease, carry a copy of a recent electrocardiogram on a portable USB drive or make sure the electrocardiogram can be accessed on the Internet.

Carry all medicines in labeled prescription bottles.

Carry a list of medical conditions, allergies, and medications with dosages.

Table 1. (Continued.)

Bloodborne and sexually transmitted infections	**Skin conditions and wounds**	**Prevention of motor vehicle and other injuries**
Use condoms in all sexual encounters; unprotected casual sex, whether with local residents or fellow travelers, always poses a high risk.	Broken skin may become infected and lead to serious problems. Any bite, cut, or broken skin should be cleaned with safe water. Apply an antiseptic solution or spray.	Avoid overcrowded transportation.
Avoid sexual relations with commercial sex workers.	Increasing pain, redness, or discharge from a cut suggests a spreading infection and may require antibiotic treatment. Seek medical help if this occurs.	Do not drink and drive.
Understand that inhibitions are diminished when traveling away from the social constraints of home; excessive use of alcohol and recreational drugs can influence behavior and encourage unintentional risk exposure.	In Africa, all clothes dried outdoors should be ironed to avoid cutaneous myiasis due to the tumbu fly.	Keep automobile doors locked and windows closed at all times, if possible.
Avoid skin-perforating procedures (acupuncture, piercing, or tattooing).	Hats and sunscreen are mandatory in the tropics. Sunscreen should always be applied to skin before an application of DEET.	Seek vehicles with seat belts, which may result in extra expense; decline vehicles without seat belts unless no other choice is available.
Unless you are in a life-threatening situation, avoid invasive medical or dental procedures in unaccredited medical facilities; request proof of accreditation by Joint Commission International or other international bodies.		Decline transportation in vehicles with worn tires, worn brakes, or inoperative lights.
Consider carrying disposable needles, syringes, and sutures for remote travel.		Avoid driving at night or alone, and never drive outside urban areas after dark.
		Never drive a motorcycle or scooter abroad; wear a helmet if you are a passenger.
		Use a helmet when bicycling, skiing, or skating.
		If you are planning a long stay, arrange for a locally purchased mobile phone to be in the vehicle, if possible.

* Picaridin products available in the United States with 20% concentration include Natrapel (Tender Corporation) and Picaridin Insect Repellent (Sawyer). Picaridin is also known as icaridin in some countries. Picaridin, unlike DEET, has a pleasant smell and does not dissolve plastic materials.
† The time from the end of the dive until the boarding of an aircraft is generally between 12 and 24 hours, depending on the type of dive.

little correlation between travel duration and the likelihood of a potential rabies exposure.[57] For short-term travel, high-risk groups include joggers, adventure travelers, bikers, hikers, cave explorers, young children, and frequent travelers.

Japanese encephalitis is endemic in rural Asia near rice paddies and pig farms and presents rare but unpredictable risks for travelers.[26] Vaccination is recommended for the following travel plans: a long stay in a rural area where Japanese encephalitis is endemic, expatriation in any country where the disease is endemic, a short-term stay involving extensive unprotected outdoor exposure (e.g., adventure travel) during transmission season in a rural area where the disease is endemic, or a short-term stay in an area with a local epidemic of the disease.

Because meningococcal epidemics occur frequently in the "meningitis belt" in sub-Saharan Africa (see the interactive graphic) during the dry season, updated vaccination with the quadrivalent ACYW-135 meningococcal vaccine is indicated. In view of the high risk of disease transmission, Saudi Arabia requires proof of vaccination within the previous 3 years for pilgrims undertaking the Hajj or Umrah pilgrimage.[33] Meningococcal B vaccine is not indicated for travel.

Efforts to eradicate poliomyelitis have been successful in most countries, and the disease remains endemic only in Pakistan and Afghanistan (www.polioeradication.org/Keycountries.aspx). Adults traveling to these two countries or to countries that have outbreaks of vaccine-derived poliomyelitis and who have previously completed a primary vaccine series should receive one booster dose in adulthood.[58]

Cholera vaccine, approved in 2016 by the Food and Drug Administration (FDA) for licensure in the United States, is recommended for aid workers, refugee workers, and health care workers exposed to displaced populations in areas where cholera is endemic or epidemic (see the interactive graphic).[43] Since the 2010 earthquake in Haiti, cholera has been endemic in that country as well as in the Dominican Republic and Cuba.

