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Risk Mitigation for Travelers: Managing Endemic and Emerging Threats

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REVIEW ARTICLE

Risk mitigation for travelers: managing endemic and emerging threats

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ABSTRACT

International travel continues to increase in numbers and complexity. Despite the availability of pretravel health advice, travelers remain at risk for exposure to common organisms as well as emerging pathogens. With low rates of travel clinic utilization, it is important for the general practitioner to remain aware of the importance of travel health, risk factors unique to individual patients, and evolving threats. This review highlights important considerations when evaluating ill travelers, incorporating emerging infectious threats.

Background International travel continues to explode, with over 1 billion international tourist arrivals per year[1,2] and an estimated 2 billion by 2030.[3,4] As a risk factor for infectious diseases, international travel has become an increasingly complex issue. Reasons for travel are numerous, and the spectrum of destinations has expanded with increasing travel to developing countries, namely, in Asia and Africa.[1,2,4,5] While most international travel is for leisure, other reasons include business, education and research, volunteer work, visiting friends and relatives (VFR), medical tourism, adoption, as well as immigration and military activities, all of which have their own unique risks.[4-8] Additionally, travelers themselves are increasingly diverse. Travelers of all ages, immunocompromised travelers, and travelers with comorbid conditions frequent high-risk destinations.[6,9-12]

The percentage of travelers who become ill ranges significantly in published studies (6%–87%), although a recently published review concluded that 43% to 79% of travelers who visited developing countries became ill.[4] These numbers are affected by patient expectations from travel (whether they choose to present to care because of travel-associated illness) and regional patterns of disease (those who reside in metropolises close to a threat may experience it already). Despite high rates of morbidity associated with travel to developing countries, most travelers do not seek pretravel counseling. The exact proportion varies considerably by study, but most reports showed rates below 50%, and in one small study, only 9% of Hong Kong travelers received pretravel advice.[1,5,7,13-16] However, even in the context of pretravel counseling and receipt of appropriate preventive measures, the rates of morbidity remain high with up to 75% of patients reporting illness during travel in one prospective cohort.[1]

The most common categories of illnesses reported in travelers are gastrointestinal syndromes, febrile illnesses, dermatologic disorders, and respiratory illnesses.[4,5,15,17] The spectrum of potential pathogens causing these syndromes is incredibly broad, and emerging threats should be considered. The impact of international travel on the visited population and the population to which the traveler returns should also be considered. International travel may contribute to the spread of disease and disease emergence, in some settings.[18] Travelers have been explicitly implicated in the spread of severe acute respiratory syndrome, influenza H1N1 virus, measles, mumps, dengue, malaria, and cholera, to name a few.[5,19,20]

In the setting of increasing international travel, traveler complexity, expanding destinations, low rates of pretravel counseling, and broad infectious differentials, primary care providers must become more aware of risk factors for acquisition of infection and emerging threats when evaluating international travelers. In this review, we highlight important considerations when evaluating travelers, with a special focus on the risk of emerging infectious diseases, by placing clinical syndromes in a travel context.

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Risk of exposure In epidemiologic studies, time spent with an exposure dominates risk profiles. Whether counseling a would-be traveler or evaluating one who has returned with a concern, early in the interview an exposure assessment is required. What did the person actually do when on travel? Where was this done in terms of the setting and season, not just location? How did the person prepare for potential risks? Why a person chooses to travel, what they intended to do, what they might have done because opportunities arose? These issues are all vital to assessing risk. One particular example of this is VFR travelers. Research has consistently demonstrated a higher risk of acquiring infection in this group, which in many cases is preventable.[21] In the United States, higher rates of hospitalization were noted among VFR travelers presenting to GeoSentinel clinics.[22] These travelers have lower rates of pretravel health visits and longer stays, which likely contributes to these differences.[22,23]

A traveler's specific reason for travel and travel itinerary can unveil unique risk factors as well. Medical care, adoption, freshwater activities, visiting or caring for the ill, medical tourism, sex tourism, refugee and other aid work, missionary work, activities at altitude, diving, food sources, and accommodations all contribute to a milieu in which travel-related disease may be acquired or nontravel-related disease may be exacerbated. In a study on travelers consulting a travel medicine clinic, 83% of over 700 respondents reported at least 1 risk behavior, and younger travelers in general participated in more risky behaviors.[24]

