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Fever in the Returning Traveler

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KEYWORDS

• Fever • Child • International travel • Tropical infections • Returning traveler

KEY POINTS

- The initial workup of a febrile child without a clear source will be based on the history, physical examination, and potential risk factors but commonly includes laboratory testing.
- Malaria, enteric fever, and dengue fever are some of the most common and serious tropical infections in pediatric travelers.
- Clinicians need to remain up-to-date on potential etiologic factors for febrile illnesses to develop a focused plan best suited to the patient's clinical picture.

INTRODUCTION

Millions of children travel annually, whether they are refugees, international adoptees, visitors, or vacationers.[1–4] In 2015, the International Tourism Organization reported 1.2 billion overseas trips.[5,6] Although most young travelers do well, many develop febrile illnesses during or shortly after their journeys.[7] In a study of European children, 53% of all pediatric patients with travel-related infections were visiting friends and relatives (VFRs), 43.4% were tourists, and 2.4% were immigrants.[8] Most illnesses are self-limited childhood infections that do not require subspecialist consultation. However, 28% of 24,920 ill American travelers sought care at travel clinics after returning home.[9] Additionally, young children with fevers can present a diagnostic dilemma because they may not report symptoms and can be at risk for severe disease, such as malaria. As awareness of tropical illnesses rise in parents, such as the increase in multidrug-resistant bacteria worldwide or the emergence of epidemics with Zika virus in South America, families may be more anxious about serious infections as an etiologic factor of fevers.

Approaching fevers in the returning traveler requires an appropriate index of suspicion to diagnose and treat the child in a timely manner. This article offers a framework

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on how to address these issues by discussing diseases based on geography, incubation period, and affected organ systems, as well as risk factors, diagnostic techniques, and resources.

GENERAL APPROACH

A thorough history is an important initial step when evaluating a pediatric traveler with a fever (**Table 1**). Discussing a detailed travel itinerary develops a timeline of exposures that can be unique to an urban or rural setting (**Table 2**).

Many children receive vaccinations and/or antimicrobial prophylaxis, but reported adherence does not preclude an illness with a particular pathogen. Up to 75% of travelers do not adhere to the recommended malaria prophylaxis.[10] Many travel vaccines, including typhoid vaccine, provide only partial protection despite proper administration of these immunizations.[11]

A medically complex individual may have sought care outside of the United States due to necessity or medical tourism, which can increase the risk of infection through body fluid exposures. Multidrug-resistant pathogens can also be associated with health care exposure. Up to half of hospitalized children in Zimbabwe are colonized with extended spectrum beta lactamase producing *Enterobacteriaceae* on admission to the hospital,[12] a problem that is increasingly seen worldwide. Underlying medical conditions, such as asplenia or immunosuppression from chemotherapy, may predispose children to overwhelming infections and sepsis. Refugee children from countries such as Syria are susceptible to vaccine-preventable diseases such as polio due to infrastructure breakdown.[13]

CLINICAL FINDINGS, DIAGNOSIS, AND MANAGEMENT

Fever is a common and anxiety-provoking sign for parents that can be exacerbated by overseas travel. Up to 34% of patients with recent travel history are diagnosed with routine infections.[3] Of the 82,825 cases of infection in travelers from 1996 to 2011 reported to GeoSentinel, a worldwide data collection network on travel-related diseases, 4% of cases were considered to be life-threatening.[14] A study in Swiss children showed that 0.45% of emergency room visits were due to travel-related morbidities with fever and gastrointestinal symptoms being the most common complaints in 63% and 50% of patients, respectively.[8] The temporality of travel to the onset of fever can offer important clues to the etiologic factors of fevers (**Table 3**). Because the causes and clinical outcomes associated with fevers in pediatric travelers vary from self-limited to deadly, a systems-based approach can lead to prompt diagnosis and treatment that evaluates for the most likely and serious diseases early in the illness course.

Fever

According to GeoSentinel, 91% of patients with an acute, life-threatening illness will present with fever.[14] There are a broad range of potential tropical infections, including malaria, dengue fever, and enteric fever. The incidence of emerging infections such as Zika virus and chikungunya are not yet known. In both adults and children, pneumonia, sepsis, meningococcemia, and urinary tract infections that were acquired at home or overseas should be on the differential diagnosis.

The initial workup of a febrile child without a clear source will be based on the history, physical examination, and risk factors but commonly includes a complete blood count, liver function tests, creatinine, urinalysis, and blood cultures.[1,3] Malaria smears are also frequently helpful. Other tests to consider include serologies for dengue fever

Table 1
Patient history for the returning traveler with fever

History	Implications
Travel itinerary	Offers information on potential diseases based on geography and other exposures
Diet history (improperly cooked meats, unpasteurized dairy products, seafood, or contaminated water and produce)	Brucellosis, *Campylobacter* infection, giardiasis, hepatitis A and E, listeriosis, traveler's diarrhea, enteric fever, trichinosis, viral gastroenteritis (ie, norovirus)
Sick contacts (both abroad and since returning to the US)	Routine viral or bacterial illnesses, Ebola infection, influenza, meningococcemia, tuberculosis
Fresh water exposure	Bacterial soft tissue infection (*Aeromonas* spp, atypical *Mycobacterium*), leptospirosis, schistosomiasis
Sexual encounters	Acute human immunodeficiency virus (HIV) infection; gonorrhea; hepatitis A, B, or C infection; primary herpesvirus 1 or 2 infection; syphilis; Zika virus infection
Insect bites	• Fleas: plague, murine typhus, rickettsioses • Flies: African sleeping sickness, leishmaniasis, sandfly fever • Lice: relapsing fever, rickettsioses • Reduviid bugs: Chagas disease • Mosquitoes: Chikungunya virus infection, dengue fever, filiarisis, Japanese encephalitis, West Nile virus infection, Zika virus infection • Ticks: African tick bite fever, babesiosis, Lyme disease, Q fever rickettsioses, tularemia
Animal bites	Cat-scratch disease, rat bite fever, rabies, simian herpesvirus B infection
Animal exposure (including exposure to urine, stool, or animal products; eg, infected carcasses or wool)	Anthrax, avian influenza, hantavirus infection, Hendra virus infection, infections from ectoparasites or endoparasites, Nipah virus infection, plague, psittacosis, toxoplasmosis
Body fluid exposures (tattoos, piercings, or medical procedures)	Acute HIV infection, babesiosis, cytomegalovirus infection, hepatitis B and C, malaria, multidrug-resistant bacteria, trypanosomiasis
Medical history (diseases associated with immunosuppression; eg, malignancy, asplenia, or immunodeficiency)	Cytomegalovirus infection, Epstein-Barr virus infection, fungal infection, mycobacterial infections
Vaccinations and prophylaxis (note: these interventions do not preclude infection with the pathogen prophylaxed against)	Malaria prophylaxis, travel-appropriate vaccines

