Chapter e18: Travel Health

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KEY CONCEPTS

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1. Travelers should consult practitioners with travel health expertise when going to tropical or developing countries.
2. For the pretravel consultation recommendations, travelers should be given written material in their language to reinforce and supplement verbal instructions.
3. The pretravel screening appointment should include a discussion of items that should be contained in a travel medical kit.
4. Pregnant travelers should consult obstetric and travel medicine experts prior to traveling to developing countries.
5. Immunocompromised patients may need longer periods of pretravel preparatory time to allow for adequate immunization, given their sometimes blunted antibody responses to vaccines.
6. Travelers to sub-Saharan Africa, Southern Asia, Central and South America, and the Caribbean experience higher rates of infection than those traveling to other parts of the world.
7. Prophylactic antibiotic use may reduce the risk of traveler's diarrhea but is generally not recommended, primarily because of the risk of developing drug resistance or *Clostridioides difficile* infection.
8. Prevention strategies are essential for limiting vector-borne infections during travel.
9. The mainstay of therapy in all altitude-related illnesses is descent to a lower altitude (typically at least a 300-m reduction in altitude).
10. Patients who have previously been diagnosed with depression should continue their prescribed medications and minimize alcohol consumption while traveling.

BEYOND THE BOOK

BEYOND THE BOOK

Design a medication kit for a family of four (two adults and two preteen children) taking a 10-day trip to Aruba.

INTRODUCTION

Global (international) travel has increased dramatically over the past 20 years. A sizable proportion of this increased travel can be explained by

individuals traveling from developed countries to developing countries.[1] Reasons for travel to developing countries are variable, but include work-related travel, leisure travel, medical tourism, visiting family, adventure travel, medical mission or outreach, and study abroad programs.

Travel to distant lands has always been associated with risks to mental and physical health. Long-standing estimates of travelers experiencing health problems have been between 22% and 64%, and more recent data tell us that travelers visiting developing and/or tropical nations may experience illness 43% to 79% of the time.[2] Many health problems arising during travel are self-limiting or not bothersome enough for travelers to seek medical care. However, approximately 8% of travelers seek help from physicians either during or soon after traveling.[3] In addition to infectious and noninfectious health problems, global travelers face potential dangers from vehicle and pedestrian traffic accidents, drowning, animal attacks, and assaults. This chapter focuses on health risks and diseases that affect global travelers, with primary emphasis on travel from developed countries to developing or tropical countries. Some travel-related information is included in other chapters, and readers will be referred accordingly.

PRETRAVEL PREPARATION

1 Travelers should review information about their destinations and itinerary and consider potential self-care options for health issues that may arise during travel. Pretravel preparation often involves the assistance of healthcare providers, which is typically more important for patients with chronic health conditions and those traveling internationally, especially to the developing world. About 35% to 50% of travelers from North America and Europe heading to developing countries seek pretravel health advice.[4] Of whom, only about 10% to 20% of travelers consult travel medicine experts or travel clinics. Informed primary care providers without extensive travel health expertise can provide adequate advice to travelers en route to low-risk destinations, but travelers should consult practitioners with travel health expertise when going to tropical or developing countries.[4]

Travel clinics and travel health experts are often underutilized.[4] Two groups of travelers that are less likely to seek expert pretravel health advise are business travelers and immigrants living in developed countries, going back to their home countries to visit friends and relatives (VFR).[5,6] VFR individuals often believe that they are immune to local diseases and do not feel the need to seek advice.[6] Unfortunately, VFR travelers often display some of the highest rates of travel health problems.[4,6] US residents traveling on global VFR trips make up about 33% of all travelers.[7] Other travelers may not seek travel expert advice for travel to resorts in nearby countries. However, even travelers staying at all-inclusive Caribbean resorts are subject to travel health issues.[8]

Practitioners seeking to become travel medicine experts can gain expertise and credentials in travel health through many different pathways. The majority of travel medicine specialists are primary care and infectious diseases physicians, but other types of physicians, pharmacists, nurse practitioners, nurses, and physician assistants can also become travel health specialists. Many US specialists complete certification programs offered by either the International Society of Travel Medicine (ISTM) or the American Society of Tropical Medicine and Hygiene (ASTMH).[4] In addition, some travel experts have specific expertise in the diagnosis and treatment of illnesses acquired in the tropics (tropical medicine). Travel health consultants with extensive travel experience can be helpful to travelers, especially if they have traveled to the same region that the traveler intends.

The Pretravel Consultation

2 Global travelers should make pretravel consultation appointments several weeks to months before traveling to allow time for adequate immunizations.[1] “Last-minute travelers” can create a unique challenge for pretravel advisors, who may have to devise less than optimal preparations.[9] The pretravel consultation should be performed in a structured and standardized manner (Table e18-1).[1,3,4,10] There should be an assessment of the traveler’s health and pertinent medical history, including a thorough medical history, travel history, medications, vaccinations, and allergies. Next there should be an assessment of the traveler’s risk, including discussion about the destinations, itinerary, accommodations, and planned activities. The consultant should have access to up-to-date travel health references on the travel destination and should provide preventative advice. Principal discussion points (depending on destination) may include vaccine-preventable illness, avoidance of insects, malaria prophylaxis (if applicable), prevention and self-treatment of traveler’s diarrhea (including food and drink safety), responsible personal behavior (ie, discussions about alcohol and substance use), sexually transmitted infections (STIs), general safety, travel medical insurance, and access to medical care during travel.[4,11] Pretravel screening also provides an excellent opportunity to assess travelers’ routine immunization status. For individuals in the United States, a review of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations will help to identify routine vaccinations that should be offered to travelers for their general health based on age, vaccination history, comorbidities, and planned

travel.[10] Travelers should receive any recommended vaccines in time to provide protection prior to travel. Refer to Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics" for a discussion of routine vaccinations. Finally, the consultant should provide posttravel advice, if relevant. This typically involves reminders about continuing malaria prophylaxis (if appropriate) and a discussion about self-assessment of any abnormal symptoms. During the pretravel consultation, travelers should be given written material in their language to reinforce and supplement verbal instructions. Written material can also include citations for online or printed resources.[4,10]

TABLE e18-1

Template of a Structured Pretravel Consultation

Stage	Elements
Risk assessment	• Assess current state of health • Complete a thorough medical history (including medication and allergy history) • Review travel itinerary (including countries visited, routes of transportation, season, and accommodations) • Discuss planned and possible activities in which the traveler might participate
Preventive advice	• Recommend routine vaccinations if not up to date • Recommend destination-specific travel-related vaccinations • Discuss prevention of vector-borne illness including need for malaria prophylaxis (if applicable) • Provide food and drink safety tips and traveler's diarrhea counseling • Review noninfectious travel conditions (motion sickness, jet lag, altitude sickness, and travel-associated venous thromboembolism) • Discuss travel medical kits
Immunizations and prescriptions	• Provide any needed recommended vaccinations • Prescribe/dispense antimalarial prophylaxis medications, motion sickness medication, and empiric medications for traveler's diarrhea
General safety and health advice	• Discuss travel health resources • Discuss personal safety and sexual health • Discuss alcohol and drug use • Comment on travel insurance and medical evacuation coverage • Provide posttravel advice • Provide written material to the traveler to reinforce and supplement verbal instructions discussed during appointment

Data from References 1, 3, 4 and 10.

Travel Medical Kits

Assembling a medical kit is an essential part of preparing for any international travel.[12,13] The kit can contain medications and health-related supplies for a single traveler, a family, or a group of travelers and can vary from a few nonprescription medications to several large containers of medications and health-related supplies for a group. Some common kit items are nonprescription medications, sunscreen, chronic prescription medications, antimalarial agents, anti-infectives for traveler's diarrhea, motion sickness medications, first aid kit items, sanitizing hand gel or wipes, insect repellant, potable water tablets, topical antibacterial ointments, rehydrating salts, and surgical masks. Table e18-2 contains a list of items that travelers could consider taking in their medical kits.

TABLE e18-2

Potential Items for Personal Travel Medicine Kits[a]

Type of Medical Kit	Items
Basic items	• Personal prescription medications as permitted by the host country • Nonprescription analgesics • Nonprescription antidiarrheals • Antihistamines • Decongestants • Laxative • Antacid • Sunscreen • Lip balm • Insect repellant • Alcohol-based hand gel • Motion sickness medications • Antimalarial prophylaxis (if needed) • Antibiotics for empiric treatment of traveler's diarrhea • Antiseptic wipes • Water purification tablets (if needed) • Basic first aid items (bandages, antibiotic ointment, tweezers) • Topical corticosteroid cream • Antibiotic cream • Tissues • Digital thermometer • Melatonin (for jet lag)
• Comprehensive personal items • *Consider for high-risk travelers like backpackers on longer independent trips to developing countries*	• Medical exam gloves • First aid dressings • Medical tape • Healing plasters • Wound closures • Blister plasters • Support bandage • Artificial tears • Eye wash • Antibiotic eye and ear drops • Topical antifungal medication • Antiemetic • Medications for altitude sickness • Temporary dental fillings • Empiric malaria treatment • Epinephrine auto-injector
Additional items for special circumstances	• Antiretroviral agents for postexposure prophylaxis (if providing direct care to HIV-infected patients)

	• Doxycycline for leptospirosis prophylaxis (consult a travel medicine specialist for need) • Condoms

[a]Table has been developed for travel to developing countries.

Data from References 12 and 13.

3 The pretravel screening appointment should include a discussion of items that should be contained in a travel medical kit based on a thorough risk assessment that considers traveler health history, destinations, duration, and type of activities. Travelers also need to anticipate available medical resources while traveling. Unfortunately, counterfeit or poor-quality medications can be found in the shops and hospitals of many countries.[1] Therefore, travelers should bring important medications from home. Limited access to hospitals, doctors, and pharmacies may require the traveler to carry many items in their medical kits. Small groups can order commercially prepared medical/first aid kits from travel specialty supply companies and web-based mass marketers (eg, Amazon.com) that can serve some of the general needs of the group while individual members assemble personal kits for individualized needs.[12] In general, most medications in kits should be suitable for self-administration. Preparation of medical kits for larger travel groups can be much more extensive and may need to be maintained by a healthcare provider.[12]

Travelers may have their medications examined by security or customs officials when entering certain countries.[12,14] To facilitate travel with medications (nonprescription or prescription), it is best to avoid having opened containers with loose tablets and capsules when possible. As a general rule, individually packaged and labeled medications ("units of use") or sealed commercial bottles will raise less scrutiny and may better protect medications. In addition, waterproof packaging may be needed for certain travel destinations or wilderness travel. Traveling with controlled substances or psychotropic medications can create additional difficulties.[12] Travelers with controlled or psychotropic medications should check the International Narcotics Control Board (INCB) website (www.incb.org) or official governmental sites of the destination country before traveling with such substances.[12,14] Countries may not permit the entry of some substances by travelers, or there may be criteria for entering with certain medications.