Geographic locations have their own individual risks. GeoSentinel surveillance has documented variable risks for certain infectious syndromes by geographic region. For instance, malaria was the most common cause of systemic febrile illness after travel to sub-Saharan Africa, while dengue was more frequent for all other locations except sub-Saharan Africa and Central America.[8] Furthermore, certain risks may be confined to specific areas or subregions even if they are commonly considered to be more broadly present. For example, yellow fever is endemic to specific tropical areas of Africa and Central and South America. Detailed information about these regions is available to providers through the United States Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC), World Health Organization (WHO), and other national-level public health agencies.

Similarly, malaria is present in specific geographic locations, with absence of transmission at higher altitudes where the vector, the Anopheles mosquito, is not encountered. Seasonal variation is also an important consideration. GeoSentinel surveillance revealed significant seasonal variation in dengue transmission, with more cases reported from September to December in South Central Asia with a peak in October. Rates in the Caribbean were highest between August and December, while March was the peak month of transmission in South America, reflecting the rainy seasons in these locations.[25] Dry weather also carries specific infectious risks. In sub-Saharan Africa, the incidence of meningococcal meningitis increases every dry season.[26]

Additionally, providers should be aware of known outbreaks (whether it is violence or infectious diseases) and other hazards near the spots included in a patient's itinerary. Notifications of outbreaks can be found on the CDC, ECDC, or WHO websites. Outbreaks and unrest often are delineated on the websites of ministries of foreign affairs. In 2019, notable outbreaks include Ebola virus disease in the Democratic Republic of the Congo (DRC), with related risk in neighboring countries; Middle East respiratory syndrome coronavirus (MERS-CoV) in Oman and Saudi Arabia; a worldwide measles outbreak; and cholera in several locations. Realized risk for emerging infectious diseases in the broad population of short-term travelers has been low. Although early cases in Europe of MERS-CoV were associated with Umrah, several large-scale studies examining Hajj and Umrah have failed to identify cases.[21,27,28] Nonetheless, when it is realized, it is very impactful. South Korea experienced a consequential nosocomial MERS-CoV outbreak associated with a single short-term traveler, and to a lesser extent so did the United States from Ebola Zaire virus.[29-31]

Travel is a common precipitating theme in Disease Outbreak News reports for micro-outbreaks.[32] In many of these instances, the traveler was exposed to an established, recognized outbreak. The purpose of their travel brought them in close proximity to areas of risk, and so a broad application of usual traveler preparation coupled with risk communication regarding emerging disease events, and careful agreement about steps to take on return if ill, would be beneficial in risk management in similar cases. Respiratory disease from novel or emerging influenzas and coronaviruses such as severe acute respiratory syndrome coronavirus are notable exceptions to this. All travelers should understand that the unexpected occurs and that travel becomes part of their history of present illness or past medical history, as appropriate. In counseling a traveler, reassurance that travel can be safe with proper precautions should not attenuate vigilance with illness on return by both the provider and patient.

Patient vulnerabilities Important patient characteristics to consider include age, pre-existing medical conditions or comorbidities, and reasons for travel. Among travelers enrolled in the Global TravEpiNet, the age range was broad (1 month to 94 years) with a median age of 34 years.[6] While increasing age is generally associated with more underlying medical conditions, and subsequently increased risk of becoming ill when traveling, one study found that older travelers complied more with medical advice, took fewer risks, and had lower rates of illness compared with younger

travelers (19% vs 34%).[33] According to Global TravEpiNet data, over half of all travelers in a single analysis reported 1 or more medical conditions and taking at least 1 daily medication.[6] Similarly, a large cross-sectional study in the greater Boston area found 74% of travelers had medical comorbidities, 18% were considered high risk, and 23% were immunocompromised.[12]

