Because the spectrum of infectious diseases varies widely across nations and continents, the international traveler can acquire, and even disseminate, diseases unknown to their hometown physicians. These unfamiliar illnesses can be misdiagnosed and mistreated.

The United States is a major contributor to the growth of international tourism. In 2013 alone, more than 60 million Americans visited another country and approximately 70 million foreign travelers entered the United States. Increasing numbers of people are also immigrating to the United States, potentially bringing with them exotic infectious diseases. In the future, many members of this new American population will return to their country of origin to visit family and friends, further increasing the opportunities for the importation of diseases unknown to most US physicians.

Globalization is not only changing world economics and world communications, it is also changing the destinations for Americans traveling abroad. Increasingly, US travelers are visiting developing countries to sightsee, seek adventure, engage in trade, and volunteer their services. But travel to developing countries can be hazardous. Substandard public sanitation, poor personal hygiene, contaminated food, tainted water, and infectious arthropod vectors (e.g., biting flies, mosquitoes,
<table>
<thead>
<tr>
<th>Routine Vaccinations</th>
<th>Recommendations</th>
<th>Travel-Specific Vaccinations</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap</td>
<td>• All travelers should have documented tetanus andacellular pertussis vacci-</td>
<td>Hepatitis A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• At risk: Travelers to areas of poor sanitation, with chronic liver disease, MSM, IV drug users</td>
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<td></td>
<td>nations within past 10 y.</td>
<td></td>
<td>• Single dose (alone provides 1 y immunity) followed by a booster in 6-18 mo.</td>
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<td></td>
<td>• 1 dose of Tdap recommended for all adults, followed by Tdap every 10 y.</td>
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<td>• Given at least 1 mo before travel generates protective antibody in 2-4 wk.</td>
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<td>• If departure date is within 2 wk then immunoglobulin may be given with vaccine.</td>
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<td>Hepatitis A&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Hepatitis B&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>At risk: HCWs, adventurers, travel sex, MSM, acupuncture, tattoos/piercings</td>
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<td></td>
<td></td>
<td></td>
<td>• Schedule: 0, 1 (50%-60% protection) and 6 mo (full protection)</td>
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<td></td>
<td></td>
<td>• Rapid schedules (for quick, good protection and if follow with 12-mo vaccination results in long-lasting immunity): 0, 1, 2 mo or 0, 1, 2 wk.</td>
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<td>• Interrupted schedules can be finished without restarting.</td>
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<td>Typhoid (live and</td>
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<td>killed vaccine)</td>
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<tr>
<td>MMR</td>
<td>• Travelers born before 1956 are considered immune to measles.</td>
<td>Rabies&lt;sup&gt;b&lt;/sup&gt;</td>
<td>At risk: Long stay, in rural area or adventure travel and children traveling to Africa, Latin America, India, and Thailand.</td>
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<tr>
<td></td>
<td>• Adults born after 1956 must get ≥1 dose of MMR (2 doses 1 mo apart is Ideally</td>
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<td>recommended)</td>
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<tr>
<td>Menin-gococcal</td>
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<tr>
<td>disease</td>
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<tr>
<td>Polio</td>
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<td>At risk: Travelers to Africa, India, Pakistan, Indonesia, Syria, Yemen.</td>
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<td></td>
<td></td>
<td></td>
<td>• Adults: 1 dose as booster. If never vaccinated, then a full series is indicated (0, 1-2, and 6-12 mo).</td>
</tr>
<tr>
<td>Varicella&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 doses 4-8 wk apart for non-immune adult travelers</td>
<td>Japanese B encephalitis</td>
<td>At risk: Traveler to Asia with long stay (&gt;2 wk) or frequent stay in rural areas or adventure mission.</td>
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<td></td>
<td>• Inactivated virus vaccine: JE-Vax: 3 doses on 0, 7, and 30 d (or Ixiaro: 2 dose)</td>
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<td></td>
<td>• Accelerated regimens: 0, 7, and 14 d (2 doses 1 wk apart provides 80% protection, -1/200 have an immediate hypersensitivity reaction).</td>
</tr>
<tr>
<td>Influenza (live</td>
<td></td>
<td>Yellow Fever&lt;sup&gt;d&lt;/sup&gt;</td>
<td>At risk: Travelers to West Africa, South America with stay ≥2 wk.</td>
</tr>
<tr>
<td>intranasal vaccine</td>
<td>• All travelers to the tropics and cruise ship tourists.</td>
<td></td>
<td>• Single dose required 10 d before entering into infected country. Some uninfected countries require International Certificate of Vaccination (yellow card valid for 10 y) from travelers arriving from an infected country.</td>
</tr>
<tr>
<td>or inactivated</td>
<td>• All unvaccinated travelers traveling to the other hemispheres.</td>
<td></td>
<td>• Booster every 10 y.</td>
</tr>
<tr>
<td>vaccine)</td>
<td>• Live intranasal vaccine can be given to immune-competent traveler aged 2-49 y</td>
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<td></td>
<td>results in a positive test for a few weeks.</td>
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</tbody>
</table>

