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International Travelers and Infectious Disease
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ABSTRACT
International travelers have an increased risk of exposure to illness from infectious diseases caused by bacteria, viruses, and parasites. Nurse practitioners in primary and emergency care settings should have a working knowledge of common infectious diseases found in international destinations. It is important to maintain a high degree of suspicion for infectious causes when examining patients after travel with common complaints. The need to refer patients to travel health clinics and infectious disease specialists for pretravel consultation and post-travel red flags are important considerations for practice.

Keywords: infectious diseases, insect-borne disease, international travelers, vaccine-preventable illnesses

United States residents travel abroad over 60 million times annually.1 With each location visited, travelers will come in contact with unfamiliar infectious agents. Nurse practitioners (NPs) consulting with these patients will need to understand the illnesses circulating in the destination during the patient’s trip. Seasonal variation and local resistance will alter pretravel recommendations provided and the choice of medications and treatment methodologies used after illness. Additionally, the spread of infectious diseases previously seen only in developing countries into commonly visited tourist regions such as the Caribbean should raise the level of suspicion for tropical infectious agents for all travelers.

PRETRAVEL CONSULTATION
The pretravel consultation should include an extensive discussion of food, water, and insect precautions and exploration of the patient’s medical history, anticipated destination, and activities planned. Once this assessment is accomplished, vaccinations to reduce the risk of infectious disease can be recommended and medications prescribed to prevent and treat common illnesses experienced by international travelers.2 Ideally, pretravel consultation should occur at least 3 weeks before travel to allow time for full vaccination efficacy. There are several important components of the pretravel consultation.

An extensive review of the traveler’s medical history, including childhood illnesses and immunizations, should be completed. Periodic resurgence of childhood illnesses such as measles is known to occur in countries off the typical cautionary list of travel destinations.2 Medical histories that include cancer, immune dysfunction, cardiac or respiratory disease, organ or bone marrow transplantation, and hematologic disorders and other serious conditions may require modification of travel plans and alter their vaccine recommendations. For example, if the traveler plans to summit Kilimanjaro or visit Cuzco, a cardiac, respiratory, or hematologic history may make this itinerary ill-advised. Issues of altitude illness, although not fully predictable, are often more severe in those with known cardiovascular, respiratory, and hematologic disorders.3 Pregnancy, lactation, and serious conditions requiring close monitoring may make rustic environments inadvisable.

It is important to explore the activities and purpose of a patient’s trip. Note if the patient will be staying in air-conditioned hotel versus open-air accommodations, in urban versus rural setting, or participating in high-altitude or adventure travel. Patients who anticipate adventure travel to rabies-endemic areas...
may require preexposure vaccination. Some accommodations indicate increased risk of vector-borne diseases such as malaria, dengue, chikungunya, tick-borne encephalopathy, and Japanese encephalitis (JE). Rural, remote destinations increase the need for heightened food and water vigilance to prevent food-borne illness.2 Country- and region-specific recommendations must also be considered. Travelers to the meningitis belt of sub-Saharan Africa should be advised to receive meningitis vaccination as should pilgrims traveling to Saudi Arabia during the Hajj or Umrah.4

Destination information will guide in the provision of appropriate antibiotics for self-administration if the patient experiences travelers’ diarrhea while abroad. The quinolones, once thought of as the primary medications for use in the empiric treatment of uncomplicated travelers’ diarrhea, are no longer effective in regions of Southeast Asia or the Caribbean, related to resistance patterns in Campylobacter and cholera isolates.5,6

Prophylactic antimarial medication choice will be driven by the distribution of Plasmodium strains found in the destination. Chloroquine resistance is common in many parts of the world, making this once standard of care ineffective in multiple locales. In the presence of chloroquine-resistant strains of malaria, doxycycline, atovaquone/proguanil, or mefloquine could be used to aid malaria prevention. Each medication has a side effect profile to be weighed against the patient’s history and current medication regimen to offer the best prescribing match.7

FOOD AND WATER
Travel to developing countries with low levels of community access to inside toileting facilities, plumbing, clean running water, and reliable refrigeration places the traveler at high risk for food-borne illness and cholera.3 Risk reduction strategies of contamination avoidance and increased vigilance should be recommended.