Cell-culture–based vaccines are available in regions of Europe and Asia where tickborne encephalitis is endemic (see the interactive graphic) but are unavailable in the United States.[44] Travelers planning to live in or to pursue extensive outdoor activities (hiking and camping) in countries where tickborne encephalitis is highly endemic should consider obtaining vaccination at the destination, if time allows.

Table 2. Vaccines That Should Be Available during Pretravel Consultation.*

Disease and Vaccine Type	Adult Dose	Route of Administration	Standard Schedule	Accelerated Schedule for Series	Estimated Duration of Protection	References
Available in the United States						
Cholera: live attenuated bacteria	1 sachet	Oral	Single dose	NA	3–6 mo	Jackson and Chen[19]
Hepatitis A: inactivated virus	1 ml	Intramuscular	2 doses: day 0 and at 6–12 mo†	Available in combined hepatitis A and B formulation: days 0, 7, and 21 and at 12 mo‡	>20 yr (seropositivity); >40 yr (antibody modeling)	ACIP,[20] Theeten et al.[21]
Hepatitis B: recombinant hepatitis B surface antigen	1 ml	Intramuscular	3 doses: day 0 and at 1 mo and 6 mo	Available in combined hepatitis A and B formulation: days 0, 7, and 21 and at 12 mo‡	30 yr	Mast et al.,[22] FitzSimons et al.[23]
Combined hepatitis A and B: inactivated virus and recombinant viral antigen	1 ml	Intramuscular	3 doses: day 0 and at 1 mo and 6 mo	4 doses: days 0, 7, and 21 and at 12 mo‡	>15 yr (data on monovalent vaccines support long-term protection from anamnestic response)	Van Damme et al.[24]
Influenza						Grohskopf et al.[25]
Inactivated virus or recombinant, trivalent or quadrivalent	0.5 ml (0.1 ml for intradermal administration)	Intramuscular (intradermal formulation for age 18–64 yr)	1 dose	NA	1 yr	
Live attenuated virus, quadrivalent	0.1 ml in each nostril	Intranasal spray	1 dose	NA	1 yr	
Japanese encephalitis: inactivated virus, derived from cell culture	0.5 ml	Intramuscular	2 doses: days 0 and 28	2 doses: days 0 and 7	1–2 yr after initial dose; >6 yr if boosted at 1–2 yr	Fischer et al.,[26] CDC,[27] Jelinek et al.,[28] EMA,[29] Paulke-Korinek et al.,[30] Rabe et al.[31]
Measles–mumps–rubella: live attenuated virus	0.5 ml	Subcutaneous	2 doses: day 0 and at 4 wk		Lifelong, after 2 doses total at any time in life	McLean et al.[32]
Meningococcal disease — quadrivalent ACYW-135: bacterial polysaccharide, conjugated§	0.5 ml	Intramuscular	1 dose (off-label for those >55 yr old)	NA	3–5 yr	Cohn et al.,[33] Baxter et al.[34]
Poliomyelitis: inactivated virus	0.5 ml	Subcutaneous	Single dose in those who received primary childhood series	NA	Lifelong, after primary series plus a booster in adulthood (age ≥18 yr)	Wallace et al.[35]

Rabies: inactivated virus, derived from cell culture	1 ml	Intramuscular (0.1 ml intradermally may be considered for use off-label)	3 doses before exposure: days 0, 7, and 21–28	NA	Patient should be informed that 2 additional doses are required on days 0 and 3 after each possible rabies exposure; no boosters are otherwise indicated	Manning et al,[36] Wieten et al.[37]
Tetanus–diphtheria–acellular pertussis (Tdap) or tetanus–diphtheria (Td): toxoid, protein antigen	0.5 ml	Intramuscular	1 dose in those who received primary childhood series	NA	10 yr; 5 yr for travelers at high risk for wounds (e.g., adventure travelers, those engaging in activities that may result in injuries, and travelers to places where medical care is substandard)	CDC[38]
Typhoid						Jackson et al.[39]
Bacterial cell-wall polysaccharide	0.5 ml	Intramuscular	1 dose	NA	2–3 yr	
Live attenuated bacteria	4 capsules	Oral	4-capsule series, one every other day		5 yr	
Yellow fever: live attenuated virus	0.5 ml	Subcutaneous	1 dose	NA	10 yr for high-risk patients (in some countries, protection is considered to be long-term)	Gershman and Staples,[40] WHO,[41] Staples et al.[42]
Not currently available in the United States						
Cholera: inactivated whole-cell bacteria combined with recombinant B subunit of cholera toxin	1 sachet	Oral	2 doses, 1 wk apart	NA	2 yr	WHO[43]
Tickborne encephalitis: inactivated virus derived from cell culture	0.5 ml	Intramuscular	3 doses: day 0, at 1–3 mo, and at 5–12 mo	3 doses: days 0, 7, and 21 (protective 7 days after dose 3)	3 yr	WHO[44]