Identification of persons with pre-existing medical conditions and immune compromising conditions is important, as research suggests higher incidence of a travel-related illness in individuals with pre-existing medical conditions and higher rates of hospitalization in immunocompromised individuals when an illness occurs during travel.[34-36] The number of living immunocompromised persons is expected to increase, especially as indications for biologic agents expand, such as monoclonal antibodies used to treat rheumatologic and oncologic conditions. A study evaluating 486 immunocompromised international travelers seen at Global TravEpiNet sites found that biologic agents such as tumor necrosis factor inhibitors were the most commonly used immunosuppressive medications.[36] Not only are these individuals at increased risk of complications related to infection, but pretravel live vaccinations may be contraindicated (ie, yellow fever or measles, mumps, rubella). Also, the extent to which a traveler's activities and stress may contribute to becoming ill when traveling is underappreciated. Pre-combat stress has well-documented impact on disease and non–battle injury rates among deployed service members.[37] An increased rate of upper respiratory tract infections with commensurate functional immunodeficiency has been observed in athletes.[38]

While travelers often do not seek pretravel health advice, when they do, sources often include general practitioners, family and friends, and the internet, with low utilization of travel clinics.[17,39,40] However, even in the setting of appropriate counseling and preventive measures, the rates of morbidity remain high.[1] Studies have demonstrated low rates of insect repellent utilization, vaccine series completion, and proper utilization of malaria prophylaxis among travelers.[13,41-43] To what extent VFR travelers tighten their selection of water sources and use of handwashing in cholera zones, or defer ritualistic funeral practices in regions with Ebola virus, for instance, is unknown. Nonetheless, tailored advice relevant to emerging infectious diseases events should be incorporated along with usual guidance on maintaining wellness while traveling, when relevant to the itinerary. For some travelers, their very activity may uniquely precipitate increased exposure to an emerging infectious disease, as occurred with leptospirosis among adventure athletes from around the world in one notable event.[44]

Recommended preventive measures are part of an important layered approach in travel risk management. In isolation, they have variable efficacy. This information is important for risk communication of the significance of layered preventative measures such as those against mosquito- and food-borne illnesses, for addressing preventative misconceptions of patients and providers relevant to risk behavior (such as the false idea that any single prevention step done alone is enough), and for properly characterizing illness in returned travelers. For instance, the protective efficacy of available typhoid vaccination is low and ranges from 50% to 55%.[45] On the other hand, the protective efficacy of hepatitis A, B, rabies, MMR, and varicella vaccinations is high, though none of them is perfectly protective in every individual.[46] While often effective, the actual efficacy of medication prophylaxis against malaria can vary widely by circumstance, and the utility of doxycycline for preventing leptospirosis remains unclear.[47] Despite this, most infections associated with travel are preventable, particularly those associated with travel to Africa.[2,48]

Fever in a traveler: a clinical syndrome in context

Physicians who evaluate ill returned travelers also must place events in the context of recent travel. The first steps towards this are defining the clinical syndrome and assessing the incubation period for risks specific to both cosmopolitan and geographical areas. As physicians, the presenting clinical syndrome is the gateway to our understanding of the patient's experience with an illness. What accompanies the patient's fever—cough, diarrhea, rash, lymphadenopathy, hepatosplenomegaly, mental status change? Where has the patient been and when—sometimes over months to years but generally in terms of the last couple of weeks, several weeks, and longer?[49,50] Some of these relationships are presented in TABLE 1. How do they come together with the patient's travel behaviors and other factors to suggest how prioritizing the most dangerous and most likely diagnoses impacts management?

A common pitfall in how this thinking is applied is to forget common infectious and noninfectious illnesses that may occur anywhere. Anyone can experience influenza. Travelers may experience intravascular thrombi, vaccine reactions and other hypersensitivity reactions, consequences of disruptions in chronic disease management, cancer (particularly breast, testicular, and hematologic in younger travelers), rheumatic diseases, such as systemic lupus erythematosus, and everything else that happens to people regardless of whether they are risk takers or because they are risk takers. Work–travel routine may disrupt usual healthcare use and increase the risk for hard-to-manage conditions while on travel, such as human papilloma virus and shingles vaccination, routine oncologic and cardiovascular screening, and dental maintenance.