Adapted from Refs.[50–52]

or other potential etiologic agents, polymerase chain reaction for Zika virus or other pathogens, chest radiographs, and cultures of the urine and stool. Patients with altered mental status may require head imaging and lumbar puncture. The most common and concerning causes of fever in a returning pediatric traveler are highlighted next.

Table 2
Tropical causes of fever based on geography

Location	Infection
Caribbean	Acute histoplasmosis, chikungunya, cholera, dengue fever, leptospirosis, malaria (Haiti, primarily *Plasmodium falciparum*)
Central America	Acute histoplasmosis, coccidioidomycosis, dengue fever, hepatitis A and B, malaria (primarily *P vivax*), tuberculosis
South America	Bartonellosis, dengue fever, malaria (primarily *P vivax*), enteric fever, leptospirosis, yellow fever
South Central Asia	Dengue fever, enteric fever, hepatitis B, Japanese encephalitis, malaria (primarily non-falciparum *Plasmodium* spp), tuberculosis
Southeast Asia	Chikungunya, cholera, dengue fever, hepatitis A, Japanese encephalitis, malaria (primarily non-falciparum *Plasmodium* spp), yellow fever
Sub-Saharan Africa	Acute schistosomiasis, enteric fever, filariasis, malaria (primarily *P falciparum)*, meningococcus, rickettsioses, yellow fever

Adapted from Centers for Disease Control and Prevention. The yellow book: health information for international travel 2018. Philadelphia: Oxford University Press; 2017. p. 704. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home. Accessed July 25, 2017; with permission.

Table 3
Incubation period for common tropical diseases causing

Disease	Incubation Period
Incubation of <14 d	
Acute HIV	7–21 d
Arboviral infections (ie, chikungunya and Zika viruses)	2–10 d
Dengue fever	4–8 d
Enteric fever	7–18 d
Leptospirosis	7–12 d
Influenza	1–3 d
Malaria	
P falciparum	6–30 d
P vivax	8 d–12 mo
Rickettsioses	3 d–3 wk
Incubation of 14 d to 6 wk	
Amebic liver abscess	Weeks–months
Hepatitis A	28–30 d
Hepatitis B infection	60–150 d
Rabies	Weeks–months
Schistosomiasis	28–60 d
Tuberculosis	Weeks for primary infection
Visceral leishmaniasis	2–10 mo

Adapted from Thwaites GE, Day NP. Approach to fever in the returning traveler. N Engl J Med 2017;376(6):548–60; and Centers for Disease Control and Prevention. The yellow book: health information for international travel 2018. Philadelphia: Oxford University Press; 2017. p. 704. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home. Accessed July 25, 2017; with permission.

Malaria

Plasmodium falciparum malaria is one of the most common tropical infections. Approximately 15% to 20% of all imported malaria cases are diagnosed in the pediatric population in industrialized countries each year.[3] Malaria is transmitted via the nocturnal-feeding *Anopheles* genus of mosquito. Children who are VFRs are more likely to become infected with malaria than traditional tourists.[3] Nonimmune children are also susceptible to severe malaria from other malaria strains such as *Plasmodium vivax*[15] and many young patients can present with atypical symptoms such as abdominal pain and vomiting.[16] Older children may present with paroxysmal fever, fatigue, myalgias, headache, abdominal pain, back pain, hepatosplenomegaly, and hemolytic anemia. Additionally, severe malaria is more common in children after the first month of travel due to the incubation period of *P falciparum* (7–90 days), especially in those who visited sub-Saharan Africa.[17,18] Overall, sub-Saharan Africa is one of the most common geographic regions for acquisition, comprising 71.5% of cases according to a GeoSentinel study of travelers migrating or returning to Canada from 2004 to 2014.[19] Malaria should remain on the differential diagnosis for up to a year in an acutely ill, febrile child after travel to an endemic area where *P vivax* and *P ovale* strains are present.[17] Interestingly, 20% of malaria cases can be acquired during trips as short as 2 weeks with less utilization of pretravel services being a contributing factor.[19]

A minimum of 3 thick and thin blood smears must be performed before malaria can be excluded, preferably collected during febrile episodes. The specificity of blood smears is high but the sensitivity can be low depending on the experience of the individual interpreting the slides.[17] Rapid diagnostic tests that detect specific proteins or lactate dehydrogenase are alternatives for diagnosis at medical centers with limited experience in microbiologic evaluation for malaria.[20] The result should be confirmed, however, through the state public health department. In general, a febrile child without a localizing source or splenomegaly, thrombocytopenia, or indirect hyperbilirubinemia, in addition to exposure to an endemic area, should be presumptively approached as having malaria until an alternative diagnosis can be made.[21]

Treatment of malaria is well-established by the Centers for Disease Control and Prevention (CDC) guidelines. Children with acidosis, hypoglycemia, hyperparasitemia, end-organ dysfunction, and severe anemia meet the criteria for severe malaria and require prompt administration of parenteral medication. There is a growing body of evidence that artesunate may reduce mortality compared with quinidine and is becoming more common as first-line therapy in pediatric patients.[22,23] Artesunate must be obtained through the CDC Malaria Hotline (1–770–488–7788) because it is not routinely available in the United States.[24] Quinidine may be initiated until the medication arrives. Completion of therapy with an oral regimen for uncomplicated chloroquine-resistant *P falciparum*, such as atovaquone-proguanil, can be offered when the child is able to tolerate the medications and the parasite burden has decreased to less than 1%. Severe disease is less common in *P vivax* and *P ovale* and infection can be treated with chloroquine or hydroxychloroquine in most areas outside of Indonesia and Papua New Guinea.