Travelers with Special Concerns

Older Adults and Travelers with Chronic Conditions

Older travelers with chronic conditions or those who lack strength and agility should be evaluated by their physician for fitness to travel. Some destinations and activities require more strength and stamina than others. Accidental traumas are a leading cause of death among older travelers, in part because of slow reaction time, poor coordination, and auditory or visual impairment.[15] The most common natural causes of death among older travelers are cardiac related. The stress of travel, poor oral intake, dehydration, physical exertion, and medication nonadherence may contribute to these deaths.[15]

Travelers of any age with chronic health issues must self-monitor their conditions and take medications appropriately. More patients with chronic conditions are traveling now due largely to advances in medicine.[16] Eighteen percent of travelers to developing countries have a chronic illness.[17] Travelers with chronic conditions should check with their physicians as they plan to make global travel plans.

Pregnant Travelers

4 The frequency of pregnant females traveling to developing countries is considerably higher among VFR travelers than non-VFR travelers.[6,18] Pregnant travelers should consult obstetric and travel medicine experts prior to traveling to developing countries.[1] Pregnancy presents added challenges for travelers heading to developing countries. For example, live vaccines are contraindicated during pregnancy. The concern with live vaccines is that they can transmit vaccine strain illness to the fetus.[18] Some live vaccines may need to be used if the benefit is believed to outweigh the risk to the fetus. With regard to antimalarials, chloroquine has been the antimalarial agent of choice in pregnancy.[18] Mefloquine, which has not been extensively studied in pregnancy, is believed to be safe and has been supported as a first-line agent.[1,19,20] Antimalarial decisions can be difficult if

traveling to chloroquine- and mefloquine-resistant regions because the safety of alternatives is less certain. Atovaquone-proguanil has not been well studied in pregnancy and carries Food and Drug Administration (FDA) category C pregnancy rating.[18] Doxycycline is contraindicated because of detrimental effects on bone and teeth development.[18] All females of childbearing age should know their pregnancy status before receiving live vaccines or malaria prophylaxis.

Pregnancy places long-distance travelers at high risk for venous thromboembolism (VTE) especially during air travel.[21] Unfortunately, VTE prevention data in pregnancy are limited. The American College of Chest Physicians (ACCP) lists two recommendations for pregnant persons making long-distance travel in the Antithrombotic Therapy and Prevention of Thrombosis guidelines[22]: (1) frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible, and (2) use of properly fitted, below-knee graduated compression stockings providing 15 to 30 mm Hg (2-4 kPa) of pressure at the ankle during travel. These actions were given a grade of 2C, which is defined as a weak recommendation from low-quality studies. These approaches are not likely to harm, and so they are frequently advised.[1,21]

The first and third trimesters of pregnancy have been the most worrisome for global travelers. Fetal development complications and miscarriages are most common during the first trimester.[18] Preventive vaccines and medications should be used with caution during this time. During the third trimester, women are generally uncomfortable and at risk of preterm labor. Airlines and cruise ships may require documentation for pregnant travelers at or beyond 36 weeks of gestation.[18] Cabin pressurization on commercial airlines is not expected to be a problem for uncomplicated pregnancies, but any influence on more complex pregnancies has not been well assessed.[23] Women who plan to travel during the third trimester should assess available medical facilities at the destination in anticipation of potential complications or early delivery. Health insurance companies should also be contacted prior to travel to confirm any coverage restrictions.[18]

Immunocompromised Travelers[26,27]

Travelers with compromised immune systems may face increased risk of infection during travel; however, this does not usually prevent them from traveling. Twenty-seven percent of US solid-organ transplant recipients reported travel outside North America and 20% to 46% of people living with human immunodeficiency virus (HIV) infection travel internationally.[24] Patients prescribed biologic agents to manage chronic inflammatory conditions may be at an increased risk of developing infections if traveling to areas with endemic fungi and tuberculosis.[25] Many immunocompromised patients are at an increased risk of traveler's diarrhea, largely because of impaired mucosal immunity.[26] Immunocompromised patients should involve travel experts and their specialist physicians in pretravel assessment.[1]

5 Immunocompromised patients may need longer periods of pretravel preparatory time to allow for proper vaccination, given their sometimes blunted antibody responses to vaccines. Additional time to assess serologic titers with possible booster immunization may be required.[26] Live vaccines are contraindicated in many immunocompromised patients, because the vaccine strain may cause an active infection. For patients with HIV infection who need vaccines for travel, immune responses are thought to be better and the chance of vaccine infectivity is reduced when the CD4+ cell count is 200 cells/mm^3 (0.2 × 10^9/L) or greater.[26,27] Counts of 500 cells/mm^3 (0.5 × 10^9/L) or greater are preferred for immunization, if possible. Live vaccine use has also been associated with organ rejection in solid organ transplant recipients.[26]

TRAVEL-RELATED DISEASES

Infectious Diseases

Infection and global travel have been linked throughout history. Up to 10% of global travelers develop infections during travel.[3] However, many of these infections could be avoided through proper vaccination and risk avoidance. Travelers themselves have served as conduits for spreading various infectious diseases across the globe. For example, travelers from China brought cases of the severe acute respiratory syndrome (SARS) to North America in 2003 and SARS-CoV-2 in 2019.[28]

6 Travelers to sub-Saharan Africa, Southern Asia, Central and South America, and the Caribbean experience higher rates of infection than those traveling to other parts of the world.[29] The major routes of infection in the developing world include (1) food or waterborne pathogens spread via

fecal-oral transmission, (2) insect vector-borne infections, (3) transcutaneous spread (eg, helminthic), (4) respiratory -spread, and (5) STIs.

Food- and Waterborne Infections

Diarrheal Illness. Gastrointestinal ailments are common among travelers.[1] Nausea, gas, and changes in stool consistency and frequency can occur in even the most cautious global travelers. These changes can be brought on by changes in diet, stress, and alteration of gastrointestinal flora.[2] Most diarrheal and gastroenteritis episodes are caused by the consumption of infectious (fecal) contaminated food or water.[4] The entity called *traveler's diarrhea* is defined as three or more unformed stools per 24 hours plus at least one additional symptom (abdominal cramping, tenesmus, nausea, vomiting, fever, or fecal urgency).[30] Traveler's diarrhea, which can be caused by bacteria, viruses, and protozoa, has an incidence of 25% for 2-week global travels.[31] The highest rates of infection occur in Asia, the Middle East, Africa, and Central America.[30,31] See Chapter 136, "Gastrointestinal Infections and Enterotoxigenic Poisonings" for additional discussion of traveler's diarrhea.

Common bacterial causes of traveler's diarrhea include: enterotoxigenic or enteroaggregative strains of *Escherichia coli*, *Campylobacter*, *Salmonella* (nontyphoidal), and *Shigella*. Common viral causes include: Rotavirus and Norovirus.[1,31,32] The most common protozoal cause of traveler's diarrhea is *Giardia species*. Less common protozoal causes include: amebiasis (*Entamoeba histolytica*), Cryptosporidiosis, and Cyclosporiasis. With the exception of Cyclosporiasis, protozoal disease onset usually takes longer because of a 1- to 2-week incubation period.[1] Infections caused by these organisms and their treatment are discussed in Chapter 136. Some humanitarian workers may also travel to areas with cholera (*Vibrio cholerae*) epidemics. These are typically in poor regions of sub-Saharan Africa, parts of southern Asia, and Hispaniola.

A key feature of the pretravel consultation should include a discussion about safe eating and drinking practices. Risk avoidance is the best way to reduce the occurrence of traveler's diarrhea, but it is difficult to avoid all risks. Even following the old adage "boil it, cook it, peel it, or forget it" may not always protect travelers.[31,32] Exposure to contaminated water during recreation or drinking (including ice cubes) remains a common cause of infection.[33,34] Several water purification techniques and products are available. They include heat, filtration, ultraviolet light treatment, halogen treatment, and chlorine dioxide-based treatment.[33] Convenient personal filter straw devices are easy to pack and carry. Each method has advantages and disadvantages that can be discussed with travel health experts. Heat is generally the most consistent method, but it has difficulty in masking bad tastes and odors.

Oral bismuth subsalicylate has been used to prevent traveler's diarrhea.[32,36] Daily use of bismuth subsalicylate was 65% effective in preventing traveler's diarrhea during a 3-week clinical trial in Mexico.[32] Common side effects include darkening of the tongue and stool. The drug is contraindicated in patients who should not take salicylates (ie, hypersensitivity to salicylates, children). Bismuth subsalicylate also interferes with the absorption of doxycycline, which is often used in travel medicine.[4,32] Probiotics are believed by some to reduce the occurrence of infection, but supportive data have not been consistent.[32]

7 Although prophylactic antibiotic use can reduce the risk of traveler's diarrhea, such use is generally not recommended, primarily because of the risk of developing drug resistance or *Clostridioides difficile* infection.[1] Travelers can bring antibiotics in their medical kit for self-directed initiation for symptomatic disease along with antimotility agents like loperamide.[12,13] The recommended adult empiric antibiotic regimen is single-dose or short-course oral fluoroquinolones (eg, ciprofloxacin 500 mg daily for 1-3 days) or azithromycin (500 mg daily for 3 days or 1,000 mg once).[32] Azithromycin may now be preferred in South or Southeastern Asia because of the increased presence of fluoroquinolone-resistant *Campylobacter*. A minimally absorbed delayed-release rifamycin tablet is approved for the treatment of travelers' diarrhea caused by noninvasive strains of *E. coli* in adults.[32] Dehydration is a serious side effect of pronounced diarrheal illness, despite antibiotics. Travelers to remote areas with high rates of traveler's diarrhea should consider packing oral rehydration solution powder.[4,31]

Good hand hygiene is also important for limiting traveler's diarrhea. Unfortunately, travelers may not always have access to soap and clean running water. This can be a concern for travelers in remote areas without water and "squat potty" restrooms. Alcohol hand sanitizers reduce the occurrence of traveler's diarrhea and thus should be used when soap and water are not available.[34]

Vaccine-Preventable Food- and Waterborne Pathogens. Typhoid fever (caused by *Salmonella enterica* serotype Typhi) is a serious disease spread by contaminated food and water. Clinical presentation may include high fever, weakness, stomach pain, headache, loss of appetite,

constipation, and rash. Internal bleeding and death can occur rarely.[1] The ACIP recommends typhoid vaccine for travelers to certain countries (see https://wwwnc.cdc.gov/travel). Vaccination may be given by either injectable killed Vi capsular polysaccharide vaccine or by oral live-attenuated Ty21a vaccine.[1,35] The injectable vaccine is recommended as a single IM injection for travelers older than or equal to 2 years. A booster is recommended if needed for travel every 2 years.[35] Immunization with the live oral capsule vaccine consists of one capsule taken every other day for four doses. A booster can be taken every 5 years if needed. The live vaccine is for travelers older than or equal to 6 years. The capsules must be refrigerated and taken with cool water. The oral vaccine has been associated with more gastrointestinal side effects and rash. The live vaccine is contraindicated in immunocompromised travelers, and pregnancy is an additional caution.[1,35]