Foods and destinations can be divided into high, intermediate, and lower risk for food-borne illness.5,6 High-risk destinations include Asia, the Middle East, Africa, Mexico, Central America, and South America. Eastern Europe, South Africa, and the Caribbean Islands are considered intermediate-risk destinations, with the industrialized destinations of the US, Canada Australia, New Zealand, Japan, and Northern and Western Europe being considered low risk. High-risk foods are any served moist or at room temperature, unpeeled raw fruits and vegetables, salad greens, berries, unpasteurized dairy, and undercooked meat and seafood. Lower-risk foods include dry products such as bread, self-prepared foods made in potable water, bottled water, and carbonated drinks. Buffet-style foods, reconstituted juices, and food prepared or served by street vendors should be avoided. Use mnemonic devices like “boil it, cook it, peel it or forget it” to educate travelers on the risks of consuming undercooked produce, dairy, or meats.5 Travelers should avoid nonpotable water sources such as tap water, ice, fountain drinks, beer and soda on tap, and water from hotel sinks and showers. Recommend hand washing with > 60% alcohol-based hand sanitizer before meals and food handling to further reduce the risk of pathogen ingestion.5

VECTOR-BORNE DISEASE
Vector-borne diseases account for more than 17% of all infectious diseases worldwide and result in more than 1,000,000 deaths annually.8 Mosquitoes, flies, fleas, triatomine bugs, and freshwater aquatic snails are vectors known to spread disease to humans. Yellow fever (YF), malaria, dengue fever, chikungunya fever, JE, and West Nile virus are all spread by the bite from a mosquito. Ticks transmit Lyme disease, tularemia, Rocky Mountain spotted fever and other rickettsial diseases, ehrlichiosis, and the newly identified Heartland virus.9 Flies can spread leishmaniasis, onchocerciasis (river blindness), and African trypanosomiasis (African sleeping sickness). The triatomine bug is implicated in the spread of American trypanosomiasis (Chagas disease) with fleas implicated as vectors for bubonic plague and freshwater aquatic snails spreading diseases such as schistosomiasis.8

Although vaccinations exist for some vector-borne diseases such as YF and JE, many diseases have none. Others, such as tick-borne encephalitis, have vaccinations only available outside of the US, making vaccination impractical for leisure travelers. The prevention of vector-borne diseases includes
avoidance of at-risk areas and behaviors coupled with consistent insecticide and repellent use. Instruct travelers to avoid wading in freshwater rivers, lakes, and streams to prevent contact with waterborne infectious agents. Travelers should not sleep in adobe brick and palm thatch huts while in South America to lessen exposure to the triatomine bugs associated with Chagas disease. Travelers should be taught to wear long sleeve woven shirts, long pants, and hats to provide a barrier to stinging and biting insects. Further precautionary measures include treating clothing with permethrin repellent and applying insecticide to skin. The Centers for Disease Control and Prevention (CDC) recommend using insecticides containing DEET, picaridin, oil of lemon eucalyptus, or IR3535 to aid in insect bite reduction. Sleeping in air conditioning and avoiding outside activities from dusk to dawn decreases the likelihood of exposure to malarial mosquitoes. If air conditioning is not available in malaria risk areas, travelers should sleep under permethrin-treated mosquito netting and use tight screening in the windows of their sleeping area.

