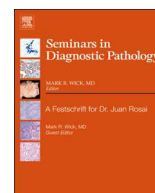




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## Review article

## Evaluation of the sick returned traveler

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## ABSTRACT

Infections are common during travel, and frontline physicians frequently must evaluate sick returned travelers. Sick travelers can be clinically challenging due to the wide range of endemic diseases in different geographic regions. To guide the diagnostic and treatment plan, consideration of endemic and emerging infections in the region of travel, as well as careful review of the travelers' exposures and preventative measures are necessary. Routine laboratory tests and cultures cannot confirm many tropical infections, and pathogen directed testing is typically required. Common tropical infections that can be severe, such as malaria, dengue, and enteric fever, should always be considered in the diagnostic evaluation. Providers should also be vigilant for rare but highly pathogenic emerging infections such as Ebola virus disease and Middle East respiratory syndrome (MERS).

## Introduction

The acutely ill returned traveler is a common clinical scenario. Depending on destination, studies indicate that the prevalence of travel-related illnesses among travelers can reach as high 80%.<sup>1,2</sup> Furthermore, international travel has dramatically increased over the past decades, and international tourist arrivals alone reached 1.2 billion in 2015, with increased numbers of traveler to destinations outside of Europe and North America.<sup>3</sup> Recent economic and popular trends have also led to an expanding range of travelers beyond business travelers, tourists, and aid workers, including budget travelers, study abroad students, medical tourists, and travelers visiting friends and relatives (VFR). VFR travelers are those returning to their countries of origin to visit friends and relatives, and as a group they tend to be at increased risk of severe travel-related infections.<sup>4</sup> The increase of international travel has also included those with special needs or medically complex travelers, including elderly, pediatric, pregnant, and immunocompromised travelers.<sup>4,5</sup> While well-known tropical diseases such as malaria, dengue, and enteric fever (typhoid and paratyphoid fevers) continue to be encountered in travelers, itineraries outside of traditional destinations and novel exposures presents providers with an increasing range of infections. Emerging infections and outbreaks further expand the infectious possibilities, and several recent epidemics including Zika, Ebola virus disease (EVD), and Middle Eastern Respiratory Syndrome (MERS) have been notable for their rapid international spread.<sup>6–8</sup>

Although the likelihood of a severe travel-related infection is relatively low compared to common ailments such as travelers' diarrhea (TD) and upper respiratory virus infections, their possibility presents a

clinical problem that is particularly challenging in travel medicine (Fig. 1). Travel-related infections typically present with nonspecific symptoms, and while the majority are not severe and even self-limiting, others can be of high-consequence and require urgent treatment or enhanced infection control. Relying on diagnostic intuition based on local clinical experience can therefore be dangerous in returned travelers. For example, while the common causes of fever in otherwise healthy ambulatory patients in North America are typically non-life threatening, febrile travelers who have returned from tropical areas may have malaria. High-consequence infections that should not be missed include malaria and other potentially clinically severe infections (e.g. enteric fever, dengue fever, leptospirosis, melioidosis, tick-borne infections, and rickettsial infections) and infections of major public health importance such as viral hemorrhagic fevers (VHFs), MERS, and anthrax. Nosocomial outbreaks of EVD in the U.S. and MERS in South Korea have demonstrated how these infections can present serious risk when unsuspected in healthcare settings.<sup>6,7</sup> Furthermore, co-infections can occur and providers should consider this possibility, particularly when the patient is not responding appropriately to treatment of a confirmed infection.<sup>9,10</sup>

A key strategy when managing a returned sick traveler is to quickly assess the probability of infections so the diagnostic and treatment plan can be directed towards likely infections as well as the high-consequence infections that cannot be missed. The challenge for physicians in the primary care and emergency department setting can be daunting, and at minimum, identification of returned travelers and the possibility of unusual infections requiring consultation with specialists or health departments is becoming a critical role for frontline physicians. In this review key strategies in evaluating acutely sick returned travelers are addressed.