* Consideration may be given to stocking human papillomavirus and herpes zoster vaccines, as well as other vaccines (e.g., pneumococcal vaccines) for travelers with chronic illnesses, since the travel consultation is an excellent opportunity to update routine immunizations. CDC denotes Centers for Disease Control and Prevention, EMA European Medicines Agency, FDA Food and Drug Administration, NA not applicable, and WHO World Health Organization.

† The Advisory Committee on Immunization Practices (ACIP) recommends that the first dose of hepatitis A vaccine and IgG be administered in travelers older than 40 years of age who are departing in less than 14 days for a destination where hepatitis A is endemic; however, this is rarely done in practice and is not included in any non-U.S. national guideline.

‡ The initial accelerated schedule, with doses on days 0, 7, and 21, provides protection for up to 1 year; the additional dose at 12 months provides long-term protection similar to that with the standard schedule.

§ The ACIP recommends use of the conjugate vaccine in persons 55 years of age or older who need repeated meningococcal vaccination, including travelers who may need another dose in 5 years or more.

Immunizations can and should be given at the same time and in any combination. If, for some reason, two live viral vaccines (Table 2) are not administered on the same day, the second vaccine should be administered 1 month after the first. Minimum intervals between vaccine doses in a series must be respected, although with the exception of rabies vaccine, an interval of 4 or fewer days before the next scheduled injection is acceptable. There is no maximum interval between doses of a primary vaccine series; an interrupted series can be resumed beginning with the dose that is overdue.

MALARIA PREVENTION

An average of 1500 imported cases of malaria are reported annually in the United States (www.cdc.gov/malaria/references_resources/mmwr.html). A malaria vaccine designed for young children in Africa is not appropriate for use in nonimmune adult or pediatric travelers.

Estimates of the risk of malaria among travelers not receiving chemoprophylaxis range from 3.4% per month of travel in West Africa to 0.34% per month of travel on the Indian subcontinent and 0.034% per month of travel in South America. Transmission, and in particular high transmission, is quite focal. The lifetime range of flight of an anopheles mosquito, which bites only from dusk to dawn, is 1 km. Daytime travel to a known focal area of disease transmission, with departure to a malaria-free area to sleep at night, confers a negligible risk. Nighttime exposure to mosquitoes for even a few hours in a high-transmission area may result in infection. Mosquito-bite prevention is a primary approach to protection from malaria (Table 1). The decision about whether to prescribe chemoprophylaxis should also take into account the distribution and type of malaria in the area of the planned itinerary and the possibility of deviation from that itinerary, as well as the traveler's personal tolerance for what may be an epidemiologically insignificant level of risk for the trip.

A general malaria-distribution map (see the interactive graphic), as well as resources for information on the current, country-specific microepidemiology of malaria, including the CDC Travelers' Health website, should be immediately accessible to clinicians prescribing malaria prophylaxis (Table S1 in the Supplementary Appendix, available at NEJM.org). Dosing and the properties of antimalarial agents that affect the choice of drug are presented in Table 3, and in Table S2 in the Supplementary Appendix; other considerations have been reviewed previously.[59] In practice, daily atovaquone–proguanil is preferable to doxycycline or mefloquine for short-term travel (<3 weeks) and is most widely prescribed.[6] Atovaquone–proguanil is associated with mild side effects and may be stopped just 7 days after the traveler has departed from an area of possible exposure. Longer courses appear to be safe but are costly. In most areas with malaria, atovaquone–proguanil, doxycycline, and mefloquine are equally effective (>95%) in preventing malaria, but disadvantages (e.g., more reports of adverse events in persons taking doxycycline or mefloquine, as well as resistance to mefloquine) may hamper their use (Table S2 in the Supplementary Appendix).[60] Chemoprophylaxis may be started well before departure (3 to 4 weeks for mefloquine) if there is concern about possible side effects of any drug. Weekly administration of mefloquine, if side effects are not an issue, is preferable for long-term travel because of lower cost and convenience. Chloroquine, an older drug that is also administered weekly, is highly effective in the few areas that are known to have exclusively chloroquine-sensitive parasites.