<sup>a</sup> At risk: Travelers to areas of poor sanitation, with chronic liver disease, MSM, IV drug users
<sup>b</sup> At risk: HCWs, adventurers, travel sex, MSM, acupuncture, tattoos/piercings
<sup>c</sup> At risk: Travelers to Asia with long stay (>2 wk) or frequent stay in rural areas or adventure travel
<sup>d</sup> At risk: Travelers to West Africa, South America with stay ≥2 wk
The pre-travel checklist.

- Age and sex
- Past medical history
  - Comorbid illnesses
  - Immune suppression
  - Vaccination history and contraindication to vaccinations
  - Medications
  - Pregnancy and breast-feeding
- Risky behaviors
- Full details on travel itinerary: dates, duration, and stopovers
- Environmental and seasonal considerations at destinations
- Styles of travel: rural or urban, budget or luxury
- Accommodation: hotel or camping
- Activities: business, tourism, adventure, safari, missionary, humanitarian, nongovernmental organization

etc.) greatly increase the risk for communicable disease. These risks can be minimized by preventive measures, such as getting vaccinations, taking prophylactic drugs, and adopting practices that limit exposure to infectious agents. The challenge is getting travelers prepared for international travel.

The first Conference on International Travel Medicine recognized this problem when it proposed in 1988 that "travel medicine" be a medical specialty. In 1991, the International Society of Travel Medicine (ISTM) was formed to foster research and education in travel medicine. ISTM also monitors the diseases acquired and transmitted by travelers and keeps both the medical community and the general public informed about the safe practices and the preventive and therapeutic strategies travelers should take before, during, and after travel.5

The Centers for Disease Control and Prevention (CDC) joined ISTM in 1995 to create GeoSentinel. GeoSentinel is a worldwide network of more than 50 travel medicine clinics that monitors and advises people departing for foreign destinations and those arriving from foreign locales, regarding travel-related health precautions.5 It is the largest compiler of travel-related illnesses and prevention measures. It is also continually expanding; there are now separate GeoSentinel databases for Canada (CanTravNet) and Europe (EuroTravNet). These networks track the preventive measures given to departing international travelers and monitor the health of arriving travelers. The resulting data analysis has provided timely insights into the changing epidemiology of travel medicine.6-13

This article offers a general overview of travel medicine, travel health precautions, pre- and post-travel assessment of travelers, and the current spectrum of travel-related infectious diseases in the United States. The goal is to provide the basic medical information to prepare patients for international travel.

Pre-Travel Evaluation

Ironically—and unlike international travelers from the rest of the world—most people leaving the United States for foreign destinations do not seek travel advice before they depart.14 Needless to say, such a timely medical encounter could significantly reduce post-travel illness. With some guidance, primary care practitioners can provide good advice for the traveler or at least direct them to someone who can provide travel advice.