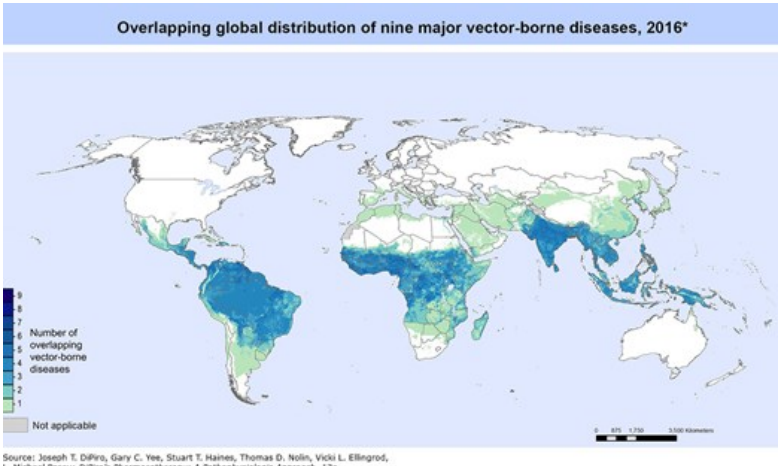
For travelers going to cholera epidemic areas, there is an oral live-attenuated vaccine available.[1] Cholera vaccines may provide some protection against some strains of enterotoxigenic *E. coli*.[3] Hepatitis A is a picornavirus shed in the feces of infected persons that can contaminate food and water. Vaccination is now widely available in the United States and other developed nations and has become a standard pediatric vaccine (see Chapter 58, "Viral Hepatitis").[36]

Vector-Borne Infections

8 Infections transmitted by arthropods (eg, insects) are common in the developing world. Vector-borne infections can range from asymptomatic to fatal. Figure e18-1 displays a WHO world map of the overlapping global distribution of nine major vector-borne diseases. The map highlights regions of the world where malaria, lymphatic filariasis, dengue, leishmaniasis, Japanese encephalitis, yellow fever, Chagas disease, human African trypanosomiasis, and onchocerciasis are endemic. The majority of vector-borne infections are attributed to arboviruses, which is a term that means arthropod-borne virus.[37] These include dengue fever, chikungunya, yellow fever, Japanese encephalitis, and Zika. Most of these infections do not have reliable treatments.[38] Therefore, prevention strategies are essential for limiting vector-borne infections. Such "risk avoidance" strategies should include avoiding infected habitats, wearing protective clothing, using protective bed netting, and applying insect repellent.[39] If available, the use of recommended vaccines would also be essential. Travelers with flexible travel plans can reduce exposure by traveling during seasons with less insect activity (ie, the dry season). Travelers should also be educated about daily insect activity patterns. While insect bites can occur at any time of day or night, there are times of increased insect activity. For example, mosquitoes that transmit dengue, yellow fever, and chikungunya bite more frequently between dawn and dusk, whereas mosquitoes that transmit malaria and Japanese encephalitis primarily bite from dusk to dawn.[1] Exposure to mosquitoes and other insects may occur indoors as well as outdoors. Exposure risk is reduced in air-conditioned buildings or in areas that do not have direct exposure to the outdoors.[38] The use of pyrethroid insecticide-treated bed netting provides a greater protective effect than untreated netting.[38]

Figure e18-1

World-wide deaths from vector-borne disease for 2002. (WHO Priority Risk Maps: Vector-borne disease. Deaths from vector-borne disease. Estimates by WHO sub-region for 2002 [WHO World Health Report, 2004]. Used with permission of the World Health Organization. © WHO 2005. All rights reserved.)



Wearing protective clothing that limits access to human skin in areas of high insect activity is highly advisable. This can be a challenge in very hot climates or when participating in outdoor activities. Application of EPA-registered insect repellants such as DEET (*N,N*-diethyl-3-methylbenzamide) or picaridin to the skin can provide protection against vector-borne disease. Unfortunately, compliance with daily application can be suboptimal.[40] For best effect and safety, DEET 20% to 50% concentration should be used.[1] Travelers should be provided with written material about proper application to reduce the risk of repellant toxicity. In addition, it is advisable to purchase repellants in developed countries to ensure product quality. Clothing can also be sprayed with repellants to increase protection.[40] This is often done before packing the clothes in luggage. Alternatively, clothing pretreated with repellants and insecticide agents like permethrin can be purchased through specialty travel vendors.

When infected with arboviruses, humans experiencing periods of high viremia can serve as amplification sources of infection if they remain in areas with mosquito activity. These individuals should continue to be protected from mosquitoes to reduce the further spread of infection.

Mosquito-Borne Infections. Malaria, which is caused by *plasmodium* protozoa and spread by *Anopheles* mosquitoes, is an important travel-related infection. Travelers to malaria-affected regions should discuss preventative strategies with an expert during pretravel consultation. The selection of prophylactic medications (if any) is based on potential efficacy, safety, and affordability. Antimalarial drugs should always be purchased before traveling overseas. In the developing world, antimalarial drugs can be purchased, but they may be counterfeit, subject to resistance, or of substandard quality.[1] Malaria is discussed in more detail in Chapter e138, "Parasitic Diseases."

Dengue fever is caused by one of four related single-stranded RNA *Flaviviruses*, named dengue virus (DENV) 1, 2, 3, or 4.[41] DENVs are endemic in over 100 countries throughout the tropics and subtropics, which includes parts of the Americas, the Caribbean, Africa, South Asia, and Oceania. Areas of recent dengue fever activity can be seen on the Healthmap.org surveillance website (https://www.healthmap.org/dengue/en/index.php). Dengue is the most common vector-borne infection affecting travelers in tropical and subtropical countries, with 100 million dengue cases per year and 10,000 deaths annually.[42] Dengue cases have surpassed malaria in all regions except for sub-Saharan Africa, but that may change.[43] Dengue is also more common in urban and suburban environments than malaria because of the type of mosquito vector.[41] DENV transmission is facilitated by the daytime-biting *Aedes aegypti* or *Aedes albopictus* mosquitoes.

Most patients with dengue fever experience either an asymptomatic (up to 80%) or a self-limiting, febrile illness that can be quite pronounced.[1,44] Classic symptoms include acute onset of high fever, severe headache, retro-orbital pain, fatigue, myalgia, arthralgias, and rash.[44] As its former name "break-bone fever" suggests, bone and joint pain can be quite intense. About 5% of infected individuals go on to develop severe infection with shock, which typically involves plasma leakage (increased vascular permeability) with or without bleeding.[42,44] Severe infections may include hepatitis, neurologic disorders, myocarditis, blood dyscrasias, shock, or severe bleeding.

The clinical course of dengue in symptomatic cases occurs in three stages: (1) febrile stage, (2) critical stage, and (3) recovery. During the first stage, fever lasts from 2 to 7 days. Patients experience defervescence as they enter the critical phase, which is characterized by some degree of plasma leakage. Most patients improve during this phase, but others progress to more severe diseases. As plasma leakage diminishes, the patient enters the recovery phase. After any DENV infection, patients usually have lifelong protection against that specific DENV serotype. Unfortunately, patients subsequently infected with a different serotype may develop an extremely severe secondary infection that is triggered by an immune response in the presence of cross-reactive nonneutralizing antibodies.[41,44,46,49,50]

Classic dengue fever is rarely fatal among travelers, but they may require hospitalization and even medical evacuation to their home countries for care. Mortality rates may be up to 20% in severe infection if left untreated, whereas patients receiving proper supportive care have only a 1% mortality rate.[41] Acetaminophen is preferred over aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) for fever reduction because of the increased risk of bleeding with symptomatic disease.[44,49] There are no established antiviral medications to prevent or treat dengue fever. However, a new quadrivalent vaccine has been approved in several countries for children with laboratory-confirmed previous dengue infection and living in endemic areas.[45] The vaccine is not being used for primary prevention because of severe subsequent infections in children who received the vaccine. Risk avoidance remains the best way to prevent dengue.[46]

The Zika virus is a related RNA flavivirus, which is also spread by the Aedes mosquitoes and became more widespread around 2015 when it appeared in Latin America.[47] Since that time, it remains endemic across parts of Central and South America.[48] Zika infection is usually asymptomatic, but can present with similar, but often milder symptoms than Dengue. Unfortunately, Zika infections in pregnant patients have been associated with

microcephalic babies.[47] There is added concern for this birth defect given that the virus can also be transmitted sexually from infected males to uninfected females. The CDC has posted advice for individuals who have traveled to endemic regions and may be at risk for spreading Zika sexually (https://www.cdc.gov/zika/pdfs/fs-zika-sex-partnertravel.pdf). No antivirals are available for Zika, but a vaccine is currently in development.[49]

Chikungunya virus (CHIKV) is a single-stranded RNA *Togavirus*. CHIKV transmission is facilitated by the daytime-biting *A. aegypti* or *A. albopictus* mosquitoes. CHIKV was initially endemic in rural parts of Africa but spread to Indian Ocean nations, Asia, and the Americas over the past 70 years.[50] Prior to 2013, CHIKV was not active in the western hemisphere.[51] Since that time, the virus has become endemic in Central America and South America and the Caribbean. The number of suspected or confirmed cases of CHIKV has now reached 2.9 million in the Americas.[52] Worldwide estimates of CHIKV activity are difficult to tabulate, but CHIKV is most endemic in South America, Central America, and parts of Southern Asia at this point.[48]

About 3% to 28% of people infected with CHIKV remain asymptomatic.[1] After an incubation period of about 3 to 7 days, symptomatic patients may abruptly manifest symptoms of high fever, headache, back pain, myalgia, and intense arthralgias.[53] A variety of skin manifestations also accompanies infection in 40% to 50% of infected persons, with maculopapular rash predominating. Given similar symptoms, the same vector, and overlapping endemic regions, it can be difficult to distinguish chikungunya from dengue. Incapacitating arthralgias (primarily of the hands and feet) are said to occur more with chikungunya.[53] Dengue patients experience more blood dyscrasias. There are no FDA-approved vaccines, but at least one in development.[54] Risk avoidance is the best way to avoid chikungunya infection. Supportive care and treatment is similar between chikungunya and dengue, except that NSAIDs can be used in the care of CHIKV-infected patients because of the lack of thrombocytopenia or hemorrhagic complications in this condition. CHIKV infection is rarely fatal (<1%), although the elderly may have worse prognoses than younger individuals.[51]

Japanese encephalitis virus (JEV) is a single-stranded RNA *flavivirus* that is transmitted to humans by the *Culex* species mosquitoes. Pigs serve as a major reservoir for the virus, but wading birds can also serve as reservoirs.[55] Endemic regions for JEV include East Asia, western Asia islands between the main continent and the northern tip of Australia, and the Indian subcontinent. The transmission risk is much lower than with dengue or malaria, with an estimated incidence of less than 1 case per 1 million travelers.[56] Rates are much higher if travelers stay longer in endemic areas or have significant rural exposure (ie, near pigs and rice paddies). In the more temperate regions of northeast Asia, JEV transmission is seasonal; epidemics are more likely to occur between April and October.[57] In the subtropics and tropics, transmission can occur year round but may intensify during the rainy season.