Enteric fever (typhoid and paratyphoid)

Enteric fever accounts for 18% of the 3655 cases with life-threatening tropical diseases reported to GeoSentinel. Most recorded cases were from the Indian subcontinent and in VFRs.[1] Infection with *Salmonella typhi* and *Salmonella paratyphi* are clinically indistinguishable with fever, abdominal pain, nausea, vomiting, myalgias, and arthralgias. Diarrhea is greater than 2.5 times more common in infants than older children or adults,[25] although constipation can also be seen. Patients can exhibit a

typhoid mask with dull features and confusion, as well as a stepladder fever progression with rising temperatures over time in untreated individuals. Relative bradycardia and rose spots are also classic signs.[25] Complications such as gastrointestinal bleeding are more common in young children who have been ill for 2 weeks or more.[1] Transmission is fecal-oral, and humans, especially adults, may be chronic carriers. Diagnosis of enteric fever is confirmed through cultures. The most sensitive sterile site is bone marrow (80%–95%). Blood culture has the highest yield during the first week of illness (70%), and stool cultures are more sensitive as the duration of illness increases.[26] Stool studies should be performed on all fellow travelers, and they must be monitored for signs of illness. Other abnormal laboratory findings include transaminitis and a normal or decreased white blood cell count.

The antimicrobial of choice for treatment varies based on the area in which the infection was acquired because multidrug resistance is increasing. Empiric treatment with ceftriaxone or fluoroquinolones is typically recommended. Strains in Latin America and the Caribbean can be susceptible to ampicillin and trimethoprim-sulfamethoxazole. South and Southeast Asian serovars more frequently require azithromycin or cefixime.[27,28] Children with multidrug-resistant strains have more complications such as myocarditis and shock than children infected with susceptible strains but case fatality is similar (1.0% vs 1.3%, respectively).[29] Relapse of infection can occur despite appropriate therapy, with the highest mortality in young children (6%).[29]

Dengue fever

Dengue remains an important cause of fever in travelers returning from all tropical regions except Africa.[30] The prevalence is rising, even in the United States, with 50 to 100 million global cases reported yearly and 22,000 deaths, primarily in children.[31] Risk factors are dissimilar from those for malaria because transmission occurs in urban areas during the daytime due to the vector *Aedes aegypti*, whereas malaria transmission is more common in rural areas from dusk to dawn with the *Anopheles* species mosquito.[32]

Some patients may be asymptomatic, whereas others have hemorrhagic fever and shock. The illness presents as 3 distinct phases: (1) febrile phase over 3 to 7 days characterized by myalgias, headache, retroorbital pain, and rash; (2) critical phase of 24 to 48 days with plasma leakage; and (3) convalescent phase.[32] A rising hemoglobin and gallbladder wall thickening due to increased vascular permeability suggests the development of severe dengue in children. Repeat infections with a different strain may lead to more severe disease.[31]

Serologies are most commonly used for diagnosis, although some rapid diagnostic tests are available. In cases in which infection is unclear, it may be helpful to repeat serologies 2 weeks after initial testing to monitor for an increase in titers. Other common laboratory findings include leukopenia and thrombocytopenia.[33]

Treatment consists of hydration and avoidance of salicylate-containing products to decrease the risk for bleeding.[32] Children who develop severe dengue with hemorrhage and shock may require blood products. No antivirals or vaccines are currently available.

Other causes of fever

In recent years, arboviral illnesses transmitted via infected *Aedes aegypti* mosquitos have caused epidemics of Zika virus and chikungunya in South America. A European study of travelers returning from Brazil in 2013 to 2016 reported that of the 29% of patients with travel-related complaints, 6% had dengue fever, 3% had chikungunya, and 3% had Zika virus infection.[34] The prevalence of yellow fever, which is seen

throughout low-resource settings and shares the same vector, has remained stable.[35] These infections are difficult to distinguish clinically with fever, retroorbital pain, conjunctivitis, and myalgias. Knowledge on perinatal infection with Zika and the neurodevelopmental sequelae of affected infants is rapidly evolving.[36] A Canadian study found that 5% of travelers developed neurologic complications such as Guillain-Barre syndrome with Zika, suggesting there is much to learn with this disease in non-perinatally acquired infections.[37] At this time, treatment is primarily supportive. Additional tropical diseases associated with fevers are outlined in **Table 4**.

Gastrointestinal Symptoms

Vomiting and diarrhea are common complaints in returning travelers. Up to 40% of children less than 2 years of age may develop diarrhea, with 15% requiring medical services.[38] Fevers, nausea, and vomiting can be seen with norovirus that occurs worldwide and is frequently associated with contaminated food and water on cruise ships.[39] Rotavirus, however, is one of the most frequent causes of diarrheal illnesses worldwide and is a common cause of infant mortality in low-resource settings.[5] The hepatitides present with a broad range of disease from mild abdominal pain and vomiting to fulminant liver failure, although serious complications are uncommon in pediatric travelers.[40]

Community-acquired *Clostridium difficile* is uncommon in children but infection should be considered if the patient received recent antimicrobials.[41] GeoSentinel data reported that 2% of patients diagnosed with *Clostridium difficile* after travel were 10 to 19 years of age.[42] There are many other causes of both febrile and nonfebrile gastrointestinal illness in children (**Table 5**).