Investigating returned travelers with a fever may pose a challenge to usual clinical laboratory processes. Assessing samples for parasitic diseases may require specialized techniques with which

TABLE 1 Diagnoses of infectious causes of fever in travelers: clinical syndrome and incubation period matrix (continued on the next page)

Incubation period	Less than 2 weeks	2 to 6 weeks	More than 6 weeks
Travel-associated undifferentiated fever	Angiostrongyliasis Arboviral encephalitis Campylobacteriosis Coccidioidomycosis, acute Dengue Genital ulcer disease Histoplasmosis, acute HIV, acute Influenza Legionellosis Leptospirosis Louse-borne typhus Malaria Meningococcemia Poliomyelitis Q fever Rabies Salmonellosis Scrub typhus Shigellosis Spotted fever Syphilis Trypanosomiasis, East African Typhoid fever Viral hemorrhagic fever	Acute HIV Acute schistosomiasis Amebic liver abscess Brucellosis Hepatitis A or E Leptospirosis Malaria Melioidosis Q fever Syphilis Trypanosomiasis, East African Typhoid fever Viral hemorrhagic fever	Amebic liver abscess Chronic mycosis Hepatitis B Hepatitis E Hookworm Leishmaniasis, visceral Lymphatic filariasis Malaria Melioidosis Paracapillariasis Rabies Schistosomiasis Strongyloidiasis Trypanosomiasis, African Tuberculosis
Fever + mental status change[a]	Angiostrongyliasis Arboviral encephalitis Louse-borne typhus Malaria Meningococcemia Rabies Scrub typhus Syphilis Tick borne encephalitis Trypanosomiasis, East African Typhoid fever Viral encephalitides	Louse-borne typhus Malaria Scrub typhus Syphilis Trypanosomiasis, East African Tick borne encephalitis Typhoid fever Viral encephalitides	Amebic liver abscess Chronic mycosis Malaria Rabies Syphilis Trypanosomiasis, African Tuberculosis
Fever + hepatomegaly without splenomegaly	Trypanosomiasis, East African Viral hepatitides	Schistosomiasis, acute Trypanosomiasis, East African Viral hepatitides	Leishmaniasis, visceral Trypanosomiasis, African Viral hepatitides
Fever + splenomegaly	Dengue HIV Infectious mononucleosis Leptospirosis Malaria Typhoid fever Typhus Viral hemorrhagic fever	Brucellosis Dengue HIV Infectious mononucleosis Leptospirosis Malaria Q fever Schistosomiasis, acute Typhoid fever Viral hemorrhagic fever	Leishmaniasis, visceral Malaria Tuberculosis

TABLE 1 Diagnoses of infectious causes of fever in travelers: clinical syndrome and incubation period matrix (continued from the previous page)

Incubation period	Less than 2 weeks	2 to 6 weeks	More than 6 weeks
Fever + lymphadenopathy	**Generalized**	**Generalized**	**Generalized**
	Dengue	Dengue	Disseminated fungal infection[b]
	Disseminated fungal infection[b]	Disseminated fungal infection[b]	HIV
	HIV, acute	HIV	Leishmaniasis, visceral
	Infectious mononucleosis	Infectious mononucleosis	
	Regional	**Regional**	**Regional**
	Anthrax	Nontuberculous mycobacteria infection	Blastomycosis
	Bacterial lymphadenitis	Trypanosomiasis	Nontuberculous mycobacteria infection
	Plague	Tuberculosis	Tuberculosis
	Scrub typhus		
	Trypanosomiasis		
	Tularemia		
	Local	**Local**	**Local**
	African tick bite fever	Nontuberculous mycobacteria infection	Nontuberculous mycobacteria infection
	Bacterial lymphadenitis	Tuberculosis	Tuberculosis
	Sexually transmitted infections		
Fever + cough or shortness of breath	Aggressive volume repletion in setting of	Bacterial pneumonia	Amebic abscess
	Dengue	Disseminated fungal infection[b]	Disseminated fungal infection[b]
	Bacterial pneumonia	Katayama fever	Malaria
	Disseminated fungal infection[b]	Leptospirosis	Melioidosis
	Legionellosis	Loffler's syndrome	Tuberculosis
	Leptospirosis	Malaria	
	Malaria	Melioidosis	
	Q fever	Q fever	
	Severe acute respiratory disease pathogens[c]	Tropical pulmonary eosinophilia	
	Transfusion lung injury		