An easy-to-remember approach to counseling the traveler is to ask the 4 questions often asked by journalists covering the news:

1. Who is the traveler in terms of age, health, vaccination history, medication use, allergies, and behaviors?
2. What will the traveler do when he or she gets to the destination?
3. Where will the traveler go and what medicolegal requirements must the traveler satisfy to enter and leave the countries he or she intends to visit?
4. When will the traveler be leaving? Will there be enough time to schedule his or her vaccinations?

The CDC offers a comprehensive pre-travel evaluation that captures the details of who, what, where, and when in a detailed format in the “Yellow Book,” which is freely accessible online.15 The Infectious Diseases Society of America (IDSA) also has a detailed set of guidelines for the pre-travel visit, including immunizations and recommendations for maintaining health while traveling.14

The aim of the pre-travel evaluation is not just to prevent illnesses by immunization and prophylactic medications, it is also to advise the traveler on how to

**KEY TO TABLE**

| HCW | health care worker; MMR, measles, mumps, and rubella; MSM, men who have sex with men; pt, patient; Tdap, tetanus, diphtheria, and pertussis (acellular) |

*Hepatitis A/B (Twinrix®): Usual schedule is 0, 1 and 6 mo; 0 and 1 mo provides adequate protection against Hepatitis A, 50% to 60% against hepatitis B. Repeat dose at 6 mo offers full protection against hepatitis B. Accelerated schedule: 0, 1, and 3 wk offers good protection; repeat at 12 mo offers full protection.

*Pre-exposure prophylaxis with 3 doses at 0, 7, and 21-28 d. Post-exposure prophylaxis after vaccination with 2 additional doses at 0 and 3 d. Post-exposure prophylaxis without vaccination needs rabies immunoglobulin injected locally into the wound with residual injected systemically and 5 doses of cell culture vaccine on days 0, 3, 7, 14, and 28 (last dose can be skipped in healthy patients).

*Zoster vaccine (Zostavax) is not a substitute for Varicella Vaccine (Varivax).

*Attenuated, live vaccine; contraindicated for infants, age >60, HIV-positive, steroids, cancer, etc. Can provide a waiver letter if vaccination not possible because of health status. May cause "flu-like" illness 5 to 7 d later.
Malaria

All travelers to malaria-endemic destinations, especially pregnant women, medical missionaries, and military personnel require malaria prophylaxis.18-21 These travelers should also be counseled about the symptoms and signs of malaria. It should also be emphasized that drug prophylaxis alone does not confer full protection; measures to prevent mosquito bites, such as bed nets, repellents, protective clothing, and avoiding outdoor activities at night are also important.

Malaria can manifest a few months after return due to ineffectiveness of the prophylactic regimens against the dormant virus (the hypnozoites seen with Plasmodium ovale and Plasmodium vivax).1 Hence, it is essential for travelers to contact the travel clinic if they develop fever, chills, headache, and so forth, even if it has been months since returning home, as other health care providers may not recognize or suspect malaria. Prophylactic drugs commonly prescribed include any one of the following.

**Atovaquone plus Proguanil:** This is a synergistic combination drug (Malarone, GlaxoSmithKline) and is the drug of choice to prevent malaria in most of the world. The recommended dose is 1 tablet (250/100 mg) daily from day 1 of travel until 7 days after exposure. Although it has less adverse effects than other antimalarials, it is expensive. There is also the unestablished potential for possible teratogenicity (Pregnancy Category C).22

**Mefloquin (various generics):** This drug is inexpensive and is safe in pregnancy. The recommended dosing schedule is 1 tablet (250 mg) on 3 Sundays before travel and then continue weekly for 4 weeks after exposure. The common adverse effects are gastrointestinal (GI) upset and vivid dreams, but on rare occasion the drug can also cause neurologic illness; it should be avoided in travelers with psychiatric illness including severe anxiety and depression. The drug also has cardiac toxicity and should be avoided in patients with cardiac conduction abnormalities as it prolongs the QT interval.23,24

**Doxycycline:** The recommended dose is 1 tablet (100 mg) daily and continued until 4 weeks after exposure. The adverse effects are skin photosensitivity and esophagitis. The drug stains dental enamel, so it is contraindicated in pregnancy and childhood (<8 years). A problem with the drug, not seen with atovaquone plus proguanil or mefloquin, is that a missed or late dose can leave the traveler vulnerable to getting malaria.