Respiratory Symptoms

In the pediatric population, common respiratory infections may be seen on return from international trips including pharyngitis, sinusitis, otitis, and pneumonia from pathogens commonly seen in the United States, such as *Streptococcus pneumoniae* and rhinovirus.[4,43] Local epidemiology of infections can be helpful in diagnosis and management and is available through the CDC. In some tropical regions, influenza may occur throughout the year and should hence remain on the differential for patients who warrant treatment with oseltamivir.[44]

Mycobacterium tuberculosis is an important etiologic factor of lower respiratory tract disease worldwide and should be considered in children with risk factors or who do not recover with antimicrobials for bacterial pneumonia.[26] Of note, children younger than 3 years of age are more likely to present with miliary tuberculosis or neurologic involvement than adult patients. There are also many other less common causes of febrile respiratory tract infections (**Table 6**).

Urinary Symptoms

Children who present with dysuria, hematuria, and fevers may require urinalysis and culture to evaluate for urinary tract infection and/or pyelonephritis. Gross hematuria with the passage of clots in an afebrile child with exposure to freshwater in Africa, the Middle East, China, and Southeast Asia should be tested for the helminth parasite from the genus *Schistosoma* via serologies or microscopic identification of eggs in stool.[45] Praziquantel is the treatment of choice and may improve anemia and nutrition in some children.[46] Patients who may have early disease or a high parasite burden may require a repeat treatment.[45] Children who are at risk for sexual abuse and adolescents should undergo testing for sexually transmitted infections such as *Chlamydia trachomatis* and *Neisseria gonorrheae*.

Table 4
Tropical diseases associated with fever

Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
Acute retroviral syndrome	HIV	Worldwide, highly prevalent in sub-Saharan Africa	Anal or vaginal sex, perinatal, needle stick, blood transfusion	1–3 wk	Arthralgia, fever, rash, lymphadenopathy, pharyngitis	HIV-1 RNA, p24 antigen, immunoassay for HIV-1 and HIV-2 antibodies (preferred)	Antiretroviral therapy, consider trimethoprim-sulfamethoxazole prophylaxis
Anthrax	*Bacillus anthracis*	Central and South America, sub-Saharan Africa, Central and Southwestern Asia, Eastern Europe	Ingestion or handling of contaminated meat, playing drums from contaminated hides, contaminated heroin in drug users	Cutaneous: 1–17 d Gastrointestinal: 1–7 d Injection: 1–4 d Inhalation: 7–60 d	Varies with infection type; black eschar, cough, fever, nausea and vomiting, meningeal signs, severe soft tissue infection, shock	Bacterial culture, RT-PCR	Combination antimicrobial therapy
Brucellosis	*Brucella* species	Central and South America, Africa, Middle East, Mediterranean basin, Eastern Europe	Unpasteurized dairy products, undercooked contaminated meat	2–4 wk	Fever, headache, malaise, myalgias, night sweats,	Culture of sterile site (blood or bone marrow), PCR	Combination antimicrobial therapy
Carrión's disease (Oroya fever)	*Bartonella bacilliformis*, *B rochalimae*, and *B ancashensis*	South America, especially Peru	Genus *Lutzomyia* (sandflies)	10–210 d	Fever, headache, myalgias, abdominal pain, anemia followed by nodular skin lesions	Bacterial culture	Antimicrobial therapy (aminoglycosides, tetracyclines, fluoroquinolones)

Cat-scratch disease	*B henselae*	Worldwide	Scratches from infected cats or kittens	1–3 wk	Fever, lymphadenitis, follicular conjunctivitis, encephalitis	Culture, serologies, PCR	Usually self-limited, antimicrobials (macrolides)
Chikungunya[33]	Chikungunya virus	Africa, Asia, Central and South America, Pacific Islands	*Aedes aegypti* and *Aedes albopictus* mosquito	3–7 d	Fever, arthritis, headache, conjunctivitis, maculopapular rash, myalgias	Virus-specific IgM, PCR	Supportive care, nonsteroidal antiinflammatory drugs for joint pain
Ebola & Marburg virus diseases[40,41]	Ebola virus & Marburg virus	Africa	Body fluids *Rousettus aegyptiacus* (fruit bat), nonhuman primate contact, sex	2–21 d	Prodrome of fever, arthralgias, headache, myalgias followed by conjunctivitis, coagulopathy, profuse diarrhea, shock	Antigen detection, RT-PCR, serologies	Experimental immune therapies & antivirals, supportive care
Endemic typhus	*Rickettsia typhi*	Worldwide, especially Southeast Asia	Rodent fleas (eg, *Xenopsylla cheopis*)	7–14 d	Fever, headache, malaise, nausea and vomiting, rash	IgM and IgG ELISA, PCR	Antimicrobial therapy (chloramphenicol, doxycycline)
Epidemic typhus	*R prowazekii*	Central Africa, Asia, Central and South America	*Pediculus humanus* (human body louse)	7–14 d	Fever, headache, malaise, nausea and vomiting, rash	IgM and IgG ELISA, PCR	Antimicrobial therapy (doxycycline)
Japanese encephalitis	Japanese encephalitis virus	Asia, Western Pacific	*Culex* species mosquito	5–15 d	Febrile illness, aseptic meningitis, acute encephalitis	IgM ELISA	Supportive care