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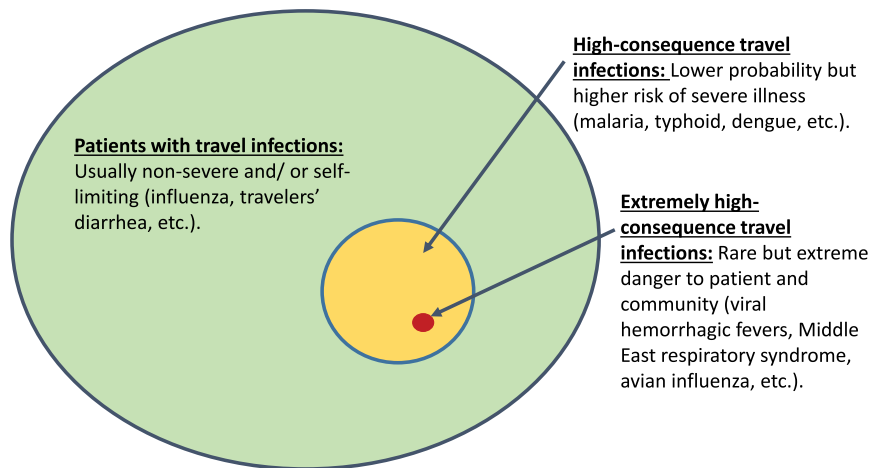


Fig. 1. The challenge of evaluating returned sick travelers. Travelers with rare but high-consequence infections may present similarly to those with common infections.

**Epidemiology and geographic considerations**

Given the wide differential diagnosis for travel-related infections, consideration of the endemic causes of major infectious syndromes in the region of travel can guide the initial approach. Common syndromes include acute undifferentiated fevers, respiratory infections, acute gastrointestinal illness (including diarrhea and hepatitis), chronic gastrointestinal illness, central nervous system infections (e.g. meningitis or encephalitis), dermatologic complaints, and eosinophilia. Although patients might have illness that include multiple syndromes (e.g. fever and eosinophilia), a syndromic approach can help direct the differential diagnosis. Table 1 lists infectious causes of febrile syndromes with relatively short incubation periods that may present in the first 2 weeks after travel. Surveillance data of sick returned travelers from systems such as GeoSentinel Surveillance can also be helpful in identifying the most commonly reported causes of illness in travelers returning from specific geographic regions (Table 2).<sup>10</sup> For example, dengue is the most confirmed infection among febrile travelers returning from the Caribbean, while malaria is less likely (unless they had traveled to Haiti or the Dominican Republic, the only areas with malaria transmission in the Caribbean). On the other hand, *Plasmodium falciparum* is most frequently identified among returned febrile travelers from Sub-Saharan Africa, and four of 28 deaths reported in GeoSentinel from 2007 to 2011 were due to *P. falciparum* from this region. GeoSentinel surveillance data have notable limitations, especially the absence of denominators to calculate rates of infections among travelers, and a general bias towards illnesses that cause patients to seek care. However, the relative proportions of different etiologies in each region is helpful in predicting more likely pathogens.

References on infectious diseases endemic in each country and outbreaks are numerous and often freely accessible online.<sup>11</sup> The U.S. Centers for Disease Control and Prevention (CDC) Travelers' Health website ([www.cdc.gov/travel](http://www.cdc.gov/travel)) provides a regularly updated resource for country level infectious disease profiles (including malaria maps), outbreaks, and pre-travel advice.

**Patient history considerations**

A detailed history is particularly critical in travel medicine and should include past medical history, details of travel (itinerary, activities, and accommodations), and preventative measures used (vaccinations, malaria prophylaxis, biting arthropod avoidance, and food and water hygiene). Patients may not readily discuss travel histories, and they often do not associate their illness with travel, particularly with infections such as some types of malaria that can have prolonged

**Table 1**

Possible causes of febrile syndromes in patients presenting within the first 2 weeks after travel. Table adapted with revision from Fairley (2018).<sup>39</sup>

Syndrome	Causes
Systemic febrile illness with initial nonspecific symptoms	<ul style="list-style-type: none"> <li>● Malaria</li> <li>● Arboviral infections (dengue, Zika, chikungunya)</li> <li>● Typhoid fever</li> <li>● Rickettsia, spotted fevers</li> <li>● East African trypanosomiasis</li> <li>● Acute HIV infection</li> <li>● Leptospirosis</li> <li>● Viral hemorrhagic fevers</li> </ul>
Fever with central nervous system involvement	<ul style="list-style-type: none"> <li>● Malaria</li> <li>● Meningococcal meningitis</li> <li>● Arboviral encephalitis (e.g. Japanese encephalitis virus, West Nile virus)</li> <li>● East African trypanosomiasis</li> <li>● Angiostrongyliasis</li> <li>● Rabies</li> </ul>
Fever with respiratory symptoms	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Bacterial pneumonia</li> <li>● Acute histoplasmosis or coccidioidomycosis</li> <li>● <i>Legionella</i> pneumonia</li> <li>● Acute Q fever</li> <li>● Malaria</li> <li>● Tularemia</li> <li>● Pneumonic plague</li> <li>● Middle East respiratory syndrome (MERS)</li> </ul>
Fever and skin rash	<ul style="list-style-type: none"> <li>● Arboviral infection (dengue, chikungunya, Zika)</li> <li>● Measles</li> <li>● Varicella</li> <li>● Rickettsia, spotted fevers</li> <li>● Typhoid fever</li> <li>● Parvovirus B19</li> <li>● Mononucleosis (Epstein-Barr virus, cytomegalovirus)</li> <li>● Acute HIV infection</li> </ul>