**Chloroquine:** The recommended dose is 300 mg base (500 salt) weekly and continued until 4 weeks after exposure. This drug is effective only for travel to areas with chloroquine-sensitive malaria.

**Primaquine:** This drug is used for prevention of Plasmodium vivax and Plasmodium ovale after prolonged exposure; at this time, it is the only drug active against the hypnozoites. The recommended dose is 30 mg base daily for 14 days after exposure. Use of this drug requires testing the traveler for glucose-6-phosphate dehydrogenase deficiency before starting, as primaquine causes hemolytic anemia in people with a genetic deficiency of this enzyme.

Travelers’ Diarrhea

Approximately 20% to 60% of travelers will develop diarrhea; destinations with the highest risk are Latin America, the Middle East, Sub-Saharan Africa, and Southeast Asia.16,25-27 Host-specific risk factors include use of acid suppressants (H2 blockers, antacids, and proton pump inhibitors), immune suppression, diabetes, and inflammatory bowel disease.

The most common microbe causing travelers’ diarrhea is enterotoxigenic Escherichia coli (ETEC), followed by campylobacter, salmonella and shigella. Viruses (rotavirus and norovirus) and parasites (notably Giardia lamblia) cause up to 25% of travelers’ diarrhea, depending on the destination.28-30 The diarrhea usually resolves in a few days without therapy, but may disrupt travel activities. Women are more likely than men to have a post-infectious irritable bowel syndrome, which is seen in 3% to 17% of patients who have had travelers’ diarrhea. The most common sources of infectious diarrhea are partially cooked or reheated foods, such
as quiches and casseroles, and contaminated water (including ice). The general advice for hygienic food consumption is: “Boil it, cook it, peel it, or forget it.” But, a recent review finds this advice may not be practical or effective for most travelers.30 The following summarizes the recommended drug therapy for travelers’ diarrhea. It is important to remember at all times that hydration with electrolyte supplementation is essential.13

Prophylaxis: Bismuth subsalicylate 2 tablets 4 times a day while traveling. Disadvantages are that it produces a black tongue and stool. Antibiotic prophylaxis (ciprofloxacin 500 mg daily or norfloxacin 400 mg daily) is not routinely recommended unless the traveler has advanced HIV, uncontrolled inflammatory bowel disease, or active immune suppression (eg, malignancy, chemotherapy, hypogammaglobulinemia, end-stage renal disease, or diabetes).12,13

Treatment: Only indicated for moderate to severe diarrhea (illness lasts more than 3 days, temperature higher than 38.5°C, pus, mucus, or blood in the stool). Drug of choice is a fluoroquinolone: oral ciprofloxacin 500 mg twice daily or oral norfloxacin 400 mg twice daily or oral levofloxacin 500 mg daily or oral ofloxacin 200 mg twice daily. Duration of therapy can be 3 to 5 days depending on response. Oral azithromycin 1,000 mg once and oral rifaximin 200 mg three times daily are alternative agents.13