This is not an exhaustive list but rather a frame of reference for initial assessment.[3,49,50] An individual patient might present with almost any sepsis clinical syndrome regardless of pathogen, and host factors may attenuate or exacerbate what normally would be a more characteristic syndrome. Patients may have more than 1 problem, for example, bacterial coinfection following a viral syndrome and occurring seemingly late. A fever and rash or arthralgia are not included, though borrelia, rickettsioses, meningococcemia, syphilis, typhoid, and viral hemorrhagic fever (VHF) are commonly associated with the former, and flaviviruses (eg, Dengue and Zika), alphaviruses (eg, Chikungunya), and borrelioses with either or both a rash and arthralgia. Malaria and VHF should be included in the broader differential diagnosis of fever and diarrhea.

a In older patients, sepsis may present as decompensated cerebrovascular disease. Fulminant sepsis may show delirium and encephalopathy.

b In particular, endemic dimorphic yeast such as histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, and others

c Such as novel influenza, coronaviruses, New World hantaviruses

even a referral academic medical center may not be acquainted.[51] The local regulatory status of tropical disease assays, such as those for leptospirosis or dengue fever, or of emerging diseases, may vary. It is useful for physicians to discuss these issues with their laboratorian counterparts in advance. While awaiting a definitive diagnosis, clinicians sometimes try to rely on the presence or absence of arcane fever patterns, such as tertiary and quaternary fever patterns that require parasite synchronization in different types of malaria; pulse-temperature disassociation in typhoid fever and other illness of the reticuloendothelial system; or saddle-back patterns in dengue fever. While these may be informative, their individual predictive power is low.

A case Patient Zed (PZ) is a 65-year-old woman who presents to a clinic with a 1-day history of diarrhea and vomiting. You had seen her in clinic 6 weeks prior in preparation for her trip to eastern Rwanda, her first travel to Africa. She returned home to a suburb in the United States last night. PZ has abdominal cramping and feels lightheaded when standing. She has had 5 loose stools in the last 24 hours, which she says were watery and large, each time beginning explosively. There was no blood or pus in her stool. Yesterday, she had 2 vomiting episodes, water and food remnants without blood. She has hypothyroidism. Her only medications are levothyroxine and atovaquone/proguanil begun 2 days prior to the start of her trip. She has no other past medical or surgical history.

Patient Zed arrived in Rwanda 10 days before presentation along with her husband and a group of friends who sponsored an eastern Rwanda village as part of a twin or sister city relationship. While they paid visits to homes, churches, and restaurants, the group stayed in a guest house

accustomed to foreign travelers. They spent 1 day in a local game park. She is not aware of having had sick contacts and says that she was mindful of safer eating and drinking practices, vector mitigation with permethrin-treated clothes and wearing mosquito repellent, has adhered to her antimalarial medication prescription, and felt well until the onset of her symptom's yesterday. She thinks that she might have eaten a dodgy snack at the airport prior to boarding her flight home 2 days ago. She had no exposure to fresh water. Review of the patient's triage card shows an oral temperature of 37.5°C, a heart rate of 95 bpm, and normal blood pressure, respiratory rate, and pulse oximetry. You had observed her enter the room and she had a normal, rapid gait. In the chair opposite you she conversed comfortably. She appears to be of European descent.