If parasites of a malaria species that transmits a relapsing form of malaria (*Plasmodium vivax* or *P. ovale*) have entered the liver as a result of exposure during travel, relapses may occur months or, in rare cases, up to a few years after the traveler has returned home, since the primary prophylactic drugs discussed above are ineffective against dormant forms (hypnozoites) in the liver. Primaquine can be used to prevent relapsing malaria after the traveler has left the area where *P. vivax* or *P. ovale* is endemic. A relapse can occur even if the traveler received primary chemoprophylaxis and did not have an initial clinical episode of malaria during or soon after the actual exposure. Prophylaxis against primary attacks of malaria with the use of primaquine instead of one of the drugs noted above can be considered when exposure is limited to areas where only *P. vivax* is endemic. This strategy has the advantage of simultaneously reducing the risk of relapses.

For stays in areas with very low rates of malaria transmission, some authorities — notably,

in Europe — advise that only a standby drug be carried for self-treatment, to be taken in the event that symptoms suggestive of malaria occur and there is no access to competent medical care or to a facility in which a competent assessment of a blood smear for malaria can be performed within 6 to 12 hours.[61] This strategy is especially attractive for long-stay travelers. A full course of atovaquone–proguanil or artemether–lumefantrine is recommended. In the United States, the CDC recommends continuous prophylaxis, as noted above, for travelers at risk but also suggests that treatment doses of these drugs may be carried for the treatment of confirmed malaria in areas where appropriate drugs for treatment may be unavailable or where there is concern about substandard or counterfeit medication.

Travelers should be instructed in writing to continue taking antimalarial drugs for the appropriate period after the last possible exposure, with the explanation that malaria can still occur despite chemoprophylaxis and that three blood smears or rapid diagnostic tests for malaria are mandatory for any febrile illness occurring within 3 months after travel. Travelers to areas where false positive tests for malaria are common in clinical practice (e.g., Africa) should be reminded to continue taking the prophylactic drug even if they receive a diagnosis of malaria. Prevention of malaria in travelers residing in malarious areas for 6 months or longer presents complex problems leading to reduced adherence to chemoprophylaxis.[62]

OTHER ARTHROPOD-BORNE DISEASES

Some infections are preventable only by antiarthropod measures (Table 1). Dengue accounts for up to 2% of cases of illness in travelers who have returned from countries where dengue is endemic and is the most common systemic febrile illness; severe dengue is very rare in travelers.[3,4,63] At least 10 dengue vaccine candidates are being evaluated in clinical trials; a vaccine recently licensed in several countries where dengue is endemic is unsuitable for use in travelers, and no antiviral drugs are available.[64] Chikungunya[65] and Zika virus infection[66] are emerging illnesses that are characterized by a rash (see the interactive graphic); they are clinically similar to dengue and occur in many overlapping areas. Chikungunya may result in debilitating arthritis. Zika virus infection is considered to cause microcephaly and other neurologic malformations in newborns and the Guillain–Barré syndrome.[66] Rickettsial diseases, transmitted by ticks, mites, and fleas, are emerging in travelers.[67] *Rickettsia africae* has been documented as the second most common cause of fever in travelers returning from sub-Saharan Africa, after malaria.[3]

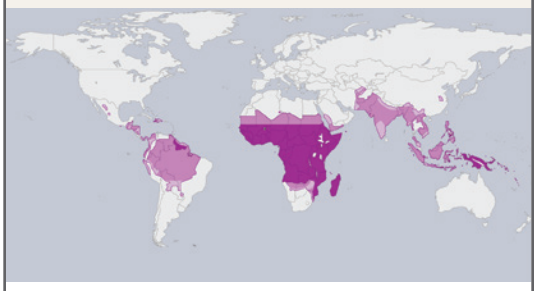
TRAVELERS' DIARRHEA

Travelers' diarrhea, defined as three or more unformed stools plus at least one accompanying symptom in a 24-hour period during travel and for up to 7 days after travel, is most frequently bacterial.[68] Protozoa account for less than 5% of cases, and in adults, detection of norovirus or rotavirus is increasing. The mean duration of travelers' diarrhea, even if untreated, is 4 to 5 days. Despite pretravel advice (Table 1), travelers' diarrhea affects 10 to 40% of travelers.[68] Treatment with a proton-pump inhibitor may increase the risk of travelers' diarrhea.[69] Chronic postinfectious sequelae of travelers' diarrhea have been reported in 3 to 17% of travelers in small studies.[70]