Altitude Sickness

Travel destinations that are more than approximately 2,500 m (8,000 ft) high carry a risk for high altitude sickness, especially if there is a rapid ascent. Acute mountain sickness (AMS) is a self-limiting illness characterized by headache, dizziness, sleep disturbance, anorexia, and fatigue. Symptoms usually disappear in 1 to 3 days if there is no further ascent. Sometimes AMS progresses to encephalopathy and ataxia, known as high-altitude cerebral edema (HACE). This can be a rapidly fatal condition due to vasogenic edema of the cerebral white matter, especially the corpus callosum (T2 hyperintensity in the splenium of the corpus callosum on magnetic resonance imaging); this in turn can cause cerebral herniation.31-33 High-altitude pulmonary edema (HAPE) is another life-threatening complication where a multitude of host-maladaptive responses to hypobaric hypoxia at high altitudes (increased sympathetic tone, poor ventilation, pulmonary vasoconstriction, etc.) result in pulmonary edema.34

The best therapy for HACE and HAPE is immediate descent. Specific medical therapy to avoid and manage AMS is as follows:

Preventive therapy: Acetazolamide, a carbonic anhydrase inhibitor, induces metabolic acidosis and hence increases ventilation at night, increases arterial oxygenation, and promotes bicarbonate diuresis after respiratory alkalosis. This is recommended for ascents higher than 8,000 to 11,000 feet with a dose of 250 mg orally twice daily beginning on the morning of ascent and continue through the day after ascent. If symptoms persist, therapy should be extended an additional day. Because it is a diuretic, patients should avoid taking it at bedtime. Some patients develop circumoral and distal extremity paresthesias, in which case, each dose is reduced by 50%. Other adverse effects include a temporary distaste for carbonated beverages. Because it is a sulfonamide, acetazolamide is contraindicated in those with allergy to sulfa-containing compounds.

Treatment: The recommended approach is avoidance of further ascent and acetazolamide 250 mg orally twice daily until symptoms abate.

With, HACE and HAPE, although experienced providers in consultation with mountaineer travelers can try hyperbaric chambers, dexamethasone, and nifedipine, there is no substitute for immediate descent; other medical measures are generally not recommended as these conditions are rapidly fatal.

Jet Lag

Travelers flying to destinations across multiple time zones (usually more than 2 time zones, particularly eastward travel) are at risk for jet lag, characterized by malaise, day-time sleepiness, loss of concentration, and poor performance.

Recommended therapy: Zolpidem 10 mg immediately before sleep. Can be used for 2 to 3 nights at each end of the trip. Should not be taken during air travel as sleeping while flying can promote the formation of blood clots. Resisting the temptation to nap during the day after arrival at the final destination helps by abbreviating the adjustment phase. Authorities do not recommend over-the-counter melatonin.

Additional Risks

Adverse climatic conditions, traffic accidents, sunburn, drowning, animal bites, falls, and violence (political and criminal) are additional risks inherent to foreign travel. The US Department of State publishes destination-specific travel warnings and alerts as well as more general destination-specific travel information.

A recent review found that more than 20% of travelers engage in casual sex with a new partner while traveling, nearly half of these encounters are unprotected.35 Alcohol, social isolation, and anonymity promote this behavior; young, single men with a past history of sexually transmitted infections (STIs) appear to be at greatest risk.13,35-37 Such activities also expose the traveler to STIs with increased resistance to antimicrobial agents. For understandable reasons, sex workers are particularly hazardous. The best recommendation is abstinence. Otherwise, the traveler should use barrier protection because of the risk for HIV, hepatitis B virus, and other STIs. Antibiotic-resistance profiles of sexually transmitted pathogens vary greatly depending on the destination.

Long-distance travel (for more than 6-10 hours) whether by air or by land carries a risk for venous thromboembolism (VTE). This risk is in addition to any host-specific risk factors that might also be present.
(such as a prior VTE, hereditary thrombophilia, estrogen-containing oral contraceptives, recent major surgery, active malignancy, pregnancy, advanced age, and obesity).38-40

Prevention: The traveler should be counseled to avoid immobility by moving around and exercising calf muscles while sitting, to not wear constrictive clothing, to maintain adequate hydration, to limit alcohol intake, and to wear below-the-knee support stockings. Aspirin is not known to be effective and the value of low-molecular-weight heparin in at-risk travelers is also unknown.13