Most humans develop asymptomatic JEV infection; less than 1% of infected patients develop symptoms.[1] The most common manifestations include fever, flu-like symptoms, acute encephalitis, or aseptic meningitis. Humans infected with JEV do not experience very high viremia and are therefore less likely to amplify the spread of infection.[55,56] JEV has been associated with severe illness and a case-fatality rate of 20% to 30% with neurologic sequelae in 30% to 50% of severe infection survivors.[56] Fortunately, vaccines are available to prevent infection. The vaccine available in North America and Europe is an inactivated JEV SA14-14-2 strain prepared in Vero cells (trade name: Ixiaro). It is administered in a two-dose series given 28 days apart.[58] The vaccine contains protamine sulfate, which may be associated with hypersensitivity reactions. Very rare but serious reactions including anaphylaxis could occur following vaccination.[4,58,59]

The JEV vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season (season varies with latitude).[56] This includes long-term travelers or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JEV transmission. The JEV vaccine should be considered for short-term (<1 month) travelers to endemic areas during the JEV transmission season if they plan to travel outside of an urban area and have an increased risk for JEV exposure (eg, spending substantial time outdoors in rural or agricultural areas; participating in extensive outdoor activities; staying in accommodations without air conditioning, screens, or bed nets), and travelers to an area with an ongoing JEV outbreak or travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel. JEV vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or periods outside of a well-defined JEV transmission season. The vaccine is FDA approved for adults and children as young as 2 months of age.[58]

Yellow fever (YF) virus is a single-stranded RNA *flavivirus* that is spread by *Aedes* or *Haemagogus* species of mosquitoes. The WHO estimates that 200,000 cases of YF and 30,000 deaths attributable to YF occur annually.[60] The major areas of endemic YF activity are equatorial South America and sub-Saharan Africa (within 15 degree of the equator). YF virus has three transmission cycles: jungle (sylvatic), intermediate (savannah), and urban,

each with different proportionate roles for nonhuman and human primates as a source of vector-facilitated transmission.[60]

Yellow fever infections cause asymptomatic or subclinical infections in the majority of infected persons.[1] Symptomatic individuals can experience variable clinical presentations that can range from mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhagic manifestations. Infected patients can experience an abrupt onset of a high fever (up to 104°F [40°C]), chills, severe headache, myalgia, back pain, anorexia, nausea, prostration, vomiting, and dizziness. Some infected patients develop a severe form of illness characterized by jaundice, hemorrhagic symptoms, shock, and multiorgan system failure, after a brief (hours to days) remission period.[1] Case-fatality rates are 20% to 50% in severe cases.[61]

While there are no effective antiviral medications to treat YF, vaccines can prevent infection. At least four live-attenuated vaccines are approved by the WHO.[1] The formulation available in North America is a 17D-204 strain (trade name: YF-Vax).[62] The vaccine is recommended as a single-dose immunization for adults and children at least 9 months of age. Immunity usually develops by the 10th postvaccination day. Reimmunization was recommended every 10 years for those at continuing risk of exposure, but most experts do not recommend a "booster" dose because the vaccine provides immune protection for many decades.[1,60]

Adverse reactions to the YF vaccine include local site reactions, mild headaches, myalgia, and low-grade fevers, which can last for 5 to 10 days.[62] The product labeling carries precautionary warning about three serious adverse reactions. The first is immediate hypersensitivity reactions including anaphylaxis, mainly seen in patients with egg allergies. The vaccine is contraindicated in anyone with a history of acute hypersensitivity reaction to any components of the vaccine (including gelatin) or a history of acute hypersensitivity to eggs or egg products. The second serious reaction is vaccine-associated neurotropic disease (referred to as YEL-AND), previously described as postvaccination encephalitis. YEL-AND also includes acute disseminated encephalomyelitis, Guillain-Barré syndrome, bulbar palsy, and Bell's palsy.[40] Finally, vaccine-associated viscerotropic disease (YEL-AVD), previously described as multiple-organ system failure, is another rare serious adverse event associated with vaccination. The relationship between YF vaccination and these subsequent illnesses is not well understood. The incidence of YEL-AND and YEL-AVD has been estimated at 0.8 cases/100,000 doses administered and 0.4 cases/100,000 doses administered, respectively.[40] However, the incidence of each appears to increase with advancing age.

Because it is a live vaccine, it is contraindicated in immunocompromised patients, including symptomatic HIV-infected patients or those with CD4+ cells less than 200/mm^3 (0.2×10^9/L), patients with malignant neoplasms, patients on immunosuppressant therapy, and children younger than 6 months. A history of thymic dysfunction is now also regarded as a contraindication due to an apparent association with YEL-AVD.[1] The vaccine should be used with caution in children 6 to 8 months of age, patients 60 years of age and older, asymptomatic HIV-infected patients with CD4+ cells between 200 and 499/mm^3 (0.2×10^9 and 0.499×10^9/L), pregnancy, and during breastfeeding. An additional precaution is used in patients with latex allergies because the vial stopper is made of latex.[62]

According to the International Health Regulations, YF vaccine must be administered only at certified YF vaccination centers.[1] Within the United States, state and territorial health departments have the authority to designate nonfederal vaccination centers. Most other countries use governmental-affiliated clinics to provide official YF vaccinations. Under International Health Regulations, any country may require proof of YF vaccination from travelers coming from countries with YF activity, even if travelers stop in a country to connect flights. A few countries (mostly in Africa) require proof of vaccination from all arriving travelers. Travelers must allow a minimum of 10 days from vaccination to country entry. Proof of vaccination must be in the form of a signed and stamped International Certificate of Vaccination or Prophylaxis.[1] The same form can be used as a waiver to document that a patient has a contraindication to receiving YF vaccination. Each country may have its own entry requirements. For example, some countries may require a YF vaccine booster at 10 years. Global travelers should check health-related entry requirements for each country they plan to visit. This information can be obtained from travel medicine consultants, foreign embassies, or governmental websites. An informed traveler is less likely to experience quarantine, refusal of entry, or vaccination in country.[1]

Tick-Borne Infections. Ticks are small hematophagous arthropods that can introduce parasites, bacteria, or viruses into vertebrates.[63] After mosquitoes, ticks are the next most common vector for transmitting human infectious diseases worldwide. In North America and Eurasia, they are actually the most common vectors. Some of the most common tick-borne infections that travelers may encounter outside of the United States are *Borrelia burgdorferi* (Lyme borreliosis), *Borrelia* spp. (tick-borne relapsing fever), *Rickettsia africae* (African tick bite fever), tick-borne encephalitis virus (TBEV; European encephalitis), *Rickettsia conorii* (Mediterranean spotted fever), *Francicella tularensis* (tularemia), and *Babesia* spp. (babesiosis).[63] While antimicrobial therapies are available to treat most of the bacterial and protozoal pathogens, prevention is the best strategy to

protect travelers from unwanted infections and complications.[1,38]

Travelers spending time in outdoor environments with tick activity should wear protective clothing, and apply DEET to unprotected skin.[38] Clothing can also be sprayed with the acaricide permethrin. Daily self-inspection is important to identify ticks early. Proper tweezer removal should be performed if ticks are found to be attached to the skin.

There are no effective treatments for TBEV, but vaccines are available outside the United States. These vaccines are often recommended for campers, hikers, or occupational workers who are likely to be exposed to ticks in the TBEV regions of Europe and Asia.[1]

Rabies. Rabies, a noninsect vector-borne infection, is an important life-threatening infection, which causes more than 60,000 deaths annually.[64] Certain wild mammals are referred to as high-risk "rabies vector species" such as raccoons, foxes, skunks, bats, and groundhogs. However, humans traveling in the developing world are more likely to contract the infection from domestic-appearing vectors, like dogs.[65] In these parts of the world, it is not uncommon to see dogs, cats, and monkeys on the streets or in tourist areas. Postexposure bite management is identical to wild and domestic exposures. The affected site should be cleaned immediately with soap and water, and then victims should be assessed for postexposure prophylaxis.[1] Unfortunately, access to quality rabies vaccine and immune globulin may be a challenge for global travelers, especially in remote areas.[4,66] In some countries, pharmaceutical quality standards may not be as high as in developed countries. In addition, supplies of available rabies products at local medical facilities may be counterfeit or poorly stored (subject to temperature variations).[1] With such a high mortality risk, exposed individuals, especially in small towns and villages, may require medical evacuation to reliable hospitals with adequate supplies of quality vaccines and immune globulin.

Respiratory-Transmitted Infections

Tuberculosis is one of the most common infectious diseases in the developing world. Travelers to developing countries can be easily exposed to infected persons with contagious "active" forms of the disease.[67] The CDC advises travelers to "avoid exposure to tuberculosis (TB) patients in crowded environments (such as hospitals, prisons, or homeless shelters)."[1] Travelers providing care to such patients should consider the use of personal protective devices, such as N-95 masks. TB infection is discussed in Chapter 135, "Tuberculosis."

Influenza is another important global infection concern. There are concerns about pandemic avian influenza epidemics occurring in the future.[4,68] Fortunately, human-to-human cases are unlikely. Global travelers should avoid markets and farms where live poultry is sold or raised and avoid contact with dead poultry, chicken blood, or undercooked chicken in avian influenza-affected areas.[1] Influenza is discussed in Chapter 131, "Influenza."

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is responsible for a severe illness that was first reported in Saudi Arabia in 2012 and has since spread to several other regions, including North America.[69] Common symptoms include severe acute respiratory illness including fever, cough, and shortness of breath. Mortality rates have been 30% to 40% among patients with laboratory-confirmed infection.[70] All reported cases have been linked to countries in and near the Arabian Peninsula. There are no antiviral medications to treat MERS-Co-V nor there are vaccines to prevent MERS-CoV infection at present time. Risk avoidance strategies in endemic areas include good hand hygiene, avoiding contact with sick people, and avoiding contact with camels and raw or uncooked camel milk or meat.[1,69]

Two vaccine-preventable infections that should be assessed as part of pretravel consultation are measles and meningococcal infections. Most travelers have immunity against measles, but an assessment of vaccine history with consideration of measuring titers should be part of a pretravel consultation. Widespread vaccination against *Neisseria meningitidis* is less likely than measles. Persons traveling to high-risk areas like the "meningitis belt" of sub-Saharan Africa should also be assessed for immunity.[1] These vaccine-preventable illnesses are discussed in greater detail in Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics."

Neglected Tropical Diseases

Neglected tropical diseases are infectious diseases that are found in some of the poorest tropical regions of the world and have not been considered a priority by funding agencies, pharmaceutical companies, or global policymakers.[71] These diseases rarely cause infection among global travelers from

more developed countries unless they spend significant time in high-risk areas. Some of the more common diseases in this category are leishmaniasis, trypanosomiasis (Chagas and African), schistosomiasis, ascariasis, lymphatic filariasis, hookworm infection, and dracunculiasis (Guinea worm). Interested readers can learn more about these in the CDC Yellow book[1] or in Chapter e138.

Sexually Transmitted Infections

Global travel has long been linked with STIs. Global travelers may alter their behavior patterns as they leave their "normal environment." Travelers may give into hedonistic tendencies, especially if they use alcohol and illicit drugs. Travelers may behave with increased promiscuity when in exotic places, including sexual activity with commercial sex workers.[72] Global travelers taking part in risky (unprotected) sexual activity put themselves at risk for infections such as syphilis, gonorrhea, chlamydia, HIV, and hepatitis B (see Chapters 140, "Sexually Transmitted Diseases" and 148, "Human Immunodeficiency Virus").