incubation periods. Therefore, when evaluating any patient with acute illness providers should routinely inquire about travel. Incorporation of travel and symptom screening into routine patient registration or triage procedures can be very useful when screening for particular infections of concern such as EVD.<sup>12</sup>

Pre-existing medical conditions may predispose travelers to certain infectious conditions. For example, pregnant travelers are at increased risk of infection or complications from numerous infections, including malaria, hepatitis E, toxoplasmosis, and other infectious diseases.<sup>13</sup>

**Table 2**

Most identified etiologies of illness reported in GeoSentinel Surveillance for gastrointestinal, febrile, and respiratory illnesses, 2007–2011. Etiologies for listed in descending order by region. Adapted from Leder (2013).<sup>10</sup>

Illness	Sub-Saharan Africa	Middle East and North Africa	Latin America and Caribbean	Southeast Asia	South-Central Asia	Northeast Asia
Gastro-intestinal	<ul style="list-style-type: none"> <li>● Giardia</li> <li>● Strongyloides</li> <li>● Campylobacter</li> <li>● Salmonella</li> <li>● Shigella</li> </ul>	<ul style="list-style-type: none"> <li>● Giardia</li> <li>● Campylobacter</li> <li>● Salmonella</li> <li>● Shigella</li> <li>● Strongyloides</li> </ul>	<ul style="list-style-type: none"> <li>● Giardia</li> <li>● Strongyloides</li> <li>● Campylobacter</li> <li>● Dientomoeba fragilis</li> <li>● Entamoeba histolytica</li> <li>● Dengue</li> <li>● <i>P. vivax</i></li> <li>● Enteric fever</li> <li>● <i>P. falciparum</i></li> <li>● Hepatitis A</li> </ul>	<ul style="list-style-type: none"> <li>● Campylobacter</li> <li>● Giardia</li> <li>● Salmonella</li> <li>● Strongyloides</li> <li>● D. fragilis</li> <li>● Dengue</li> <li>● <i>P. falciparum</i></li> <li>● <i>P. vivax</i></li> <li>● Chikungunya</li> <li>● Enteric fever</li> </ul>	<ul style="list-style-type: none"> <li>● Giardia</li> <li>● Campylobacter</li> <li>● Shigella</li> <li>● E. histolytica</li> <li>● D. fragilis</li> <li>● Enteric fever</li> <li>● Dengue</li> <li>● <i>P. vivax</i></li> <li>● Chikungunya</li> <li>● Extra-pulmonary TB</li> </ul>	<ul style="list-style-type: none"> <li>● Campylobacter</li> <li>● Giardia</li> <li>● Ascaris</li> <li>● D. fragilis</li> <li>● Tapeworm</li> <li>● Dengue</li> <li>● Extra-pulmonary TB</li> <li>● Hepatitis E</li> <li>● Hepatitis A</li> <li>● Enteric fever</li> </ul>
Febrile	<ul style="list-style-type: none"> <li>● Plasmodium falciparum</li> <li>● Rickettsia, SF</li> <li>● Dengue</li> <li>● Plasmodium vivax</li> <li>● Enteric fever</li> </ul>	<ul style="list-style-type: none"> <li>● Hepatitis A</li> <li>● <i>P. falciparum</i></li> <li>● Brucellosis</li> <li>● Enteric fever</li> <li>● Dengue</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Legionella</li> <li>● Pertussis</li> <li>● Atypical mycobacteria</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Streptococcal pharyngitis</li> <li>● Atypical mycobacteria</li> <li>● <i>Legionella</i></li> </ul>	<ul style="list-style-type: none"> <li>● Pulmonary TB</li> <li>● Influenza</li> <li>● Streptococcal pharyngitis</li> <li>● Pertussis</li> <li>● High-altitude pulmonary edema</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Legionella</li> <li>● Atypical mycobacteria</li> <li>● Pertussis</li> </ul>
Respiratory	<ul style="list-style-type: none"> <li>● Pulmonary TB</li> <li>● Influenza</li> <li>● Atypical mycobacteria</li> <li>● Pertussis</li> <li>● <i>Legionella</i></li> </ul>	<ul style="list-style-type: none"> <li>● Pulmonary TB</li> <li>● Influenza</li> <li>● Streptococcal pharyngitis</li> <li>● Atypical mycobacteria</li> <li>● Pertussis</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Legionella</li> <li>● Pertussis</li> <li>● Atypical mycobacteria</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Streptococcal pharyngitis</li> <li>● Atypical mycobacteria</li> <li>● <i>Legionella</i></li> </ul>	<ul style="list-style-type: none"> <li>● Pulmonary TB</li> <li>● Influenza</li> <li>● Streptococcal pharyngitis</li> <li>● Pertussis</li> <li>● High-altitude pulmonary edema</li> </ul>	<ul style="list-style-type: none"> <li>● Influenza</li> <li>● Pulmonary TB</li> <li>● Legionella</li> <li>● Atypical mycobacteria</li> <li>● Pertussis</li> </ul>