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Table 4
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Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
Lassa fever and other arenaviral infections	Argentine hemorrhagic fever, Lassa virus, Lujo virus, LCMV	Africa, Asia, Europe, North America, and South America	Rodent urine and feces	2–21 d	Fever, myalgia, arthralgia, headache, meningeal signs, retrosternal pain, coagulopathy, birth defects (Lassa and LCMV)	Cell culture, IgM ELISA, RT-PCR	Antimicrobial therapy (ribavirin for Lassa fever), supportive care
Leptospirosis	*Leptospira* species	Caribbean, sub-Saharan Africa, South America, Southeast Asia	Infected animal body fluid or urine, contaminated water, food, or soil	2–30 d	Fever, conjunctival suffusion, back pain, rash, diarrhea, vomiting, renal and liver failure	IgM and IgG ELISA, PCR	Antimicrobial therapy (penicillins, doxycycline)
Lyme disease	*Borrelia burgdorferi*	Europe, Northern to Central Asia	*Ixodes* ticks	3–30 d	Fever, cranial nerve palsy, erythema migrans, headache, malaise, myalgia, myocarditis, meningitis	2-tiered serologic testing (ELISA or IFA & Western blot)	Antimicrobial therapy (beta-lactams, doxycycline)
Murray Valley encephalitis	Murray Valley encephalitis virus	New Guinea, Northwestern or southeastern Australia	*Culex* mosquito	7–28 d	Fever, meningeal signs, seizures	IgM ELISA, neutralizing antibodies, RT-PCR	Supportive care
Plague	*Yersinia pestis*	Central and Southern Africa, Central Asia, Northeastern South America	*X cheopis* flea	1–6 d	Varies with infection type; fever, lymphadenitis, overwhelming pneumonia, sepsis with gangrene	Culture, serologies	Antimicrobial therapy (aminoglycoside, fluoroquinolone, tetracyclines)

Poliomyelitis	Enterovirus types 1,2,3	Sub-Saharan Africa, Middle East, South and Southeast Asia	Fecal-oral	7–21 d	Flaccid paralysis, respiratory failure	Cell culture, NAAT, PCR	Supportive care
Q fever	*Coxiella burnetii*	Africa, Middle East, Europe	Aerosolized birth fluids or feces from infected livestock	2–3 wk	Self-limiting respiratory illness, pneumonia, hepatitis, cardiac disease	Serial IgG IFA, PCR	Antimicrobial therapy (doxycycline, trimethoprim-sulfamethoxazole, fluoroquinolones)
Rabies	Rabies virus	Africa, Asia, Central and South America	Saliva from infected animal bite (especially bats)	Weeks–months	Prodrome of fever, pain, paresthesias followed by hydrophobia, delirium, seizures, death	Neutralizing antibodies, RT-PCR, IFA	Supportive care, experimental Milwaukee protocol
Rat lungworm	*Angiostrongylus cantonensis*	Caribbean, Asia, Pacific islands	Ingestion of infected snails & slugs or contaminated produce	1–3 wk	Fever, meningeal signs, paresthesias	Serum antibodies, PCR	Supportive care
Relapsing fever	*Borrelia recurrentis*	Sub-Saharan Africa	*Pediculus humanus* (human body louse)	4–14 d	Fever, headache, myalgia, arthralgia, rash	Microscopic evaluation of blood smear, IgM and IgG ELISA, PCR	Antimicrobial therapy (doxycycline)
Rickettsioses	Genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Neorickettsia*, *Neoehrlichia*, *Anaplasma*	Africa, Europe, India, and Middle East	Ectoparasites (fleas, lice, mites and ticks)	7–14 d	Fever, headache, eschar (*R conorii*) at bite site, malaise, nausea and vomiting, rash maculopapular or petechial)	Clinical diagnosis, PCR, serologies, biopsy of eschar	Antimicrobial therapy (doxycycline)

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Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
RVF and other bunyaviral infections	RVF virus, CCHF, hantavirus	Africa, Eurasia, Middle East, North and South America	*Aedes* species mosquito, *Hyalomma* ticks, infected animal carcasses, rodent urine and feces	2–21 d	Fever, myalgia, arthralgia, headache, meningeal signs, vision loss (RVF), coagulopathy, renal failure (hantavirus), ecchymoses (CCHF)	Cell culture, IgM ELISA, RT-PCR	Antimicrobial therapy (ribavirin for CCHF), supportive care
Rubella	Rubella virus	Africa, Middle East, South and Southeast Asia	Person-to-person and droplet	14 d	Fever, conjunctivitis, lymphadenopathy, rash; congenital defects	Serologies, RT-PCR	Supportive care
Scrub typhus	*Orientia tsutsugamushi*	Asia, Pacific regions	Larval mite (chigger)	6–20 d	Fever, headache, malaise, nausea and vomiting, rash	IgM and IgG ELISA, PCR	Antimicrobial therapy (chloramphenicol, doxycycline)
Sleeping sickness	*Trypanosoma brucei*	Sub-Saharan, Central, and Western Africa	*Glossina* species (tsetse) fly	7–21 d	Fever, chancre at bite site, splenomegaly, renal failure, sleep cycle disruption	Microscopic examination of sterile sites or chancre-tissue biopsy	Antimicrobial therapy (suramin for early stage, eflornithine & nifurtimox for late stage)
Tetanus	*Clostridium tetani*	Worldwide, most common rurally	Contaminated wounds with dirt, excrement; punctures	10 d	Cranial nerve palsies, muscle spasms and rigidity, respiratory failure	Clinical diagnosis	Human tetanus immune globulin, tetanus toxoid, supportive care