Miscellaneous Travel Infections

Ebola virus belongs to the family of filoviruses and causes a viral hemorrhagic fever. Ebola can be spread through direct contact with the blood or body fluids of an infected person through broken skin or mucous membranes in the eyes, nose, mouth, or other areas.[73] Ebola has long been feared because of its ability to spread with an insidious incubation period of up to 21 days. There have been at least 20 recognized outbreaks of Ebola, all occurring in Africa. Estimated fatality rates have been between 25% and 90%.[75] The largest Ebola outbreak in West Africa in 2014 attracted worldwide attention. Healthcare workers from around the globe went to the region to assist, and many of them contracted the virus and died.[74]

Noninfectious Diseases

Altitude Sickness

Altitude sickness or high-altitude illnesses (HAI) result when the partial pressure of oxygen in the inspired air is lower than that to which the patient is accustomed. Three main syndromes can develop from high-altitude exposure: (1) acute mountain sickness (AMS), (2) high-altitude cerebral edema (HACE), and (3) high-altitude pulmonary edema (HAPE). These different manifestations depend upon the terminal altitude, the rate of ascent, the time spent at maximum altitude, and the altitude when sleeping. The reduction in oxygen inspired over short periods leads to physiologic changes that place stress on the body and may lead to severe illness and even death.[75,76,77,78] Patients who are exposed to reduced oxygen concentrations gradually can compensate. This process is called acclimatization. However, when individuals ascend too rapidly, they will experience a characteristic set of symptoms.[79]. An individual who ascends too rapidly will begin to hyperventilate, become tachycardic, and could experience other symptoms (eg, dizziness, confusion, fatigue). These can be early signs that an individual may be ascending too rapidly and would be at risk for AMS.

The diagnostic symptomatology for AMS includes headache combined with one of the following symptoms: anorexia, nausea or vomiting, fatigue, insomnia, or dizziness.[79] If the appropriate steps are not taken to treat or abate the progression of AMS, the individual could deteriorate further and develop HACE. This deterioration can occur in as little as 12 hours and could subsequently lead to death from vasogenic edema and decreased cerebral perfusion. The signs and symptoms of HACE are ataxia, seizures, slurred speech, neurologic deficits (rare), altered mentation, and decreased consciousness. Decreased consciousness and cerebellar ataxia are the most useful signs in identifying HACE.[79] Although patients may present with pulmonary edema in addition to central nervous system effects, patients may also present only with pulmonary edema. HAPE presents as increased breathlessness upon exertion and progresses to increased breathlessness during rest with weakness and cough. HAPE is due to a noncardiogenic, hydrostatic pulmonary edema.[80] Individuals who ascend to high altitude will experience some degree of hypoxic pulmonary vasoconstriction that leads to pulmonary hypertension and increased capillary pressure in patients who are susceptible to HAPE. HAPE has the potential to be more rapidly fatal than any of the other HAIs.[76-85]

9 The mainstay of therapy in all altitude-related illnesses is descent to a lower altitude (typically at least a 300-m reduction in altitude). The administration of oxygen is an appropriate adjunct in severe cases and potentially is an option in mild cases. Due to the lack of availability in the field and the repercussions of mismanagement of deteriorating cases, oxygen therapy is not a likely option for treatment until the patient can descend to a base station with supplies.

Several medications have shown benefit in treating or preventing HAI and could be used as adjunctive therapy to decent and oxygen therapy.[76,80,81] Acetazolamide has been used for many years for the treatment and prevention of AMS and HACE. Acetazolamide is a carbonic anhydrase inhibitor that reduces hydrogen ion secretion in the proximal renal tubules and increases renal excretion of sodium, potassium, bicarbonate, and water leading to metabolic acidosis. This metabolic acidosis leads to compensatory hyperventilation and increased oxygenation of the blood. This mechanism facilitates the acclimatization process and quickly improves AMS and HACE. Due to its sulfonamide chemical structure, individuals with documented allergies to sulfonamides should avoid acetazolamide.[76-78,82,84,87] One side effect of acetazolamide, which is a potential issue for travelers who plan to have a rapid ascent to high altitude, is muscle fatigue. Carbonic anhydrase inhibitors as a class can cause fatigue but variations between individual agents exist. Methazolamide causes less muscle fatigue after exercise and may have a place in therapy or prevention of altitude sickness.[83]

Some inhaled medications have shown benefits in the prevention of AMS at 72 hours of exposure to high altitude. Inhaled salbutamol/ipratropium (a beta-2 agonist/anticholinergic combination) may have the most benefit in the prevention of AMS. The dose that was used in clinical studies is 3 mg/0.5 mg of salbutamol/ipratropium twice daily for 3 days during the time at high altitudes. Of the other medications tested, inhaled budesonide, a corticosteroid, showed moderate benefit in reducing the effects of AMS but was unsuccessful at preventing AMS.[84] Along with reducing the effects of AMS, Inhaled budesonide may also reduce the incidence of mild AMS; however, that same effect has not been demonstrated for severe AMS.[85]

Dexamethasone is a corticosteroid alternative to acetazolamide in the treatment and prevention of AMS, HACE, and even HAPE. Once initiated, dexamethasone should not be discontinued at altitude prior to acclimatization due to the possibility of rebound cerebral and pulmonary edema. The mechanism by which dexamethasone provides benefit in patients with AMS, HACE, and HAPE has not been well established but is thought to act through its anti-inflammatory properties and antagonism of vascular endothelial growth factor.[78,82,83]

Nifedipine is a calcium channel antagonist that has proven efficacy for the treatment of HAPE. Nifedipine causes pulmonary arterial vasodilation, which improves alveolar fluid clearance and oxygenation of the blood. Reduced pulmonary artery pressure and pulmonary vascular resistance contribute to the positive effects of nifedipine on HAPE.[78-80]

Phosphodiesterase-5 inhibitors (evidence exists for sildenafil and tadalafil) are effective in preventing HAPE, but there is a paucity of studies regarding their use as monotherapy for the treatment of HAPE. Although evidence for the treatment of HAI does not exist for vardenafil, it would likely have the same beneficial effect as prophylaxis given its mechanism of action. The theoretical concern that these agents have a risk for systemic hypotension is present; however, the clinical relevance of this risk in healthy populations without medication interactions is questionable.[75,79,86]

Opioid analgesics should be avoided in individuals who will be ascending to high altitude (or even in individuals ascending to a higher relative altitude prior to acclimatization) due to their ability to reduce the hypoxic ventilator response.[79]

Several nonpharmacologic modalities for the prevention of AMS have shown varied benefits. Pre-ascent staging for 2 days at a high altitude below that of the final targeted altitude showed decreased incidence when compared to a direct ascent control group.[87] This further supports the importance of gradual ascent and acclimatization when planning ascent to high altitude. Another modality that was studied is the use of expiratory resistance devices to create positive expiratory pressure. This was shown to improve oxygen saturation in hypobaric hypoxic environments and would provide a noninvasive way to improve oxygenation during ascent and potentially prevent or delay the onset of AMS.[88]

Jet Lag

Jet lag is a syndrome that develops when travelers cross one or more time zones and are unaccustomed to the new time zone. This syndrome can be characterized by fatigue, malaise, and a disorganized sleep-wake cycle that can lead to poor performance and gastrointestinal distress. The syndrome is created by misaligning an individual's normal activity schedule with their circadian rhythm. The main treatment for jet lag is to realign the circadian rhythm with the new schedule.[89] The use of natural methods for adjusting circadian rhythms, such as sunlight exposure, phototherapy, or pretravel sleep schedule modification, is typically inexpensive, easy to administer, and provides good outcomes.[89] Adjustment of a sleep schedule prior to travel may be difficult depending on the individual's normal habits and the destination of their travel. As the number of time zones increases, the difficulty of adjustment of sleep schedule also increases. This is also true regarding the severity of jet lag experienced. Other treatment modalities, such as supplemental melatonin, may provide a more flexible treatment method.[89-91]

In the majority of double-blind, placebo-controlled trials, melatonin was beneficial for the treatment of jet lag.[92] Melatonin is produced endogenously by the pineal gland and is essential in the regulation of circadian rhythms. Positive effects on the quality of sleep were seen when patients were given melatonin prior to sleep. The dosing range varies among studies but doses from 0.5 to 8 mg appear to have equal efficacy.[93] Melatonin also has some hypnotic effects and can aid in the initiation of sleep. Melatonin's status as a dietary supplement lends to it being readily available, and the known side effects of melatonin are relatively mild (eg, dizziness, enuresis, headache, and nausea). There is also no definitive evidence of toxicity associated with high dosages of melatonin.[1,89,94-96]

Sedative hypnotics, such as benzodiazepines and other medications that agonize the benzodiazepine receptors, are also effective at initiation of sleep and maintenance of sleep, but have inherent drawbacks to their use. Although safe to use in most patients, cognition and alertness can be impaired after benzodiazepine-induced sleep. They are also potentially habit forming and should be reserved for severe cases that are not effectively managed with light therapy and melatonin.[89,90] Stimulants, such as modafinil or amphetamines, can be used to increase alertness and performance during the adjustment period after travel if the patient's daily life or performance at work is impaired. Side effect profiles, drug–drug interactions, and abuse potential also limit their utility for regular use.[89]

Traveler's Thrombosis

Traveler's thrombosis, also referred to as travel-associated venous thromboembolism (TAVTE), can occur in otherwise healthy individuals who are not known to be hypercoagulable. Individuals traveling for multiple hours in confined spaces that limit ambulation are at particular risk for thrombosis. Other risk factors for traveler's thrombosis include personal height less than 63 in. (160 cm) and height over 75 in. (190 cm) in individuals traveling by air.[97] Those who are less than 63 in. (160 cm) will likely be unable to place their feet firmly on the floor during the flight and may experience increased pressure on the popliteal vein. This pressure contributes to the development of venous stasis, which is one of Virchow's classic triad of risk factors for VTE. Individuals over 75 in. (190 cm) in height are more likely to be restricted from movement when in a standard seat. This restriction could limit blood flow and also cause venous stasis. Other factors shown to increase the risk of TAVTE are genetic predispositions to clotting (Factor V Leiden), obesity, and oral contraceptive use.[96-98]

Although the increased fluid intake is helpful for preventing TAVTE, scientific evidence does not support this theory.[99] However, this should not dissuade passengers from staying well hydrated. While hydration may have no direct beneficial effect on prevention of traveler's thrombosis, the need to urinate may prompt the individual to ambulate to the restroom. Average healthy urine production ranges from 40 to 80 mL/hr, and the adult bladder capacity ranges from 300 to 400 mL. The urge to void usually occurs when the bladder is one-quarter full. This would mean that assuming normal hydration the average healthy traveler would be prompted to urinate every 1 to 2 hours. Ambulation and the use of lower extremity muscles, by isometric exercises performed during long-haul travel, are the best known ways to prevent VTE and traveler's thrombosis. Compressions stockings reduce asymptomatic clots when appropriately fitted.[100] Compression stockings that have not been custom fitted or appropriately sized do not add any additional protection and in some cases could cause more issues. Pharmacologic prophylaxis is not warranted in most situations and should be avoided due to an increased risk of major bleeding. Patients who have previously been diagnosed with VTE, undergone recent major surgery, or have known malignancy are at high risk of VTE without the added impact of confined travel and therefore should be considered on an individual basis for pharmacologic prophylaxis.[22] The use of aspirin for prevention of traveler's thrombosis is not supported by the literature and should not be recommended for prophylaxis in travelers.[97,98]

Mental Health

Travel, whether short or long, exposes the traveler to both physical and mental stress. Traveling into regions with disrupted personal routines and unfamiliar environmental and cultural elements can make assimilation difficult. This process of exposure and reaction to a different culture has been referred to as acculturation or "culture shock."[101] Controlled psychiatric illnesses and undiscovered predispositions to mental illness may be induced by exposure to these stressful situations. Pretravel screening and education are essential for travelers who are going to be abroad for a substantial amount of time. Patients with a history of mental illness should be counseled on the need for an adequate medication supply and impeccable adherence while abroad.