Malaria
Malaria is caused by Plasmodium species of parasites that are spread via the bite of an infected female anopheles mosquito. In 2012, an estimated 627,000 people died of malaria worldwide, disproportionately impacting children in sub-Saharan Africa. In the US, approximately 1,500 to 2,000 cases of malaria are identified annually. Between 1957 and 2011, 63 outbreaks of locally transmitted malaria occurred in the US. These outbreaks were brought into the US by international travelers who were infected abroad, allowing the parasite to be transferred to a new local person through a mosquito bite. Malaria can also spread from mother to unborn child, sharing used needles, blood transfusion, and organ transplantation. Symptoms of infection generally occur between 10 days and 4 weeks after infection, although some report symptoms as early as 7 days postinfection or up to 1 year later. Plasmodium vivax and Plasmodium ovale can have a remitting and exacerbating symptomatology, which can further complicate diagnosis. Symptoms of malaria include fever, chills, malaise, nausea, vomiting, diarrhea, myalgia, back pain, headache, anemia, jaundice, neurologic changes including dizziness and confusion, and coma leading to death if not properly identified and treated. Plasmodium falciparum and Plasmodium knowlesi are considered the most lethal of all known human Plasmodium species with a rapid progressive illness pattern that quickly deteriorates to neurologic symptoms and death.

The determination of species and drug susceptibility is narrowed via evaluation of the travel destination. P falciparum and Plasmodium malariae are distributed worldwide in tropical and subtropical regions, P vivax is predominantly in Asia and Latin America and limitedly in Africa, P ovale is found primarily in West Africa and the islands of the Western Pacific, and P knowlesi has been identified in Southeast Asia and Malaysia. Confirmatory testing is needed so the appropriate treatment regimen can be initiated.

Determine the treatment approach for malaria with the following stepwise approach: proper identification of the infecting Plasmodium species, the patient’s clinical status, and Plasmodium drug susceptibility. Malaria is identified via the use of thick and thin blood smears with staining. The interpretation of smears needs to be performed immediately after collection by a clinician familiar with malaria. One negative blood smear does not preclude the diagnosis of malaria, but rather repeat smears should be completed every 12-24 hours for a total of 3 sets. If three sets of smears, prepared and read by a qualified technologist, are read as negative, the diagnosis of malaria can be ruled out. If Plasmodium is identified on stained smears, the parasite density should be estimated via microscopy. Polymerase chain reaction testing is done to finalize the determination of species and drug resistance. The CDC will perform testing and offer treatment regimens for all cases of malaria diagnosed in the US.

Dengue Fever
Dengue fever is caused by a single-stranded RNA flavivirus transmitted to humans by a bite from the Aedes aegypti mosquito primarily and to a lesser degree Aedes albopictus, Aedes polynesiensis, and Aedes scutellaris mosquitoes. Dengue virus (DENV) has four distinct serotypes identified with a wide spectrum of clinical symptomatology. DENV is the most common arbovirus with an estimate of over 100
million infections annually worldwide. DENV has been identified in Africa, Asia, the Americas, and the Caribbean. DENV symptoms range from asymptomatic infection to severe disease with shock and hemorrhage. Symptoms include fever, myalgia, arthralgia, retro-orbital pain, nausea, vomiting, abdominal pain, rash, positive petechiae via the tourniquet test, laboratory abnormalities of leukopenia, increased hematocrit, and a rapid decrease in platelet count. DENV can progress to severe organ impairment, shock, hemorrhage, and fluid accumulation with respiratory distress. Many cases of DENV go unreported and undiagnosed because they often occur in regions where malaria is also endemic. DENV has no vaccination and no curative treatment regimen, with supportive care only for symptom management. If a patient has traveled to a malaria-endemic region and malaria has been ruled out, other causes of internationally acquired illness must be explored. Even if malaria has been confirmed, coinfection with DENV and chikungunya virus (CHIKV) cannot be excluded without further diagnostic testing.

**Chikungunya Fever**

Chikungunya fever is caused by an alphavirus that transmits to humans via a bite from the *A. aegypti* or *A. albopictus* mosquito. CHIKV infection begins with vague complaints of febrile illness with fatigue, headache, nausea, vomiting, muscle pain, and rash. The characteristic that often differentiates CHIKV symptoms from DENV is severe persistent joint pain. No hemorrhagic symptomatology is noted with CHIKV, and infection is rarely fatal. Treatment focuses on supportive care and symptom management. CHIKV has been identified in Africa, Asia, the Americas, and the Caribbean. DENV and CHIKV infections are often mistaken for the other and commonly overlooked for malaria. Symptoms can appear between 2 and 12 days after infection and typically occur within 3–7 days. CHIKV confers lifelong immunity to reinfection regardless of symptomatology.