Tick-borne encephalitis[39]	Tick-borne encephalitis virus	Central and Eastern Europe and Northern Asia	*Ixodes* species ticks, ingestion of unpasteurized dairy products	4–28 d	Prodrome of febrile illness followed by aseptic meningitis, encephalitis, myelitis	IgM ELISA, RT-PCR	Supportive care
Toxoplasmosis	*Toxoplasma gondii*	Worldwide	Ingestion of undercooked meat or contaminated water, cat feces	5–23 d	Fever, lymphadenopathy, chorioretinitis, encephalitis or pneumonitis if immunocompromised; congenital syndrome	Serologies, ocular examination, computed tomography or MRI for intracranial lesions	Supportive care or antimicrobial therapy (pyrimethamine, sulfadiazine, leucovorin)
Yellow fever[39]	Yellow fever virus	Sub-Saharan Africa, South America	*Aedes* species mosquito	3–6 d	Fever, headache, back pain, nausea, vomiting, coagulopathy, shock	RT-PCR, IgM ELISA	Supportive care
Zika[35,36]	Zika virus	Africa, Asia, South and Central America	*Aedes* species mosquito, body fluids, sex	3–12 d	Fever, arthralgia, conjunctivitis, headache, rash; congenital syndrome	RT-PCR, serologies	Supportive care

Abbreviations: CCHF, Crimean-Congo hemorrhagic fever; ELISA, enzyme-linked immunoassay; Ig, immunoglobulin; IFA, immunofluorescence assay; LCMV, lymphocytic choriomeningitis; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; RVF; Rift Valley fever.

Adapted from Centers for Disease Control and Prevention. The yellow book: health information for international travel 2018. Philadelphia: Oxford University Press; 2017. p. 704. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home. Accessed July 25, 2017; with permission.

Table 5
Tropical diseases associated with gastrointestinal symptoms

Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
amebiasis	*Entamoeba histolytica*	Worldwide	Fecal-oral, contaminated food or water	Days–weeks	Abdominal cramps, watery or bloody diarrhea, weight loss, liver abscess with abdominal pain	Microscopic evaluation of stool, serologies	Antimicrobial therapy (metronidazole + iodoquinol or puromycin)
Campylobacteriosis	*Campylobacter jejuni*, *Campylobacter coli*	Worldwide	Contaminated foods (raw poultry) and water, unpasteurized milk, fecal-oral	2–4 d	Abdominal pain, fever, bloody diarrhea, nausea and vomiting, pseudoappendicitis, reactive arthritis, Guillain-Barre syndrome	Stool culture, darkfield microscopy, NAAT	Supportive care, antimicrobial therapies (fluoroquinolone, macrolide)
Chagas disease	*T cruzi*	Central and South America	Reduviid bug, contaminated food or water, blood transfusion	7 d	Chagoma (eg, Romaña sign), ventricular arrhythmias, megacolon, megaesophagus	Microscopic evaluation of blood smear, IgM ELISA, PCR (acute disease only)	Antimicrobial therapy (benznidazole, nifurtimox)
Cholera	*Vibrio cholerae* O-group 1 or O-group 139	Africa, Caribbean, Southeast Asia	Aquatic plants, brackish water, shellfish	5 d	Profuse, watery diarrhea, nausea and vomiting, muscle cramps, hypovolemic shock	Stool culture	Supportive care, antimicrobial therapy (azithromycin, doxycycline)
Cyclosporiasis	*Cyclospora cayetenensis*	Worldwide	Contaminated produce and water	2–14 d	Watery diarrhea, anorexia, weight loss, abdominal cramps, myalgias, vomiting	Microscopic evaluation of stool for oocysts	Antimicrobial therapy (trimethoprim-sulfamethoxazole)

Echinococcosis	*Echinococcus* species	Eurasia, Central and South America, Africa	Contaminated dog feces, contaminated food or water	5–15 y	Hydatid cysts in liver and lungs, abdominal pain, liver failure	Imaging (ultrasound, computed tomography scan), serologies	Supportive care, surgical excision if cyst >10 cm, antimicrobial therapy (albendazole, praziquantel)
Traveler's diarrhea	Enterotoxigenic *Escherichia coli* (ETEC)	Worldwide	Fecal-oral, contaminated food or water	9 h–3 d	Abdominal pain, watery diarrhea	Clinical diagnosis, NAAT	Supportive care, antimicrobial therapy (ciprofloxacin, azithromycin)
Fascioliasis	*Fasciola hepatica* and *F gigantica*	South America, Middle East, Southeast Asia	Watercress or other aquatic plants, freshwater	6–12 wk	Intermittent, fever eosinophilia, abdominal pain, weight loss, urticaria, biliary colic, liver failure	Microscopic evaluation of stool, serologies, liver imaging	Antimicrobial therapy (triclabendazole)
Giardiasis	*Giardia intestinalis*	Worldwide	Fecal-oral, sexual contact, contaminated water	1–2 wk	Abdominal pain, anorexia, foul-smelling diarrhea, flatulence, nausea, reactive arthritis	Microscopic evaluation of stool, DFA	Antimicrobial therapy (metronidazole, tinidazole, nitazoxanide)
Peptic ulcer disease	*Helicobacter pylori*	Worldwide	Fecal-oral, oral-oral	Unknown	Epigastric pain, nausea and vomiting, anorexia, gastric cancer	Fecal antigen assay, urea breath test	Antimicrobial therapy (proton pump inhibitor + clarithromycin + amoxicillin)
Pinworm	*Enterobius vermicularis*	Worldwide	Fecal-oral, contaminated objects	1–2 mo	Perianal pruritus	Scotch tape test, microscopic evaluation of fingernails	Antimicrobial therapy (albendazole, pyrantel pamoate)

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Table 5
(*continued*)

Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
Sarcocystosis	*Sarcocystis* species	Worldwide, especially Southeast Asia	Undercooked beef or pork	2 wk	Fever, malaise, myalgia, headache, cough, arthralgia, nausea and vomiting, diarrhea, palpitations	Microscopic evaluation of stool, PCR, muscle biopsy	Antimicrobial therapy (trimethoprim-sulfamethoxazole)
Soil-transmitted helminths	*Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* (hookworm), *Necator americanus* (hookworm), *Trichuris trichiura* (whipworm)	Worldwide	Fecal-oral, skin penetration with contaminated soil (hookworms)	Variable	Abdominal pain, malnutrition, bowel obstruction, anemia, cough, chest pain	Microscopic evaluation of stool	Antimicrobial therapy (albendazole, mebendazole)
Strongyloidiasis	*Strongyloides stercoralis*	Worldwide	Auto-inoculation, skin penetration	Variable	Pruritic rash at penetration site, serpiginous rashes (larva currens), respiratory symptoms (Löffler-like pneumonitis), abdominal pain, diarrhea, severe disease if immuno-compromised	Microscopic evaluation of stool other body fluids if disseminated (eg, sputum, CSF)	Antimicrobial therapy (ivermectin, albendazole)