Standard self-treatment for travelers' diarrhea consists of oral hydration together with an antimotility medication (usually loperamide), an antisecretory medication, or both for symptomatic relief. The addition of a single dose of a self-administered quinolone (500 mg of ciprofloxacin or levofloxacin) or azithromycin (1 g) can be considered for more rapid cessation of severe diarrhea. Three days of therapy with a quinolone or azithromycin at a dose of 500 mg per day may also be used. Azithromycin is the only option for persons traveling to Southeast Asia, India, or Nepal, where several common enteric pathogens are resistant to quinolones. The benefit of either antibiotic class should be weighed against the known side effects and drug interactions. Antibiotic prophylaxis for travelers' diarrhea is not recommended except in rare circumstances.

Antibiotic use for travelers' diarrhea has been associated with intestinal colonization with antibiotic-resistant bacteria in returning travelers,[71-73] but the use of loperamide alone has not.[74] In South Asia, studies have shown that 80% of travelers with travelers' diarrhea who were treat-

Travel-Related Medical Considerations.



The image shows the geographic distribution of malaria, with darker purple indicating greater concentration of disease.

For further information on the geographic distribution of diseases and behavioral strategies that can reduce the risk of disease when traveling, see the interactive graphic, available at NEJM.org.

An interactive graphic is available at NEJM.org

ed with antimicrobial agents acquired extended-spectrum β-lactamase–producing Enterobacteriaceae,[71-73] and in one study, 10% of carriers were still excreting the organisms 3 months after their return.[72] The potential for spread is of concern, although the public health implications are still unclear. A balanced approach should be sought to enable travelers to treat themselves for an often debilitating, if not life-threatening, problem while abroad, especially in developing countries where available local medications and health care may be substandard. Beyond bloody diarrhea, diarrhea with fever, or dysentery, the definition of severe diarrhea is subjective. However, knowing that antibiotic use contributes to antibiotic-resistant infections may encourage travelers to adhere to preventive measures and recommendations for managing symptoms.

ALTITUDE ILLNESS

Common high-altitude destinations for leisure travel include La Paz, Bolivia; Cuzco, Peru; Lake Titicaca, on the border of Bolivia and Peru; Quito, Ecuador; Lhasa, Tibet; and Mount Kilimanjaro, Tanzania. Whether the ascent is made by motor vehicle or airplane, acute mountain sickness occurs in at least 25% of people who ascend rapidly, instead of gradually over a period of several days, to an altitude of 2500 m or higher and occurs in most people who ascend rapidly to 2800 m or higher.[75] Even with a gradual ascent, the risk of altitude illness is unpredictable for first-time travelers to high-altitude destinations. For prevention, acetazolamide is effective at a dose of 125 mg twice daily beginning 24 hours before an ascent to an altitude of 2800 m or higher and continuing through the day after the highest altitude is reached. Severe complications such as pulmonary or cerebral edema, which are uncommon at altitudes below 3500 m, are best treated with supplemental oxygen and an immediate descent. Persons traveling to destinations at an altitude of 3500 m or higher for a stay of more than a few hours should consult an expert.