**VACCINE-PREVENTABLE ILLNESS**

A working knowledge of vaccinations is imperative when providing care to international travelers. Use the CDC traveler Web site to review vaccinations and general recommendations for a particular destination. Although helpful, no Web site should be viewed as the final word on which vaccinations are recommended for a particular patient in a particular destination. Develop a plan of care based on a review of commonly circulating illnesses, a patient’s medical and vaccination history, and knowledge of contraindications for the vaccinations and medications suggested. For NPs in primary care, this nuance in prescribing for many destinations should trigger a referral to a travel health clinic. Travelers’ health clinics provide consultations for international travelers and are valuable resources in the continuum of care for patients. If a patient’s travel includes a country that requires YF vaccination, referral to a certified YF clinic will be necessary.

**Live Vaccinations**

**YF.** YF is caused by a flavivirus that is spread via the bite of an infected female *A. aegypti* mosquito. YF is currently isolated to regions of Africa and South America. Symptoms of YF begin 3–6 days after infection and include fever, chills, headache, and myalgia and may progress to jaundice, hemorrhagic complications, shock, multisystem organ failure, and death. Proof of vaccination is an entry requirement for many countries and will require an official YF document be provided from a certified YF clinic. YF is a live vaccine and should not be given to pregnant women; children under the age of 6 months; or anyone with an immune-altering condition, allergies to eggs, chicken proteins, or gelatin. Additionally, conditions such as DiGeorge syndrome, myasthenia gravis, a thymoma, or surgical removal of the thymus are absolute contraindications to vaccination. If a
patient is over 60 years of age or between the ages of 6-8 months, special consideration of the true risk of disease in an area need to be weighed against potential complications from the vaccine.10 It is not uncommon for the risk of disease to be much different from the entry requirement documents of a specific country. If a patient is found to be inappropriate for vaccination, a YF clinic can issue a deferment certificate. NPs in primary care should refer any patient traveling to Africa or South America to a YF clinic for evaluation of the potential need for vaccination or documentation of YF deferment status. Additionally, if the patient’s trip will take them through a YF country, even with just an airplane layover stop, vaccination or documentation may be required. The YF clinic will make the determination of vaccination or documentation needs and provide the necessary certificate to the traveler. The YF certification document is valid for 10 years after the date of issue. A list of YF clinics can be found on the CDC Web site.10

**Typhoid Fever.** Typhoid fever (TF) is a bacterial illness caused by *Salmonella typhi*. Ingestion of food or water contaminated by feces via either food handling by infected carriers or direct inoculation is the most common route. An estimated 21 million people contract TF worldwide, and over 200,000 will die from the disease annually.19 Of those infected, approximately 3%-5% will become chronic carriers who are asymptomatic yet capable of spreading the disease. TF is endemic in developing countries worldwide and is common in all but the most industrialized nations such as the US, Canada, Western Europe, Australia, and Japan. Symptoms of TF include a fever of 39°C-40°C, weakness, abdominal pain, headache, anorexia, and, in some cases, a rose-colored spotted rash. TF is definitively diagnosed via blood and stool sampling for the presence of *S typhi*.19

Vaccination is available in a live oral or an inactivated injectable form. Do not give the live oral form to children younger than 6 years old; persons with immune-altering conditions, serious gastrointestinal disease, active nausea, or vomiting; or patients on oral antibiotics. Oral typhoid vaccination can be given without consideration of spacing of other live vaccinations. Patients take the live oral vaccination in four capsules, with one capsule taken by mouth every other day, on an empty stomach with a full glass of water. A booster is recommended every 5 years if exposure to typhus continues. The inactivated vaccination is given as one injection with booster recommended every 2 years if exposure to typhus continues.19