Taeniasis	*Taenia solium* (pork) and *T saginata* or *T asiatica* (beef)	Central and South America, Africa, South and Southeast Asia	Undercooked contaminated pork or beef	8–10 wk for *T solium*, 10–14 wk for *T saginata*	Abdominal discomfort, weight loss, anorexia, perianal pruritus, insomnia, weakness	Microscopic evaluation of stool for eggs	Antimicrobial therapy (praziquantel, niclosamide unless symptomatic neurocysticercosis)
Visceral leishmaniasis	*Leishmania donovani* and *L infantum-chagasi*	South America, Central and Southwest Asia, East Africa	Phlebotomine sand fly, blood transfusions	Weeks–months	Fever, weight loss, hepatosplenomegaly, pancytopenia	Light-microscopic evaluation of specimens, culture, molecular methods	Antimicrobial therapy (amphotericin B, miltefosine)
Yersiniosis	*Yersinia enterocolitica*	Japan, Northern Europe	Undercooked contaminated pork, contaminated water, unpasteurized dairy	4–6 d	Fever, abdominal pain (pseudoappendicitis), bloody diarrhea, necrotizing enterocolitis in infants, reactive arthritis, erythema nodosum	Stool culture (or other body sits; eg, CSF, blood)	Supportive care, antimicrobial therapy if severe (trimethoprim-sulfamethoxazole, fluoroquinolones, aminoglycosides)

Abbreviations: CSF, cerebrospinal fluid; DFA, direct fluorescent antibody.

Adapted from Centers for Disease Control and Prevention. The yellow book: health information for international travel 2018. Philadelphia: Oxford University Press; 2017. p. 704. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home. Accessed July 25, 2017; with permission.

Table 6
Tropical diseases associated with respiratory symptoms

Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
Avian bird flu	H5N1 and H7N9 influenza A virus	East and Southeast Asia	Poultry	2–8 d	Fever, malaise, myalgia, headache, nasal congestion, cough, acute respiratory distress syndrome (ARDS)	RT-PCR	Supportive care
Diphtheria	*Corynebacterium diphtheriae*	Asia, South Pacific, Middle East, Eastern Europe, Caribbean	Person-to-person (oral or respiratory droplets), fomites	2–5 d	Fever, dysphagia, malaise, anorexia, pseudomembranes	Bacterial culture	Supportive care, equine diphtheria antitoxin (DAT), antimicrobial therapy (erythromycin, penicillin)
Coccidioidomycosis	*Coccidioides immitis* and *Coccidioides posadasii*	Central and South America	Inhalation of spores from soil	7–21 d	Fever, malaise, cough, headache, night sweats, myalgias, arthritis, rash	Culture, IgM and IgG ELISA, immunodiffusion and complement fixation	Supportive care, antimicrobial therapy if ill or at high risk of dissemination (amphotericin B, azoles)
Histoplasmosis	*Histoplasma capsulatum*	Worldwide, especially river valleys	Inhalation of spores from soil, bird droppings, bat guano	3–17 d	Fever, headache, cough, pleuritic chest pain, malaise	Culture, microscopic examination, PCR, EIA on serum or other samples, immunodiffusion complement fixation	Supportive care, antimicrobial therapy (azole for mild to moderate disease, amphotericin B for severe)

Legionellosis (Legionnaire's disease and Pontiac fever)	*Legionella* species	Worldwide	Inhalation of freshwater aerosol	2–10 d	Fever, headache, myalgias, pneumonia, respiratory distress	Urine antigen assay, paired serologies, PCR	Antimicrobial therapy (fluoroquinolones, macrolides)
Melioidosis	*Burkholderia pseudomallei*	Central and Southeast Asia, northern Australia, South America	Subcutaneous inoculation, inhalation, ingestion; body fluids	1–21 d	Fever, cough, weight loss, pneumonia	Culture, indirect hemagglutination assay	Antimicrobial therapy (ceftazidime, meropenem)
Middle Eastern Respiratory Syndrome (MERS)	MERS coronavirus	North Africa, Middle East	Dromedary camel, person-to-person	2–14 d	Fever, cough, arthralgia, diarrhea, myalgia, acute respiratory failure, multiple organ dysfunction	RT-PCR	Supportive care
Pertussis (whooping cough)	*Bordetella pertussis*	Worldwide	Person-to-person (aerosolized respiratory droplets, respiratory secretions)	7–10 d	Paroxysmal cough, post-tussive vomiting, apnea in infants	Culture, serologies, PCR	Antimicrobial therapy (macrolides)

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Table 7
Tropical diseases associated with dermatologic symptoms

Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
B virus	*Macacine herpesvirus I* or B virus	Worldwide	Bites, scratches, body fluids of infected macaque	3–30 d	Fever, headache, myalgias, vesicular lesions near exposure site with neuropathic pain, ascending encephalomyelitis	PCR, virus-specific antibodies	Supportive care, postexposure prophylaxis (valacyclovir), antimicrobial therapy (acyclovir, ganciclovir)
Cutaneous leishmaniasis	*Leishmania* species	Middle East, Southwest and Central Asia, North Africa, Southern Europe, Central and South America	Phlebotomine sand fly	Weeks–months	Papules that progress to ulcerated plaques, regional lymphadenopathy, and nodular lymphangitis	Light-microscopy evaluation of specimens, cultures, molecular methods	Antimicrobial therapy (miltefosine, amphotericin B)
Cutaneous larva migrans	*Ancylostoma* species (hookworms)	Caribbean, Africa, Asia, South America	Skin contact with contaminated sand	1–5 d	Serpiginous track on skin with pruritus and edema	Clinical	Supportive care, antimicrobial therapy if desired (albendazole, ivermectin)
Loiasis (African eye worm)	*Loa loa*	Central and West Africa	Genus *Chrysops* (deerflies)	7–12 d	Localized edema of extremities and joints (Calabar swelling), diffuse pruritus, eye pruritus and pain, and photophobia	Microscopic evaluation of adult worm from eye, microscopic evaluation of microfilariae on blood smear, serologies	Surgical excision of adult worms, antimicrobial therapy (diethylcarbamazine, albendazole)

Lymphatic filariasis	*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*	Sub-Saharan Africa, Southern Asia, Pacific Islands, South America, Caribbean	*Aedes*, *Culex*, *Anopheles*, *Mansonia* mosquitoes	Years	Lymphatic dysfunction with affected limb edema and pain	Microscopic evaluation of peripheral blood smear, serologies	Antimicrobial therapy (diethylcarbamazine, doxycycline)
Myiasis	Maggots of *Dermatobia hominis* (human bot fly), *Cochliomyia hominivorax* (screw worm), and others	Central and South America, Africa, Caribbean	Bites of infected flies or egg laying on open wounds	1–2 wk	Localized skin nodule, pruritus, discharge from punctum	Clinical, serologies	Surgical excision of larvae
Rat-bite fever	*Streptobacillus moniliformis* and *Streptobacillus minus*	Worldwide	Bites, scratches, oral secretions of infected rats; unpasteurized milk or contaminated food or water	7–21 d	Relapsing fever, maculopapular or purpuric rash, migratory polyarthritis, lymphadenopathy	Culture, darkfield microscopy, stained peripheral blood smear	Antimicrobial therapy (penicillin G)
River blindness (onchocerciasis)	*Onchocerca volvulus*	Sub-Saharan Africa, Middle East, South America	Genus *Simulium* (blackflies)	Weeks – years	Pruritic, popular rash with subcutaneous nodules, lymphadenitis, ocular lesions, vision loss	Microscopic evaluation of skin shavings with microfilariae, histologic evaluation, serologies	Antimicrobial therapy (ivermectin + doxycycline)

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Table 7
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Disease	Etiologic Pathogen	Geographic Regions	Vector or Exposure	Incubation Period	Presentation	Diagnosis	Management
Scabies	*Sarcoptes scabiei* var. *Hominis*	Worldwide	Prolonged skin-to-skin contact, fomites if crusted scabies	2–6 wk	Nocturnal pruritus, papulovesicular rash, crusts and scales if crusted scabies	Microscopic evaluation of skin scraping	Antimicrobial therapy (permethrin, ivermectin creams)
Strongyloidiasis	*Strongyloides stercoralis* (roundworm)	Worldwide	Skin penetration with contaminated soil	Unknown	Localized, pruritic, erythematous popular rash, pulmonary symptoms (Löffler-like pneumonitis), diarrhea, abdominal pain, eosinophilia, serpiginous urticarial rash (larva currens)	Microscopic evaluation of stool, peripheral blood eosinophilia if disseminated, serologies	Antimicrobial therapy (ivermectin, albendazole)
Tungiasis	*Tunga penetrans* (chigoe flea, jigger, sand flea)	Africa, South America	Skin penetration (especially walking barefoot)	1–2 d	Localized pruritus and pain with lesions and ulcerations with central black dot	Clinical	Extraction of flea using sterile needle

Adapted from Beeching N, Beadsworth M. Fever on return from abroad. In: Acute medicine-A practical guide to the management of medical emergencies. 5th edition. 2017. p. 207–14; and Centers for Disease Control and Prevention. The yellow book: health information for international travel 2018. Philadelphia: Oxford University Press; 2017. p. 704. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home. Accessed July 25, 2017; with permission.

Dermatologic Symptoms

Rashes are a source of concern for parents without the context of travel and may be even more worrisome after going abroad. The differential diagnosis includes typical childhood illnesses, such as roseola or staphylococcal cellulitis, in addition to tropical infections. A study of Canadian travelers from 2009 to 2012 found that cutaneous larva migrans (13%) and skin and soft tissue infections (12.2%) were some of the most common infectious dermatologic complaints among tourists.[47]

In countries where vaccination rates are low, varicella zoster virus or rubella may cause disease, especially in young children who have not completed their immunization series. Measles remains an important risk, with tourists comprising 44% of the 94 cases reported to GeoSentinel from 2000 to 2014, and 13% of patients being younger than 18 years of age, although this may represent underreporting due to the surveillance system's primarily adult focus.[48] Petechiae on the extremities in an ill-appearing child may indicate a serious systemic process such as meningococcal or rickettsial infection. There are many other infections with primarily dermatologic manifestations that may not cause fevers (**Table 7**).[49]

SUMMARY

As the numbers of children who travel abroad continues to increase, clinicians need to remain up-to-date on potential etiologic factors for febrile illnesses on families' return home. After ruling out life-threatening disorders that can be acquired locally or internationally, physicians are able to develop a focused diagnosis and management plan best suited to the patient's clinical picture. There is a growing body of resources to assist clinicians, such as the CDC (www.cdc.gov/travel/) and GeoSentinel (www.istm.org/geosentinel) for data on epidemiology, geography, and other risk factors.

In the future, physicians will need to be prepared to deal with the global epidemic of antimicrobial drug resistance, evolving epidemics and pandemics caused by emerging pathogens, reemerging infections due to vaccine hesitancy or international conflicts, and medical tourism in both healthy and medically complex children.

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