As you are ready to perform a physical examination while suspecting a traveler's diarrhea from an enterotoxigenic *Escherichia coli* or a similar pervasive threat, you recall that cases of Ebola virus have been recently reported in Goma (DRC), which abuts the Rwandan border.[52,53] You remember your conversation with PZ prior to her trip and discussing that Rwanda was considered a high priority for preparedness activities, though it had not experienced an observed case. You check the CDC travel notices portal and see no warnings listed for Rwanda.[54] Knowing that situations like that in the DRC change quickly, you also check the WHO Disease Outbreak News and see an update on the DRC from 3 days ago that said there were no confirmed cases outside the DRC.[32] You start rising from your desk as a Twitter feed alert appears on the task bar of your screen, and it is from the WHO Director General confirming that cases have been found in South Kivu near the Rwandan border. This raises the risk for Rwanda of experiencing the current emergency, but it has not been observed yet. Taking a closer look at an online map, the place where your traveler visited is well away from the DRC border. Nonetheless, you ask the patient another set of questions about healthcare-associated work, ritual practices during the visit, and the health of her fellow travelers. Her responses were unremarkable, although she said that on reflection several members of her group had mild abdominal symptoms yesterday morning while on layover for a connecting flight home. But none of them were as bad as hers and seemed to self-resolve. They all had shared the dodgy airport snack.

Feeling reassured, you complete the physical examination, which is normal other than very mild abdominal discomfort with deep palpation. While washing your hands and reminding your patient to do so regularly, you ask your staff to provide her with oral rehydration solution followed by water, and within 45 minutes in the waiting room, her symptoms of orthostasis are gone and her heart rate is 80 bpm. While she did not experience a bowel movement during the visit, given the severity of her symptoms overnight as well as potential risk for fall and its consequences at her age if she gets further behind in volume status, you prescribe a brief course of antibacterial therapy, though you appreciate that other providers might reasonably wait another day and follow her symptoms. Thinking about her normal temperature (although in the upper part of the range) and that not all people's perceptions of what adherence means with antimalarial preventive medications are the same, you decide that you will call her by telephone tomorrow to make sure that she has not manifested a fever, her symptomatology is improving, and that her group has not shown more illness. She is not a food handler, daycare provider, or healthcare worker, and so you are not concerned about occupational restrictions from a potentially communicable enteric disease.

Over the remainder of the day, you consider how the visit and day would have been different if the patient had been a healthcare missionary closer to the DRC, a fever had been present, and she had looked a bit sicker, or if she had presented from an area with novel influenza or had small farm poultry exposure in Asia or camel or inpatient hospital contact in the Middle East and was experiencing cough, or was a long-time healthcare missionary and presented with cough and weight loss. You reflect that your concerns about potential connection to a public health emergency did not appear in the clinic until PZ had registered at the desk, spent time in the waiting area interacting with other patients, undergone triage, possibly used the bathroom or patient water cooler, and come through to your office. Your clinic staff decides to have an end-of-day debrief on the event and introduce signage so that patients self-identify immediately when communicable symptoms are present regardless of an itinerary or a potential pathogen (eg, cough, rhinorrhea, diarrhea, vomiting, bleeding), or an itinerary or contact of concern; make handwashing and masks readily available in the waiting room; and generate procedures for how to proceed when risk is recognized. Additionally, you review the process for alerting and seeking counsel from local public health authorities, generate an explicit procedure for contacting them incorporating their required forms, when appropriate, and have an exploratory call with those authorities to test that procedure. You reflect on the original pretravel counseling you provided to PZ and whether current circumstances would have made that counseling different, then implementing those changes systematically. You also think about the pervasive travel threats that more commonly impact travelers, such as motor vehicle accidents, heat injury, insufficient preparation for chronic disease management or urgent and emergent care, and how to ensure that they remain a key part of pretravel counseling and preparation even when focus increases on emerging infectious diseases events.

Summary Travel is an enriching and valuable activity. It should be undertaken appreciating

and managing the usual and unusual risks of traveling, the pervasive threat and the emerging threats, and the particular needs of patients. Ideally, when patients experience an illness while traveling, they should contact their travel medicine physician. When they experience illness following travel, they should exercise a predetermined plan for presenting for care. Anyone might see such a patient before or after travel. When they do, they should have a plan for conducting or referring the patient to get robust pretravel advice and for receiving such patients safely and effectively should they return with an illness. Infection prevention and control as well as public health requirements should be considered. And, every case is an opportunity to reflect and improve care practices.

ARTICLE INFORMATION

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