**Measles, Mumps, and Rubella.** Measles outbreaks occur worldwide with recent outbreaks in the US, Philippines, Europe, and Brazil. The CDC reports a record number of 514 US measles cases reported from January 1 through June 20, 2014. Unvaccinated or underimmunized persons traveling abroad are frequently the transporter of measles and other vaccine preventable diseases into the US after visiting areas where these illnesses are common.20 Measles are highly contagious and easily spread via the respiratory tract from 1 person to another. Symptoms typically occur 7-14 days after exposure and generally present with a mild to moderate fever, cough, sore throat, runny nose, and conjunctivitis. Three to five days after the early symptoms first appear, a blotchy rash and high fever occur and are often accompanied by increasing malaise and Koplik spots in the mouth and throat. The rash typically begins at the hairline and spreads downward over the neck, trunk, arms, legs, and feet. As the fever subsides, the rash fades. A person with measles is contagious for approximately 4 days before and up to 4 days after the rash appears.20 Advise international travelers who transit into or through a country with a current outbreak to verify immunity via titer or receive a booster of measles vaccination if not contraindicated.

**Inactivated Vaccines**

In addition to the aforementioned inactivated typhoid vaccination, other vaccinations may be recommended based on the traveler’s itinerary. Although many of these vaccinations are also given in the US as a matter of routine primary care, an understanding of increased risk when traveling should necessitate a careful review of vaccine history.

**Hepatitis.** Hepatitis A is an RNA picornavirus that is spread via the fecal-oral route, much as is *S typhi*. According to the CDC, hepatitis A is 1 of the most common vaccine-preventable infections
acquired by international travelers. The virus infects the liver and can cause symptoms such as abdominal pain, anorexia, nausea, dark urine, clay-colored stool, or jaundice. Occasionally, rash and joint pain are also present. In infants and young children, hepatitis A infection is often asymptomatic. A person infected with the hepatitis A virus may be contagious up to 2 weeks before exhibiting any symptoms of illness and remains contagious until all symptoms resolve. The incubation period averages 28 days but ranges from 15-50 days. If symptoms appear, illness ranges from mild symptoms for 1-2 weeks up to a severe illness lasting several months. The hepatitis A vaccine series consists of two injections given 6 months to 1 year apart. Pediatric and adult formulations are available. The first dose provides coverage for the 12 months until the final dose is given. Full vaccination is believed to confer lifelong immunity.

Hepatitis B is a partially double-stranded DNA virus in the *Hepadnaviridae* family spread via contaminated body fluids. Recommend vaccination for travelers to hepatitis B—endemic countries who anticipate medical or dental procedures, tattooing, piercing, acupuncture, or unprotected sexual activity. Incubation of hepatitis B ranges from 60-150 days with an average incubation of 90 days. The virus infects the liver and can cause abdominal pain, anorexia, nausea, dark urine, clay-colored stool, or jaundice. Occasionally, rash and joint pain will also be present. In infants and young children, hepatitis B infection is often asymptomatic. Serologic testing is necessary to determine which hepatitis virus is responsible for the patient’s symptoms in order to determine a plan of care. If hepatitis B is identified, the serologic markers will determine if the patient is in an acute, resolving, or chronic infective state. Chronic hepatitis B infection places the patient at increased risk of liver cirrhosis and liver cancer. The hepatitis B vaccine series is given in three doses with the second dose given 1 month after the first and the final dose given at 6 months after the first dose. Full vaccination is believed to confer lifelong immunity.