10 The most common psychiatric reason for evacuation from an international trip is depression.[102] Patients who have previously been diagnosed with depression should continue their prescribed medications and minimize alcohol consumption while traveling. Nearly all psychiatric illnesses that are

experienced while traveling require treatment with medication.[102] Proper preparation for the trip will reduce the difficulties associated with acquiring appropriate medications and medical care. Given the propensity for exacerbations of mental illness while traveling internationally and the possibility of suicide due to untreated or unrecognized depression, it is prudent to purchase travel insurance that includes medical evacuation coverage and coverage for repatriation of remains. The costs associated with medical evacuation can be high, and travel insurance is typically quite affordable in comparison.[101,102]

Healthcare Outreach

Global Health Organizations and Nongovernmental Organizations

Global health organizations provide many services to developing and developed countries along with information and education resources. Guidance to travelers regarding issues they may encounter while in country is one of these services. From travel advisories to health emergencies, organizations like the WHO provide timely information and guidance for the prevention of illnesses that could lead to significant morbidity or mortality. Many countries have organizations similar to the WHO that serve the country in which they are based. These organizations also provide guidelines and statistical information regarding travel and disease in their specific impoverished areas.[103]

Nongovernmental organizations (NGOs) are nonprofit, voluntary citizens' groups that organized on a local, national, or international level.[104] They provide substantial quantities of quality medical care to patients throughout developing countries.[104] Due to NGOs' contributions to the impoverished population's care, they have established themselves as a major contributor to improving the health of individuals who would normally not have access to quality healthcare. These contributions improve the quality and quantity of life in developing countries.[104]

Medications and Supplies for Medical Missions and Outreach

Providing medical services in other countries requires supplies similar to those used in the country of origin. There is a varied approach to the regulation of medications in different parts of the world. There are concerns with the acquisition and use of medications in these countries that must be considered. Many countries do not have an organization that regulates the standards for the purity and the quality of the products that are distributed. Consequently, medications acquired abroad could be impure or contain varied amounts of the active medication.[104] Due to this variability, it is advisable to obtain medications in the origin country or from a company that has a good reputation for standardization and quality. Medication costs also differ among countries, and the cost could be lower or higher depending on site-specific factors. Medications that undergo quality and safety checks are typically more expensive due to the time required to validate the methods and verify product quality. In many parts of the developing world, medication acquisition is as simple as walking into a pharmacy and requesting the medication with or without a prescription.[14]

The transport of medications into a country may require significant documentation regarding the origin of the medication, visual inspection of the product, and potential taxation. Legal regulations of medications also vary significantly. Seizure of supplies by customs agents could lead to fines and cancellation of the planned provision of medical care. Researching custom law of the destination country is vital to facilitate the entrance and exit of the country. Many organizations have paid employees that deal with this aspect of the trips to ensure there are no issues. However, this may be a role for pharmacists given their product knowledge and versatility.[14]

ABBREVIATIONS

ACCP	American College of Chest Physicians
ACIP	Advisory Committee on Immunization Practices
AMS	acute mountain sickness
ASTMH	American Society of Tropical Medicine and Hygiene
CDC	Centers for Disease Control and Prevention

CHIKV	chikungunya virus
DEET	*N*,*N*-diethyl-3-methylbenzamide
DENV	dengue virus
GCS	Graduated compression stockings
FDA	Food and Drug Administration
HAI	high-altitude illnesses
HACE	high-altitude cerebral edema
HAPE	high-altitude pulmonary edema
HIV	human immunodeficiency virus
HVR	Hypoxic ventilator response
INCB	International Narcotics Control Board
ISTM	International Society of Travel Medicine
JEV	Japanese encephalitis virus
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NGO	nongovernmental organizations
NSAID	nonsteroidal anti-inflammatory drug
NTD	neglected tropical diseases
PDE-5	phosphodiesterase-5
PO_2	partial pressure of oxygen
SARS	severe acute respiratory syndrome
STIs	sexually transmitted infections
TAVTE	travel-associated venous thromboembolism
TB	tuberculosis
TBEV	tick-borne encephalitis virus
VFR	visit friends and relatives
VTE	venous thromboembolism

WHO	World Health Organization
YEL-AND	yellow fever vaccine-associated neurotropic disease
YEL-AVD	yellow fever vaccine-associated viscerotropic disease
YF	yellow fever

REFERENCES

1. Bruette GW, Nemhauser JB. Centers for Disease Control and Prevention. *CDC Yellow Book 2020: Health Information for International Travel*. New York: Oxford University Press; 2019.

2. Angelo KM, Kozarsky PE, Ryan ET, et al. What proportion of international travellers acquire a travel-related illness? A review of the literature. *J Travel Med.* 2017;24(5):10.1093/jtm/tax046. doi: 10.1093/jtm/tax046.

3. Freedman DO. Protection of travelers. In:Bennett JE, Dolin R, Blaser MJ eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* 9th ed. Philadelphia, PA: Elsevier Saunders; 2020:3818–3827 eds.

4. Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43(12):1499–1539. [PubMed: 17109284]

5. Chen LH, Leder K, Barbre KA, et al. GeoSentinel Surveillance Network. Business travel-associated illness: A GeoSentinel analysis. *J Travel Med.* 2018;25(1):10.1093/jtm/tax097. doi: 10.1093/jtm/tax097.

6. Rapheal E, Stoddard ST, Anderson KB. Surveying Health-Related Knowledge, Attitudes, and Behaviors of U.S.-Based Residents Traveling Internationally to Visit Friends and Relatives. *Am J Trop Med Hyg* 2020;103(6):2591–2599. 10.4269/ajtmh.20-0508.

7. Heywood AE, Zwar N. Improving access and provision of pre-travel healthcare for travellers visiting friends and relatives: A review of the evidence. *J Travel Med.* 2018;25(1). doi: 10.1093/jtm/tay010.

8. Angelo KM, Stoney RJ, Brun-Cottan G, et al. Zika among international travellers presenting to GeoSentinel sites, 2012-2019: Implications for clinical practice. *J Travel Med.* 2020;27(4):taaa061. doi: 10.1093/jtm/taaa061.

9. Yates JA, Rao SR, Walker AT. Characteristics and preparation of the last-minute traveler: Analysis of vaccine usage in the Global TravEpiNet Consortium. *J Travel Med.* 2019;26(6):taz031. doi: 10.1093/jtm/taz031.

10. Freedman DO, Chen LH, Kozarsky PE. Medical considerations before International Travel. *N Engl J Med* 2016;375(3):247–60. 10.1056/NEJMra1508815.

11. Sanford C, McConnell A, Osborn J. The pretravel consultation. *Am Fam Physician*. 2016;94(8):620–627. [PubMed: 27929232]

12. Goodyear L, Gibbs J. Travel medical kits. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:61–64 eds.

13. Terry AC, Haulman NJ. Travel medical kit. *Med Clin North Am* 2016 Mar;100(2):261–77. 10.1016/j.mcna.2015.09.007.

14. Mutie M, Cooper G, Kyle G, Naunton M, Zwar N. Travelling with medications and medical equipment across international borders. *Travel Med*

Infect Dis 2014;12(5):505–510. 10.1016/j.tmaid.2014.07.007.

15. Suh KN, Flaherty GT. The older traveler. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:247–253 eds.

16. McCarthy AE, Burchard GD. The travelers with pre-existing disease. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:261–267.

17. Stienlauf S, Strlstin B, Meltzer E, et al. Chronic illness in travelers to developing countries. *Trav Med Infect Dis* 2014;12:757–763. 10.1016/j.tmaid.2014.10.004.

18. Mackell SM, Borwein S. The pregnant and breastfeeding traveler. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:225–236.

19. Gonzalez R, Hellgren U, Greenwood B, Menendez C. Mefloquine safety and tolerability in pregnancy: A systematic literature review. *Malaria J.* 2014;13:75. doi: 10.1186/1475-2875-13-75.

20. Roggelin L, Cramer JP. Malaria prevention in the pregnant traveler: A review. *Trav Med Infect Dis* 2014;12(3):229–236. 10.1016/j.tmaid.2014.04.007.

21. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018;2(22):3198–3225. 10.1182/bloodadvances.2018022954.

22. Kahn SR, Lim W, Dunn AS, Cushman M, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S–226S. [PubMed: 22315261]

23. Shalev Ram H, Ram S, Miller N, et al. Air travel during pregnancy and the risk of adverse pregnancy outcomes as gestational age and weight at birth: A retrospective study among 284,069 women in Israel between the years 2000 to 2016. *PLoS One*. 2020 Feb 6;15(2):e0228639. doi: 10.1371/journal.pone.0228639.

24. Schwartz BS, Rosen J, Han PV, et al. Immunocompromised travelers: Demographic characteristics, travel destinations, and pretravel health care from the U.S. Global TravEpiNet Consortium. *Am J Trop Med Hyg.* 2015;93(5):1110–1116. 10.4269/ajtmh.15-0185.

25. Click B, Regueiro M. Managing risks with biologics. Curr Gastroenterol Rep. *Curr Gastroenterol Rep.* 2019;21(2):1. 10.1007/s11894-019-0669-6.

26. Aung AK, Trubiano JA, Spelman DW. Travel risk assessment, advice and vaccinations in immunocompromised travelers (HIV, solid organ transplant and haematopoeitic stem cell transplant recipients): A review. *Trav Med Infect Dis.* 2015;13:31–47. 10.1016/j.tmaid.2014.12.007.

27. Bourque DL, Solomon DA, Sax PE. Health considerations for HIV-infected international travelers. *Curr Infect Dis Rep.* 2019;21(5):16. doi: 10.1007/s11908-019-0672-y.

28. Worobey M, Pekar J, Larsen BB, et al. The emergence of SARS-CoV-2 in Europe and North America. *Science*. 2020;370(6516):564–570. 10.1126/science.abc8169.

29. Scaggs Huang FA, Schlaudecker E. Fever in the returning traveler. *Infect Dis Clin North Am.* 2018;32(1):163–188. 10.1016/j.idc.2017.10.009.

30. Steffen R. Epidemiology of travellers' diarrhea. *J Travel Med.* 2017;24(Suppl 1):S2–S5. 10.1093/jtm/taw072.

31. Giddings SL, Stevens AM, Leung DT. Traveler's diarrhea. *Med Clin North Am.* 2016;100(2):317–330. 10.1016/j.mcna.2015.08.017.

32. Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: A clinical review. *JAMA.* 2015;313:71–80. 10.1001/jama.2014.17006.

33. Backer H. Water disinfection for international travelers. In:Keystone JS, Kozarsky PE, Connor BA eds. *Travel Medicine*. 4th ed. Atlanta, GA: Elsevier; 2019:31–41.

34. Henriey D, Delmont J, Gautret P. Does the use of alcohol-based hand gel sanitizer reduce travellers' diarrhea and gastrointestinal upset?: A preliminary survey. *Trav Med Infect Dis.* 2014;12:494–498. 10.1016/j.tmaid.2014.07.002.

35. Jackson BR, Iqgal S, Mahon B. Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015. *MMWR.* 2015;64:305–308.

36. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep.* 2020;69(5):1–38. 10.15585/mmwr.rr6905a1.

37. Mayer SV, Tesh RB, Vasilakis N. The emergence of arthropod-borne viral diseases: A global prospective on dengue, chikungunya and zika fevers. *Acta Trop.* 2017;166:155–163. 10.1016/j.actatropica.2016.11.020.

38. Alpern JD, Dunlop SJ, Dolan BJ, et al. Personal protection measures against mosquitoes, ticks, and other arthropods. *Med Clin N Am.* 2016;100:303–316.

39. Fradin MS. Insect protection. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:43–52.

40. Banks SD, Murray N, Wilder-Smith A, Logan JG. Insecticide-treated clothes for the control of vector- borne diseases: A review on effectiveness and safety. *Med Vet Entomol.* 2014;28(Suppl 1):14–25. doi: 10.1111/mve.12068.

41. Guzman MG, Harris E. Dengue. *Lancet*. 2015;385:453–465. doi: 10.1016/S0140-6736(14)60572-9.

42. Hamer DH. Dengue—Perils and prevention. *N Engl J Med.* 2021;384(23):2252–2253. doi: 10.1056/NEJMe2107325.

43. Mordecai EA, Ryan SJ, Caldwell JM, et al. Climate change could shift disease burden from malaria to arboviruses in Africa. *Lancet Planet Health*. 2020;4(9):e416–e423. doi: 10.1016/S2542-5196(20)30178-9.

44. Silva NM, Santos NC, Martins IC. Dengue and Zika viruses: Epidemiological history, potential therapies, and promising vaccines. *Trop Med Infect Dis.* 2020; 5(4): 150. doi: 10.3390/tropicalmed5040150.

45. Tully D, Griffiths CL. Dengvaxia: the world's first vaccine for prevention of secondary dengue. *Ther Adv Vaccines Immunother.* 2021;9:1–8. doi: 10.1177/25151355211015839

46. Vannice KS, Wilder-Smith A, Barrett ADT, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. *Vaccine*. 2018;36:3411–3417. doi: 10.1016/j.vaccine.2018.02.062

47. Petersen LR, Jamieson DJ, Powers AM, et al. Zika virus. *N Engl J Med.* 2016;374(16):1552–1563. doi: 10.1056/NEJMra1602113

48. Puntasecca CJ, King CH, LaBeaud AD. Measuring the global burden of chikungunya and Zika viruses: A systematic review. *PLoS Negl Trop Dis.* 2021;15(3):e0009055. doi: 10.1371/journal.pntd.0009055.

49. Tebas P, Roberts CC, Muthumani K, et al. Safety and immunogenicity of an anti-zika virus DNA vaccine. *N Engl J Med.* 2021;385 (12):e35. doi: 10.1056/NEJMoa1708120.

50. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med.* 2015;372(13):1231–9. doi: 10.1056/NEJMra1406035.

51. Staples JE, Fischer M. Chikungunya virus in the Americas—What a vectorborne pathogen can do. *N Engl J Med.* 2014;371;887–889. doi:

10.1056/NEJMp1407698.

52. Yactayo S, Staples JE, Millot V, et al. Epidemiology of chikungunya in the Americas. *J Infect Dis.* 2016;214(suppl 5):S441–S445. doi: 10.1093/infdis/jiw390.

53. Gasque P, Bandjee MC, Reyes MM, et al. Chikungunya pathogenesis: From the clinics to the bench. *J Infect Dis.* 2016; 214(suppl 5):S446–S448. doi: 10.1093/infdis/jiw362.

54. Voigt EA, Fuerte-Stone J, Granger B, et al. Live-attenuated RNA hybrid vaccine technology provides single-dose protection against chikungunya virus. *Mol Ther.* 2021;29(9):2782–2793. doi: 10.1016/j.ymthe.2021.05.018.

55. Kulkarni R, Sapkal GN, Kaushal H, et al. Japanese encephalitis: A brief review on Indian perspectives. *Open Virol J.* 2018;12:121–130. doi: 10.2174/1874357901812010121.

56. Hills SL, Walter EB, Atmar RL, et al. Japanese encephalitis Vaccine: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2019;68(2):1–33. doi: 10.15585/mmwr.rr6802a1.

57. Lindquist L. Recent and historical trends in the epidemiology of Japanese encephalitis and its implication for risk assessment in travellers. *J Travel Med.* 2018;25(suppl_1):S3–S9. doi: 10.1093/jtm/tay006.

58. *Ixiaro (Japanese Encephalitis Virus Vaccine) Prescribing Information*. Livingston, UK: Intercell Biomedical Ltd.; 2018.

59. Rabe IB, Miller ER, Fischer M, Hills SL. Adverse events following vaccination with an inactivated, Vero cell culture-derived Japanese encephalitis vaccine in the United States, 2009-2012. *Vaccine*. 2015;33:708–712. doi: 10.1016/j.vaccine.2014.11.046.

60. Staples JE, Bocchini JA, Rubin L, Fischer M. Yellow fever vaccine booster doses: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64(23):647–650. [PubMed: 26086636]

61. Torresi J, Kollaritsch H. Recommended/required travel vaccines. In: Keystone JS, Kozarsky PE, Connor BA, et al., eds. *Travel Medicine*. 4th ed. Atlanta, GA: Elsevier; 2019:101–124.

62. YF-VAX (Yellow Fever) Vaccine prescribing information. Swiftwater, PA: Sanofi Pasteur Inc.; 2020.

63. Eldin C, Parola P. Update on tick-borne bacterial diseases in travelers. *Curr Infect Dis Rep.* 2018;20(7):17. doi: 10.1007/s11908-018-0624-y.

64. Gautret P. Rabies: An important zoonotic threat for travelers. *Trav Med Infect Dis.* 2014;12:557–558. doi: 10.1016/j.tmaid.2014.10.010

65. Fisher CR, Streicker DG, Schnell MJ. The spread and evolution of rabies virus: Conquering new frontiers. *Nat Rev Microbiol.* 2018;16(4):241–255. doi: 10.1038/nrmicro.2018.11.

66. Henson KER, Santiago AAC, Namqui SS. Counterfeit rabies vaccines: The Philippine experience. *Open Forum Infect Dis.* 2020;7(8):ofaa313. doi: 10.1093/ofid/ofaa313.

67. Mohajan HK. Tuberculosis is a fatal disease among some developing countries of the world. *Am J Infect Dis Microbiol.* 2015;3(1)18–31. doi: 10.12691/ajidm-3-1-4

68. Tripathi A, Dhakal HC, Adhikari K, et al. Estimating the risk of pandemic avian influenza. *J Biol Dyn.* 2021;15(1):327–341. doi: 10.1080/17513758.2021.1942570.

69. Pavli A, Tsiodras S, Maltezou HC. Middle East respiratory syndrome coronavirus (MERS-CoV): Prevention in travelers. *Trav Med Infect Dis.* 2014;12:602–608. doi: 10.1016/j.tmaid.2014.10.006.

70. Oboho IK, Tomczyk SM, Al-Asmari AM, et al. 2014 MERS-CoV outbreak in Jeddah: A link to health care facilities. *N Engl J Med.* 2015;372:846–854. doi: 10.1056/NEJMoa1408636.

71. Berkowitz AL, Raibagkar P, Pritt BS, et al. Neurologic manifestations of the neglected tropical diseases. *J Neurologic Sci.* 349 (2015):20–32.

72. Rogstad KE. Sexually transmitted infections and travel. *Curr Opin Infect Dis.* 2019;32(1):56–62. doi: 10.1097/QCO.0000000000000513.

73. Brouqui P, Ippolito G. Ebola and travel: Management of imported cases. *Trav Med Infect Dis.* 2014;12:561–562. doi: 10.1016/j.tmaid.2014.10.008.

74. Meyers L, Frawley T, Goss S, Kang C. Ebola virus outbreak 2014: Clinical review for emergency physicians. *Ann Emerg Med.* 2015;65:101–108. 10.1016/j.annemergmed.2014.10.009.

75. Simancas-Racines D, Arevalo-Rodriguez I, Osorio D, Franco JV, Xu Y, Hidalgo R. Interventions for treating acute high altitude illness. *Cochrane Database Syst Rev.* 2018;6(6):CD009567. Published 2018 Jun 30 [PubMed: 29959871]

76. Wilkins MR, Ghofrani HA, Weissmann N, Aldashev A, Zhao L. Pathophysiology and treatment of high-altitude pulmonary vascular disease. *Circulation*. 2015;131:582–590. doi: 10.1161/CIRCULATIONAHA.114.006977.

77. Luks AM. Physiology in medicine: A physiologic approach to prevention and treatment of acute high-altitude illnesses. *J Appl Physiol.* 2015;118:509–519. 10.1152/japplphysiol.00955.2014.

78. Dietz TE, Hackett PH. High-altitude medicine. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:387–400.

79. Yaron M, Paterson RD, Davis CB, et al. High-altitude medicine. In: Marx JA, Hockberger RS, Walls RM, eds., et al. *Rosen's Emergency Medicine Concepts and Clinical Practice*. Philadelphia, PA: Elsevier; 2014:1928–1940.

80. Bhagi S, Srivastava S, Singh SB. High-altitude pulmonary edema: Review. *J Occup Health*. 2014;56:235–243. 10.1539/joh.13-0256-ra.

81. Luks AM, McIntosh SE, Grissom CK, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 update. *Wilderness Environ Med.* 2014;25(4 suppl):S4–14. 10.1016/j.wem.2014.06.017.

82. Hermand E, Lhuissier FJ, Larribaut J, Pichon A, Richalet JP. Ventilatory oscillations at exercise: Effects of hyperoxia, hypercapnia, and acetazolamide. *Physiol Rep.* 2015;3(6):e12446. doi: 10.14814/phy2.12446.

83. Dominelli PB, McNeil CJ, Vermeulen TD, et al. Effect of acetazolamide and methazolamide on diaphragm and dorsiflexor fatigue: A randomized controlled trial. *J Appl Physiol.* 2018;125(3):770–779. 10.1152/japplphysiol.00256.2018.

84. Wang X, Chen H, Li R, Fu W, Yao C. The effects of respiratory inhaled drugs on the prevention of acute mountain sickness. *Medicine*. 2018;97(32):e11788. doi: 10.1097/MD.0000000000011788.