Abbreviations: SF (spotted fevers), TB (tuberculosis).

Immunosuppression due to organ transplantation, HIV infection, or immunosuppressive therapy for autoimmune diseases or malignancy can also increase the risk of infections and limit use of live vaccinations.<sup>14</sup> It should be noted that when evaluating the acutely ill returned traveler, the provider must always consider infections and conditions unrelated to travel, whether the result of the travelers’ chronic condition or due to exposures acquired before or after the trip.

In addition to destination, the exact timing of travel is critical to review, since incubation periods for most infections will fit within specific ranges (Tables 1 and 3). Specific causes of illness can sometimes be ruled out based the duration of time between possible exposure and onset of symptoms. For example, because many arboviral infections (e.g. dengue fever, chikungunya fever, and Zika) have incubation periods between 3 and 14 days, many of these infections can be ruled out in a returned traveler with onset of illness greater than 2 weeks after departing the endemic area (assuming an accurate travel and symptom onset history is obtained). On the other hand, the minimum incubation period of malaria is seven days, and a traveler becoming febrile immediately after a weekend trip to an endemic area can be essentially ruled out for malarial fevers, assuming no previous exposure risk. Caution must be taken when ruling out infections based on travel timing alone, as travelers often do not recall exact travel dates, and itineraries can be complicated by transit stops. Furthermore, transmission of tropical infections such as malaria in non-endemic areas including airports are rarely reported.<sup>15</sup>

**Adherence to preventative measures**

Assessment of adherence to preventative measures, including pre-travel vaccinations, malaria prophylaxis, and standard advice such as mosquito avoidance and food and water hygiene is important for risk stratification for specific infections. However, since level of adherence can be difficult to assess and the efficacies of these measures are never 100%, ruling out infections based on reported adherence is usually not advised. Efficacies of travel vaccines range widely. Hepatitis A vaccination can be over 94% effective, while the efficacy of typhoid vaccination can range from 60 to 80%.<sup>1</sup> All vaccines might have decreased efficacy in populations with advanced age or medical problems. Currently recommended malaria prophylaxis regimens are highly effective in preventing *P. falciparum* malaria, although adherence can be difficult to confirm and failure of prophylaxis can occur, particularly with

**Table 3**

Causes of fever, by typical incubation periods.

Incubation period*	Cause of Fever
< 14 days	<ul style="list-style-type: none"> <li>● Malaria</li> <li>● Arboviral infection (dengue, chikungunya, Zika, etc.)</li> <li>● Rickettsia, spotted fevers</li> <li>● <i>Legionella</i></li> <li>● Meningococcal disease</li> <li>● Relapsing fever</li> <li>● Middle East respiratory syndrome (MERS)</li> </ul>
< 1 to 4 weeks	<ul style="list-style-type: none"> <li>● Malaria</li> <li>● Leptospirosis</li> <li>● Enteric fever</li> <li>● Acute HIV</li> <li>● Mononucleosis: Epstein-Barr virus (EBV), cytomegalovirus (CMV)</li> <li>● Bartonellosis</li> <li>● Melioidosis</li> <li>● Ebola virus disease, Lassa fever</li> <li>● African trypanosomiasis</li> </ul>
Potentially prolonged incubation (one or more weeks to months)	<ul style="list-style-type: none"> <li>● Malaria</li> <li>● Acute schistosomiasis syndrome</li> <li>● Amoebic liver abscess</li> <li>● Hepatitis A and E</li> <li>● Tuberculosis</li> <li>● Brucellosis</li> <li>● Acute Q fever</li> <li>● Visceral leishmaniasis</li> <li>● Filariasis</li> <li>● Rabies</li> </ul>