THROMBOSIS

A causal but modest link between lack of mobility during travel and deep venous thrombosis or pulmonary embolism in otherwise healthy persons has been established. The overall absolute incidence of symptomatic venous thromboembolism in the month after a flight lasting more than 4 hours is 1 in 4600 flights and increases by 18% for each additional 2 hours in flight.[76] The risk of severe pulmonary embolism is negligible on flights lasting less than 6 hours.[77] Passengers with known risk factors are at highest risk. Preventive measures include avoiding dehydration and performing leg exercises while in flight. Of the many recommendations for prevention, only the use of graduated compression stockings (15 to 30 mm Hg) for passengers at increased risk is supported by data from randomized clinical trials,[76] though prophylaxis with subcutaneous administration of low-molecular-weight heparin just before departure and again 24 hours later for travelers with thrombophilia or previous thrombotic events is often used in practice. Aspirin is of no proven benefit for travelers.[76] Aisle seating promotes mobilization; no intrinsic benefit of premium-class seating has been shown.[76]

CONCLUSIONS

A summary of pretrip preparations for persons seeking medical consultation in the United States for travel to selected common overseas destinations is shown in Table 4. A body of knowledge in travel medicine has been published by the International Society of Travel Medicine (www.istm.org/bodyofknowledge). Available publications, especially those from GeoSentinel, which

Table 3. Drug Regimens for Prophylaxis against Malaria.*

Drug (trade name)	Tablet Size	Adult Dose	Use in Children†	Use in Pregnancy	Initiation	Discontinuation
Primary drug for all malaria species in all areas						
Atovaquone–proguanil (Malarone and generics)	Adults: 250 mg of atovaquone and 100 mg of proguanil; children: 62.5 mg of atovaquone and 25.0 mg of proguanil	250 mg and 100 mg once daily	Yes; FDA-approved for body weight ≥11 kg (for weight of 5 to <11 kg, recommended off-label by CDC)	No (insufficient data; not recommended by CDC)	1–2 days	7 days
Alternative drugs for all malaria species						
Mefloquine hydrochloride (generics only in U.S.)	250 mg (228-mg mefloquine base)‡	250 mg once weekly	Yes, all ages	Yes	3 wk preferable; 1–2 wk acceptable	4 wk
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brand names, and generics); doxycycline monohydrate (Monodox, Adoxa, and generics)	Hyclate: 20 mg, 50 mg, 100 mg; monohydrate: 100 mg	100 mg once daily	Contraindicated for age <8 yr because of staining of dental enamel	No (teratogenic)	1–2 days	4 wk
Alternative drug for areas with exclusively chloroquine-sensitive malaria						
Chloroquine phosphate (generics only in U.S.)	500 mg (300-mg chloroquine base); some generics available in 250-mg tablets (150-mg base)	500 mg once weekly	Yes, all ages	Yes	1 wk	4 wk
Alternative drug for areas with exclusively *Plasmodium vivax* malaria						
Primaquine phosphate for primary prophylaxis (off-label use)§	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes, all ages	No (potential toxic effects for fetal erythrocytes)	1 day	7 days
Primary drug for relapse prevention (*P. vivax* or *P. ovale* only)						
Primaquine phosphate for relapse prevention	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes, all ages	No	As soon as possible after exposure, for which another agent taken for primary prophylaxis	14 days total

* Initiation is defined as the time before the first exposure to malaria, and discontinuation as the time after the last exposure (with the exception of primaquine phosphate for relapse prevention, for which discontinuation is 14 days after the start of primaquine). AV denotes atrioventricular, G6PD glucose-6-phosphate dehydrogenase, and RCT randomized clinical trial.
† See http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria#4661 for dosing information for children.
‡ In some countries, 250-mg Lariam tablets contain 250 mg of mefloquine base, equivalent to 274 mg of mefloquine hydrochloride.
§ Intensive-exposure areas warranting postexposure primaquine treatment after any trip duration include but are not limited to Papua New Guinea, Timor-Leste, and certain areas of Indonesia. In other areas with *P. vivax* or *P. ovale*, persons who have had prolonged exposure (>6 months) or intensive exposure should consider postexposure primaquine treatment.

Table 4. Major Considerations during Medical Consultation before Leisure Travel to Common Destinations.*