85. Nepal G, Yadav JK, Rehrig JH, et al. Efficacy and safety of inhaled budesonide on prevention of acute mountain sickness during emergent ascent: A meta-analysis of randomized controlled trials. *BMC Emerg Med.* 2020;20(1):38. doi: 10.1186/s12873-020-00329-8.

86. Xu Y, Liu Y, Liu J, Qian G. Meta-analysis of clinical efficacy of sildenafil, a phosphodiesterase type-5 inhibitor on high altitude hypoxia and its complications. *High Alt Med Biol.* 2014;15:46–51. 10.1089/ham.2013.1110.

87. Beidleman BA, Fulco CS, Glickman EL, et al. Acute mountain sickness is reduced following 2 days of staging during subsequent ascent to 4300 m. *High Alt Med Biol.* 2018;19(4):329–338. 10.1089/ham.2018.0048.

88. Rupp T, Saugy JJ, Bourdillon N, Verges S, Millet GP. Positive expiratory pressure improves arterial and cerebral oxygenation in acute normobaric

and hypobaric hypoxia. *Am J Physiol Regul Integr Comp Physiol.* 2019;317(5):R754–R762. 10.1152/ajpregu.00025.2019.

89. Markwell P, McLellan SLF. Jet lag. In:Keystone JS, Kozarsky PE, Connor BA, et al. eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:417–422.

90. Arendt J. Approaches to the pharmacological management of jet lag. *Drugs*. 2018;78(14):1419–1431. 10.1007/s40265-018-0973-8.

91. Ambesh P, Shetty V, Ambesh S, Gupta SS, Kamholz S, Wolf L. Jet lag: Heuristics and therapeutics. *J Family Med Prim Care*. 2018;7(3):507–510. 10.4103/jfmpc.jfmpc_220_17.

92. Simmons E, McGrane O, Wedmore I. Jet lag modification. *Curr Sports Med Rep.* 2015;14(2):123–128. 10.1249/JSR.0000000000000133.

93. Baird MB, Asif IM. Medications for sleep schedule adjustments in athletes. *Sports Health*. 2018;10(1):35–39. 10.1177/1941738117743205.

94. Arendt J. Melatonin: Countering chaotic time cues. *Front Endocrinol.* 2019;10:391. doi: 10.3389/fendo.2019.00391.

95. Hardeland R. Divergent importance of chronobiological considerations in high- and low-dose melatonin therapies. *Diseases*. 2021;9(1):18. doi: 10.3390/diseases9010018

96. Marques MA, Panico MDB, Porto CLL, Milhomens ALM, Vieira JM. Venous thromboembolism prophylaxis on flights. *J Vasc Bras*. 2018;17(3):215–219. 10.1590/1677-5449.010817.

97. Ringwald J, Grauer M, Eckstein R, Jelinek T. The place of new oral anticoagulants in travel medicine. *Travel Med Infect Dis.* 2014;12:7–19. 10.1016/j.tmaid.2013.11.005.

98. Cannegieter S, Rosendaal F. Travelers' Thrombosis. In:Keystone JS, Kozarsky PE, Connor BA eds. *Travel Medicine*. 4th ed. Atlanta, GA: Elsevier; 2019:469–473.

99. Zubac D, Buoite Stella A, Morrison SA. Up in the air: Evidence of dehydration risk and long-haul flight on athletic performance. *Nutrients*. 2020;12(9):2574. doi: 10.3390/nu12092574.

100. Clarke MJ, Broderick C, Hopewell S, Juszczak E, Eisinga A. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev.* 2021;4(4):CD004002. doi: 10.1002/14651858.CD004002.pub3.

101. Doki S, Sasahara S, Matsuzaki I. Stress of working abroad: A systematic review. *Int Arch Occup Environ Health*. 2018;91(7):767–784. 10.1007/s00420-018-1333-4.

102. Valk T. Mental health issues of travelers. In:Keystone JS, Kozarsky PE, Connor BA eds. *Travel Medicine* 4th ed. Atlanta, GA: Elsevier; 2019:463–467.

103. United Nations: Civil Society. Available at: https://www.un.org/en/civil-society/page/about-us. Accessed October 1, 2021.

104. The United Nations and the Rule of Law, non-governmental organizations. Available at: https://www.un.org/ruleoflaw/what-is-the-rule-of-law-archived/. Accessed October 1, 2021.

SELF-ASSESSMENT QUESTIONS

1. Which one of the following actions should not be part of a pretravel health consultation?

   A. Conduct a medical history

   B. Prescribe or recommend empiric antibiotic for symptomatic traveler's diarrhea

C. Assess the risk of malaria at the traveler's destination

D. Provide travelers insurance or medical evacuation insurance

2. Which one of the following vaccines requires an International Certificate of Vaccination?

A. Dengue vaccine

B. Injectable polio vaccine

C. Japanese encephalitis vaccine

D. Yellow fever vaccine

3. A 55-year-old man who is HIV positive comes to travel clinic to get vaccinated before traveling to Malaysia. His current CD4+ cell count was 140 cells/mm^3 (0.14×10^9/L). Which vaccine would be relatively contraindicated because of the risk of causing an infection?

A. Hepatitis A vaccine

B. DtaP

C. Varicella zoster (live)

D. Inactivated Influenza vaccine

4. Which one of the following statements is FALSE regarding dengue?

A. Humans can get infected in urban areas.

B. Infection with serotype 1 provides protection against the other three serotypes.

C. Acetaminophen is preferred over ibuprofen as an antipyretic agent.

D. The critical phase of illness often involves plasma leakage.

5. While preparing a medical kit for travel to Thailand, a traveler notes that there have been increased reports of norfloxacin-resistant *Campylobacter* in the region he plans to travel. His first-line antibiotic for empiric treatment of traveler's diarrhea should be:

A. Azithromycin

B. Bismuth subsalicylate

C. Ciprofloxacin

D. Metronidazole

E. Antibiotics should never be used to empirically treat traveler's diarrhea

6. Which antimalarial prophylactic agent carries the strongest safety warning about use in pregnant travelers?

A. Chloroquine

B. Doxycycline

C. Mefloquine

D. Atovaquone-proguanil

7. This group of travelers frequently encounter higher rates of illness when traveling to tropical or developing regions when compared to general traveler populations:

   A. Women aged 40 to 50 years

   B. Immigrant travelers visiting friends and relatives back in native countries

   C. Travelers with limited healthcare coverage

   D. Study abroad students

8. All of the following are advisable methods for limiting mosquito-borne infection in high-risk areas except:

   A. Applying 10% DEET repellent on a daily basis

   B. Using insecticide-treated bed netting

   C. Wearing protective clothing that limits access to human skin

   D. Spraying clothing with insect repellant or insecticide

9. This vector-borne infection has become endemic in Central America, South America, and the Caribbean since 2015 and a majority of infected patients have symptoms.

   A. Japanese encephalitis

   B. Hepatitis A

   C. Chikungunya

   D. Dengue

   E. Typhoid

10. The first-line treatment for all high-altitude illnesses is:

    A. Nifedipine

    B. Hydration

    C. Descent

    D. Melatonin

    E. Dexamethasone

11. If a patient reports having had anaphylaxis to sulfa drugs, which one of the following altitude sickness medications would carry the highest risk for hypersensitivity?

    A. Sildenafil

    B. Acetazolamide

    C. Acebutolol

    D. Nifedipine

    E. Oxycodone

12. The following medication would be the most appropriate treatment to adjust circadian rhythms in patients with jet lag who cannot adjust their sleep patterns prior to travel.

    A. Modafinil

    B. Melatonin

    C. Clonidine

    D. Diazepam

    E. Zolpidem

13. Which of the following risks lead to traveler's thrombosis specifically in patients >75 in. (190 cm) tall?

    A. Popliteal vein compression

    B. Inability to recline

    C. Restricted movement in a standard seat

    D. Decreased venous valves

    E. Reduced need to ambulate

14. The most cost-effective approach for VTE prevention on long-haul airline trips is:

    A. Ambulation with isometric exercises

    B. Aspirin

    C. Compression stockings

    D. Low molecular weight heparin

15. Which of the following is the most common psychiatric reason for evacuation from international travel?

    A. Generalized anxiety disorder

    B. Schizophrenia

    C. Agoraphobia

    D. Mania

    E. Depression

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** From the "Pretravel Preparation" section: Provision or sales of insurance is not an integral part of pretravel health consultation. All other items listed are important parts of pretravel health consultation. Travelers can be provided with information on where to get travel insurance and names of insurers.

2. **D.** From the "Yellow Fever" section: Under International Health Regulations, any country may require proof of YF vaccination from travelers coming from countries with YF activity, even if travelers stop in a country to connect flights. A few countries (mostly in Africa) require proof of vaccination from all arriving travelers. Proof of vaccination must be in the form of a signed and stamped International Certificate of Vaccination or Prophylaxis.

This is the only vaccine listed that requires this.

3. **C.** Varicella is the only live vaccine listed here. From the "Immunocompromised Travelers" section: Live vaccines are generally contraindicated where the benefit versus risk must be considered in immunocompromised patients.

4. **B.** From the "Dengue" section: Patients subsequently infected with a different serotype may actually develop an extremely severe secondary infection which is triggered by an immune response in the presence of cross-reactive non-neutralizing antibodies.

5. **A.** From the "Diarrheal Illness" section: Current recommendations for antibiotic therapy are for single-dose or short-course fluoroquinolones or azithromycin. Azithromycin may now be preferred in south or southeastern Asia because of increased presence of fluoroquinolone-resistant *Campylobacter*.

6. **B.** From the "Pregnant Travelers" section: Doxycycline is contraindicated because of bone and teeth development.

7. **B.** From thr "Pretravel Preparation" section: VFR travelers often display some of the highest rates of travel health problems.

8. **A.** From the "Vector-Borne Infections" section: DEET needs to be 20% to 50% to provide the best effectiveness in high-risk areas.

9. **C.** From the "Chikungunya" section: The number of suspected or confirmed cases of chikungunya has now reached 1.74 million in the Americas, with about 80% of CHIKV infections come from six countries (Dominican Republic, Colombia, El Salvador, Guadeloupe, Honduras, and Martinique). Only about 3% to 28% of people infected with CHIKV remain asymptomatic.

10. **C.** From the "Altitude Sickness" section: The mainstay of therapy in all altitude-related illnesses is descent to a lower altitude.

11. **B.** From the "Altitude Sickness" section: Due to its sulfonamide chemical structure, individuals with documented allergies to sulfonamides should avoid this medication.

12. **B.** From the "Jet Lag" section: Melatonin is produced endogenously by the pineal gland and is essential in the regulation of circadian rhythms.

13. **C.** From the "Traveler's Thrombosis" section: Those individuals who are over 75 in. (190 cm) are more likely to be restricted from movement when in a standard seat.

14. **A.** From the "Traveler's Thrombosis" section: Ambulation and the use of lower extremity muscles, by isometric exercises performed during long-haul travel, are the best-known ways to prevent VTE and traveler's thrombosis. Obviously no costs are associated with this activity.

15. **E.** From the "Mental Health" section: The most common psychiatric reason for evacuation from an international trip is depression.