Post-Travel Illness

A wide variety of illnesses afflict travelers. A focused discussion of these individual diseases is beyond the scope of this review. GeoSentinel (including CanTravNet and EuroTravNet), with its worldwide clinic-based surveillance (54 travel medicine clinics and 235 additional clinics, across 40 countries and 6 continents), serves as the major source of epidemiologic and clinical information regarding post-travel illness.8

Surveillance data for the period 1997 to 2011, from 22 such GeoSentinel sites in the United States reported 13,059 diagnoses from 10,032 patients after travel. The most common diagnostic groupings were acute diarrhea (22%), non-diarrheal GI (15%), febrile systemic illness (14%), and dermatologic disorders (12%). Most common destinations of exposure were Sub-Saharan Africa (23%), followed by Central America (15%), South America (12%), the Caribbean (9%), South Central Asia (8%), and Southeast Asia (7%). Other regions of exposure included western Europe (5%), northeast Asia (3%), the Middle East (2%), North Africa (2%), eastern Europe (1%), Oceania (1%), North America (<1%), and Australia and New Zealand (<1%). Of the 1,802 patients with a febrile illness, the most common diagnosis was P. falciparum malaria (19%).41

More recently, surveillance data from all GeoSentinel sites (US and non US) for the period between 2007 and 2011, reported that approximately 42,000 travelers became sick after visiting Asia (32.6%), Sub-Saharan Africa (26.7%), and Latin America and the Caribbean (19.2%).11 Only 10.9% of North American sick travelers had a pre-travel evaluation for health maintenance (vaccines, preventive therapy, and travel precautions), but overall, 40.5% of travelers worldwide had a pre-travel evaluation. Most of the illnesses fell into 3 categories: GI infections (34%), febrile illnesses (23.3%), and dermatologic diseases (19.5%). Of the GI illnesses, 40% had acute diarrhea (presumptive enterotoxigenic Escherichia coli), 20% had a specific parasitic cause (most commonly: Giardia; primarily from India and environs), 10% had a specific bacterial cause (most commonly: Campylobacter, Salmonella, and Shigella; primarily from Asia, Africa, and the Middle East).

Of those travelers with diarrhea lasting more than 2 weeks, 40% developed a post-infectious irritable bowel syndrome. In travelers with a febrile illness, 29% had malaria (primarily travelers to Africa), 15% had dengue (primarily travelers to Southeast Asia, Latin America, and the Caribbean), and the remaining portion included a variety of acute febrile illnesses, notably enteric fever (typhoid and paratyphoid), Chikungunya, rickettsial diseases, viral hepatitis, leptospirosis, tuberculosis, and acute HIV. Forty percent of cases with fever remained undiagnosed, but were presumed to be viral in etiology. Only 8% of travelers sick with a respiratory infection, had influenza (0.9% of all sick travelers).11

Summary

The GeoSentinel network has compiled and published extensive statistics on the health care preparation of travelers before departure and on the descriptive epidemiology of the illnesses travelers bring back with them. Although this is the best information we have on travel-related illness, the GeoSentinel studies do not provide data on the proportion of travelers who did and did not become ill. Nevertheless, it is evident that travel-related illness is common and the spectrum of illness ranges from the rare and exotic to the frequent and mundane. Most importantly, this burden of disease can be reduced by timely pre-travel evaluation, immunization, prophylactic and therapeutic medications, and counseling on how to maintain health.

Perhaps more important than documenting the importance of travel illness, is the finding by the GeoSentinel network that all too frequently the North American traveler has failed to obtain a pre-travel evaluation, a medical encounter that could have prevented illness and injury. As international travel continues to become more common, health care providers should emphasize the value of the timely pre-travel medical evaluation to minimize the health risks posed by international travel.

References


2. Key facts about International Travel and Tourism to the United States: U.S. Department of Commerce, International Trade Administration, Industry & Analysis, National Travel and Tourism Office;