Destination or Itinerary	Vaccines	Malaria Prevention	Key Risk-Prevention Strategies	Other Common Disease Risks
Peru: Machu Picchu and Cuzco with Amazon or jungle extension	Hepatitis A and typhoid for all destinations, yellow fever for Amazon or jungle	Chemoprophylaxis for Amazon or jungle; chloroquine effective in Madre de Dios region but not in other jungle areas	Take altitude precautions for Cuzco and Machu Picchu	Dengue, chikungunya, and Zika virus infection; cutaneous leishmaniasis in jungle areas
India	Hepatitis A and typhoid for all destinations, Japanese encephalitis for long stays or exposure to intensive rural farming during shorter stays, rabies for at-risk travelers and long stays	Chemoprophylaxis for most destinations except those at an altitude of >2000 m in north and some short-stay urban destinations; consult detailed maps†	Take precautions against mosquitoes, especially in rural farming areas because of Japanese encephalitis risk; avoid animal contact; take strict food and water precautions and precautions against motor vehicle injury	Dengue, chikungunya, tuberculosis, typhoid, paratyphoid, hepatitis E, and enteric bacterial disease
Kenya or Tanzania (East Africa), South Africa, Zambia, or Botswana (southern Africa) — short-stay safari tours	Hepatitis A for all destinations, typhoid for adventure travel, yellow fever for Kenya	Chemoprophylaxis for all game parks except certain parks in South Africa; consult detailed maps†	Take tick and tsetse precautions; avoid Kenya if medical contraindications to yellow fever vaccine	Tick-bite fever (*Rickettsia africae*) in southern Africa; schistosomiasis in all rivers, lakes, streams, and ponds; African trypanosomiasis in Kenya, Tanzania, and Zambia
Mexico and Caribbean countries — tourist resorts	Hepatitis A and typhoid for rural destinations, adventure travel, and long stays	Caribbean: chemoprophylaxis for Haiti, all resorts in the Dominican Republic, and no other Caribbean destination; Mexico: no chemoprophylaxis for any typical tourist destination; limited risk in some remote areas; chloroquine effective throughout risk areas in Caribbean and Mexico	Take precautions regarding sun, swimming, water exposure, and marine hazards and against sexually transmitted infections	Dengue, chikungunya, and Zika virus infection; complications from medical tourism
China — usual urban tourist destinations and major river cruises	Hepatitis A and typhoid for all destinations, Japanese encephalitis for long stays or exposure to intensive rural farming during shorter stays; rabies for at-risk travelers and long stays	Chemoprophylaxis not needed; risk of malaria in a few remote areas infrequently visited	Avoid animal contact; avoid markets with live poultry and do not eat undercooked poultry	Air pollution (poses substantial risk for persons with cardiopulmonary disease), schistosomiasis, influenza, acute respiratory illness, and avian influenza
Vietnam, Cambodia, Thailand, and Laos — urban and suburban tourist destinations, including major beach resorts and islands in Thailand	Hepatitis A and typhoid for all destinations, Japanese encephalitis for long stays or exposure to intensive rural farming during shorter stays or Mekong River cruises during farming season; rabies for at-risk travelers and long stays	Chemoprophylaxis not needed for itineraries if all overnight stays are in Ho Chi Minh City, Hanoi, coastal cities of Vietnam, Mekong River cruise boats, Siem Reap, Luang Prabang, Phnom Penh, Bangkok, Chiang Mai, and major beach resorts and islands in Thailand	Avoid animal contact; avoid markets with live poultry and do not eat undercooked poultry; take precautions against mosquitoes (especially in rural farming areas because of Japanese encephalitis risk), chiggers, and fleas and against sexually transmitted infections	Dengue, chikungunya, leptospirosis, scrub typhus, and murine typhus

* For all the considerations, the assumption is that all travelers are up to date with routine vaccines (i.e., MMR [measles–mumps–rubella], Tdap [tetanus–diphtheria–acellular pertussis], pneumococcal, varicella, and influenza vaccines). Hepatitis B vaccine should be considered for all travelers, with a lower priority for short-stay travelers without specific risk behaviors. All persons traveling to tropical destinations at any time of the year and all those traveling to destinations with temperate climates during influenza season should have received the most recent influenza vaccine available in their home country. Complications from medical tourism (i.e., travel outside the home country for medical treatment) have been reported from all countries listed. Some countries listed that do not have a local risk of yellow fever may have a requirement for proof of yellow fever vaccination for travelers arriving from areas where there is a risk.

† Sources of information are provided in Table 1 in the Supplementary Appendix.

is the International Society of Travel Medicine–CDC database of travel-related illnesses,[1-3] and online resources (Table S1 in the Supplementary Appendix) should be consulted frequently to stay up to date on constantly changing epidemiology. Preventive strategies and medical interventions need to be individualized. No traveler should leave the consultation without understanding the importance of seeking expert medical advice immediately if fever develops after the return home.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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