\* Approximate ranges. Some infections such as malaria can have a wide range of incubation periods.

relapsing species of malaria, *P. vivax* and *P. ovale*.<sup>1</sup> Therefore, malaria should never be ruled out based on reported history of prophylaxis.

Adherence to insect avoidance measures and food and water hygiene can vary widely among travelers and be particularly difficult to ascertain. Furthermore, persons infected with arthropod-borne infections might not recall observing biting arthropods or a history of bites. Ingestion of specific foods can present specific infectious concerns, and it is important to inquire about ingestion of raw vegetables and fruits, undercooked or raw meats (including bushmeat, seafood, and

shellfish), and unpasteurized dairy products. In addition to common foodborne infections (e.g. *Salmonella*), undercooked animal products have risks of less common infections, such as *Vibrio* from shellfish and Ebola virus from bushmeat.<sup>16</sup> Consumption of potentially contaminated water (including untreated tap water and ice) can increase risk of waterborne infections such as enteric fever, hepatitis A, and protozoal infections. Food and drink that mix different ingredients that might be uncooked or contaminated are particularly risky, including salads, salsas, mixed beverages, and smoothies. Although food from street vendors have increased risk of contamination, unsafe food handling practices can also be common in high end establishments.

Certain environmental exposures can introduce risk of specific infections. Direct contact with freshwater bodies (via swimming, wading, rafting, etc. in rivers, ponds, and lakes) can expose patients to waterborne infections. While some infections such as leptospirosis are present worldwide, other such as schistosomiasis and melioidosis are present in specific endemic areas. Certain helminthic infections, e.g. strongyloidiasis and hookworm, can be acquired via direct soil to skin contact in tropical areas worldwide; however, most short-term travelers who wear covered shoes are unlikely to have significant exposure risk. History of animal contact and bites is important to ascertain. Notably, exposure to birds (poultry and pets, including visiting live poultry markets) have been linked to avian influenza in Asia<sup>17</sup> and some MERS cases have been linked to camel exposure.<sup>18</sup> Animal bites should be assessed for rabies risk. Even if the travelers' illness is not consistent with rabies, post-exposure prophylaxis might be indicated.

Many sexually transmitted infections and blood borne pathogens such as HIV, hepatitis B, and hepatitis C are more prevalent outside the U.S., and providers should ask about any sexual encounters, percutaneous exposures (e.g., tattoos, piercings, and injection drug use), or use of local healthcare facilities with inadequate infection control. Furthermore, contact with healthcare facilities (whether as patient, visitor, or travelling medical personnel) or sick individuals should be assessed, as some infections are often transmitted in healthcare settings, such as tuberculosis, measles, viral hemorrhagic fevers, and MERS.

Travelers who adopt local living standards (i.e., accommodations, food and water hygiene, etc.) can face a higher risk of endemic infections. These can include VFR travelers, long-term expatriates (e.g. missionaries or long-term business travelers), or budget travelers. Travelers staying in rustic accommodations (e.g. local homes or hotels without screened in windows), or those that are camping can be at increased risk of arthropod bites, especially if precautions such as repellents and bed nets are not used. Expatriates often discontinue preventative measures, such as malaria prophylaxis. All long-term travelers have inherently increased risk of infections due to their prolonged exposure periods.

### Physical examination and general laboratory testing

An immediate goal of the physical exam is to assess the clinical stability of the acutely ill returned traveler and determine if triage to a higher level of care is indicated. As with any acutely ill patient, a thorough exam of all body systems is essential to find diagnostic clues to the etiology of illness. Since many travel-related infections are arthropod-borne and/or have associated rashes, a detailed skin examination to assess for rashes, arthropod bites, eschars, and attached ticks is important. General laboratory testing, such as complete blood counts, cell differentials, metabolic panels (including hepatic function tests) can offer diagnostic clues (e.g. anemia associated with malaria) or indicate the clinical syndrome (e.g. eosinophilia, hepatitis, etc.). Diagnostic procedures such as lumbar puncture and CSF fluid analysis, radiographic imaging, etc. might be urgently indicated depending on the clinical presentation.