**JE.** JE is caused by a flavivirus and spreads via the bite of an infected *Culex* mosquito. JE is the leading cause of vaccine-preventable encephalitis in Asia and
the Western Pacific. Most infected persons will experience either no or mild symptoms.24

Symptoms will typically occur 5-15 days after infection. For patients with severe disease, sudden onset of fever, chills, fatigue, headache, malaise, nausea, and vomiting can progress quickly to seizures, coma, paralysis, and death. Neurologic changes in JE can be mistaken for parkinsonian-like features of masklike facies, tremor, cogwheeling, and rigidity as well as a poliomyelitis-like acute flaccid paralysis. JE is diagnosed by examination of the cerebrospinal fluid to detect virus specific immunoglobulin M antibodies. JE antibodies are detectable 3-8 days after illness onset and persist for 30-90 days.25,26

Polio. Polio is caused by an RNA picornavirus and spreads through the fecal-oral route or person to person via oral secretions. There are three known serotypes of the poliovirus, meaning that infection with 1 serotype does not provide immunity to all serotypes. Approximately 95% of persons infected with polio are asymptomatic but can spread the disease to others. Approximately 4%-8% of infections present with common complaints of upper respiratory tract infection, gastrointestinal complaints, or febrile illness and may go undiagnosed. Aseptic meningitis will be observed in 1%-2% with flaccid paralytic symptoms noted in only 1% of all infections. Patients are most infectious 7-10 days before and after symptoms present with poliovirus present in the stool for up to 6 weeks after exposure. Although polio was eradicated in the US by 1979, it remains a threat in parts of Asia, Africa, and the Middle East. Recommend an adult booster for travelers to countries where polio infection persist even in persons who received the full immunization series in childhood or in persons who report a history of polio in childhood.26

Table 2. Role of the Primary Care Nurse Practitioner

- Pretravel
  - Assess for travel destination specific information
  - Antimarial/TD medications
  - Air-conditioned accommodations
  - Adventure/altitude/long stay travel
  - Discuss food/water/insect precautions
  - Provide vaccinations/medications or refer to travel clinic
  - Be alert to special considerations (patient health and yellow fever)
- Posttravel
  - Assess for travel-related illness
    - Fever
    - Nausea/vomiting/diarrhea
    - Skin conditions
    - Respiratory conditions
    - May perform baseline testing BUT do not delay infectious disease referral waiting for test results
  - When patients present to primary care with possible infectious disease, always ask about history of travel
- Referral
  - Pretravel: travel clinic for specialized considerations/vaccinations
  - Posttravel: infectious disease for suspected travel-related illness assessment and treatment

POST-TRAVEL CONSULTATION
A post-travel consultation is recommended for patients who traveled to developing countries, those who develop illness while traveling abroad or soon after their return, and those who develop any febrile illness within 3-4 months of return from a malaria-endemic region. Conduct a careful review of itinerary, activities, and exposures. Make note of all symptoms known to accompany travel-related infectious diseases common in areas visited including date symptoms first appeared, progression, remission, and recurrence. Many infectious diseases acquired abroad initially present with vague, nonspecific complaints that are often overlooked, underreported, or misdiagnosed (Table 1).27 Once this initial phase passes, the patient’s symptoms and clinical status may decline rapidly. Special testing to differentiate the infectious agent and determine appropriate treatment should be done under the care of an infectious disease (ID) specialist.

For NPs in primary care, a complete history and physical along with baseline testing of complete blood count with differential, complete metabolic panel (CMP), and renal and liver function tests are appropriate as are basic ovum and parasite stool testing if gastrointestinal symptoms are reported (Table 2). A qualified laboratory with specific instructions provided by the ordering NP should perform blood smears for malaria, polymerase chain reaction, and serologic testing for specific viral antigens as well as specific repeat stool testing for giardia and cyclospora.5-7,10-15,25-27

Referral to a
qualified ID or major medical center with an ID should not be delayed while awaiting the return of baseline test results. Any case of suspected infectious disease acquired while abroad should trigger an immediate and rapid referral.

Primary care NPs should not attempt to definitively diagnose or manage these infections without specialist intervention. Cases of infectious disease acquired internationally and those diseases that can be transmitted person to person locally such as Middle East Respiratory Syndrome Coronavirus (MERS CoV), tuberculosis, measles, polio, and typhoid fever will have reporting requirements within your municipality, state, and the CDC. As international travel increases and globalization of the marketplace continues, it is imperative that NPs have a working knowledge of emerging disease patterns and trends worldwide.

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