In febrile travelers, bacterial cultures of blood and other bodily fluids are the diagnostic gold standard for some serious travel-related infections including enteric fever and meningococcal disease. Travelers

are certainly also at risk for universally encountered bacterial pathogens such *Staphylococcus aureus*, streptococci, and enterobacteriaceae. Stool cultures for bacterial pathogens can be helpful when evaluating travelers with diarrhea or suspected enteric fever. However, for acute travelers' diarrhea, which is often self-limiting or empirically treated, results from conventional stool cultures are typically not available soon enough to guide management. Stool assays for *Clostridium difficile* toxins should be considered in travelers with diarrhea when there is a history of antibiotic use, since travel-associated *C. difficile* infection is increasingly described in travelers.<sup>19</sup> Stool microscopy for ova and parasites, as well as specific protozoa antigen tests such as those for *Giardia lamblia* and *Entamoeba histolytica*, are often performed in returned sick travelers. While these can be useful for patients with chronic gastrointestinal symptoms, their utility in the returned traveler with acute severe illness is limited since most gastrointestinal parasites are unlikely causes of acute febrile illness. Although acute schistosomiasis syndrome (Katayama fever) and amoebic liver abscess are classic causes of fever in the returned traveler, microscopy of stool (and urine for *Schistosoma haematobium*) is insensitive for these conditions.<sup>20,21</sup>

Recent studies indicate potentially high rates of colonization by drug resistant bacteria in returned travelers, particularly extended spectrum  $\beta$ -lactamase producing enterobacteriaceae (ESBL). Highest rates of ESBL colonization are observed in those returning from the Indian subcontinent, with over 60% colonized in studies.<sup>22</sup> Decreasing risk is observed among those returning from other parts of Asia (50%), the Middle East 36%), Africa (34%), and South and Central America (19%).<sup>22</sup> Episodes of travelers' diarrhea and receipt of antibiotics are risk factors for colonization. Although the contribution of travel to the burden of drug-resistant bacteria in healthcare setting is unknown, providers should consider travel as a risk factor for colonization (and possibly infection) with drug-resistant bacteria.

### Malaria and targeted testing for other specific pathogens

In non-endemic areas, malaria is one of the most commonly encountered causes of severe illness in returned travelers. Thick and thin blood smears are the diagnostic gold standard as they provide species identification and parasite density (parasitemia) that can guide treatment. Importantly, three smears 12–24 h apart are needed to rule out infection;<sup>23</sup> however, availability of testing or timely results reporting in non-endemic areas can vary. Delays in diagnosis after patients present to healthcare facilities appears to contribute to the delay in malaria treatment that is common in non-endemic countries, although delays in seeking healthcare by the patient appears to be the largest factor.<sup>24</sup> Surveys of malaria diagnostic capacity in U.S. hospitals has suggested recent improvement, although still only 12% of laboratories that responded met all Clinical and Laboratory Standards Institute (CLSI) guidelines for analysis and reporting of malaria testing.<sup>25,26</sup>

Antigen-based rapid diagnostic tests (RDTs) can expedite malaria diagnosis, particularly in situations where expert readings of blood smears are not immediately available. Malaria RDTs can range in accuracy but are generally most sensitive for *P. falciparum*, with decreased sensitivity for *P. vivax*, and very low sensitivity for *P. ovale* and *P. malariae*.<sup>27</sup> Malaria RDTs do not provide parasite density information; furthermore, sensitivity is lowest with lower parasite densities, and false-positive results are possible.<sup>27</sup> The only RDT approved for use by the U.S. Food and Drug Administration (FDA), BinaxNOW (Abbott, Lake Forest, Illinois), cannot differentiate non-*P. falciparum* species (*P. vivax*, *P. ovale*, and *P. malariae*). Reported sensitivity for *P. falciparum* infections is generally high in returned travelers (> 90%), while lower sensitivity is observed with the other species.<sup>28,29</sup> Given the limitations of RDTs, follow-up testing with blood smears or PCR is important.<sup>23</sup> In our center, RDTs are the first line diagnostic tool performed 24 h 7 days a week which are reported as soon as the test is completed. Thick and thin smears always accompany the RDT; however, reading of smears is only performed in our microbiology laboratory by few technologists

competent in parasitology once daily. This algorithm allows for rapid diagnosis of *P. falciparum* malaria while diagnosis and differentiation of non-*P. falciparum* species can take up to a day. Malaria serology, useful in confirming previous infection, does not have a role in the diagnosis or management of the acutely ill patient.

Targeted testing for other specific pathogens with serologic, antigen, and molecular assays are the mainstay for many tropical diseases. As with malaria testing, there is varying availability and accuracy of these tests, and their utility relies on the ability of the provider to consider the pathogen when evaluating the returned sick traveler. Serology has historically been the primary diagnostic modality for many viruses (e.g. dengue, Zika, and chikungunya viruses) and some difficult to culture bacteria (e.g. rickettsia and leptospirosis). However serology has inherent limitations in the acute clinical setting, since testing of a convalescent specimen might be necessary. Serologic cross-reactivity, often seen among flaviviruses,<sup>30</sup> can also present diagnostic challenges. For enteric fever, commonly used serologic testing (Widal test) and rapid diagnostic tests have limited accuracy, and cultures of blood or bone marrow remain the gold standard.<sup>31</sup> Molecular PCR-based assays are becoming more available for clinical use, and these can be helpful for arboviral infections and some bacterial infections. Real-time PCR appears promising for leptospirosis, which has been historically challenging to confirm with culture and serology.<sup>32</sup>

Increasingly, syndromic-based molecular panels that test for multiple pathogens are available,<sup>33</sup> raising hope that the diagnostic approach for returned sick travelers might be simplified and expedited. Multiplex PCR platforms for multiple bacterial, viral and protozoal causes of gastroenteritis are available and potentially useful for providing a rapid etiologic diagnosis in the travelers with diarrhea.<sup>34</sup> However, further validation of these assays in clinical practice is needed, as multiple positive targets are common in a single specimen, and interpretation of results is often necessary.<sup>34,35</sup> Furthermore, this assay does not provide antimicrobial susceptibility data, so follow-up with conventional cultures might be useful for specimens that are positive for bacterial pathogens. Several multiplex PCR platforms to detect common respiratory viruses and bacteria are also available.<sup>33</sup> The FilmArray Respiratory Panel 2 plus (BioFire, Salt Lake City, Utah) is notable as MERS Coronavirus (MERS-CoV) is included as a target and has been cleared by FDA. This panel is useful for diagnosis of cases meeting MERS-CoV clinical and/or epidemiologic criteria.<sup>36</sup>

Testing for some infections of public health importance (e.g. rabies, VHF, MERS, etc.) are typically performed at designated reference or public health laboratories, and assistance with local public health authorities should be sought immediately if these infections are suspected. Case definitions based on clinical and epidemiologic criteria to identify individuals that should be evaluated for some highly pathogenic infectious diseases (i.e., persons under investigation, “PUI”) such as EVD and MERS are provided by CDC to assist clinicians and health departments.<sup>37,38</sup>

### Summary of approach

With increasing travel, frontline healthcare providers must identify patients who might have severe travel-related illness and consult with infectious diseases, tropical diseases, or public health experts. Unlike other clinical situations, the evaluation of the sick returned traveler is particularly challenging due to the wide differential diagnosis that can vary significantly depending on the host and destinations of travel. Consideration of disease endemicity and outbreak reports are important, and online resources can be helpful in providing up to date regional risk profiles. Detailed review of traveler activities and exposures can also indicate risk of specific infections, and infections can often be ruled out based on incompatible incubation periods or absence of necessary exposures.

Testing for infectious etiologies with culture methods and specific assays is typically necessary to confirm and rule out infections of

concern. A diagnostic strategy guided by likelihood, severity, treatability, and public health importance of infection can be helpful when the differential diagnosis is broad. Malaria remains a relatively common cause of severe illness in travelers with delays in diagnosis and treatment, thus providers should always consider the possibility. Interpretation of test results in light of disease probability and test performance parameters is important, especially when assays have limited sensitivity and specificity.

Although treatments should be directed towards confirmed infections, empiric treatment for dangerous infections such as malaria and enteric fever can be necessary in the severely ill returned traveler when they cannot be immediately ruled out. Continued reassessment is important, and alternative diagnoses or co-infections must be considered when patients do not recover or respond to treatment as expected.

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