

Fever in the Returned Pediatric Traveler

Global Pediatric Health
Volume 8: 1–16
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DOI: 10.1177/2333794X211026188
journals.sagepub.com/home/gph



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Abstract

Global mobility has been steadily increasing in recent years. The assessment of the febrile child returning from international travel is a diagnostic challenge. The COVID-19 pandemic has profoundly affected international travel and made evaluation and management of the sick returned traveler more challenging. Children visiting friends and relatives abroad remain at higher risk of infection compared to tourists. This review presents a guidance on the initial assessment of a traveling febrile child including interpretation of medical history, physical examination, and laboratory findings. Important clues to etiology include exposure to different infectious agents, incubation periods of pathogens, and prophylaxis regimens and vaccines received. Early identification of potentially life-threatening and highly contagious infections is essential. In this article, we discuss the epidemiology, evaluation, and management of specific travel related infections such as malaria, typhoid fever, dengue fever, viral hemorrhagic fever, rickettsiosis, leptospirosis, schistosomiasis, gastrointestinal, and respiratory infections.

Keywords

fever, child, travel, infections

Received May 26, 2021. Accepted for publication May 30, 2021.

Introduction

Fever is a presenting symptom in 10% to 42% of returned ill travelers to any destination. Among travelers to tropical areas, 15% to 70% report illness in association with travel.¹⁻³ Of those ill travelers, 15% to 54% become ill enough to seek medical attention and 1% to 6% require hospitalization. The etiology of illness in the returned traveler may fall into the following categories: A non-infectious condition that may be unrelated to travel, an infection that has cosmopolitan distribution, an infection related to travel destination including a classical tropical disease or a new or emerging infection not previously recognized.^{4,5} Fever in returning child travelers is most frequently due to common cosmopolitan infections that are easily treatable such as respiratory, gastrointestinal, or urinary tract infections.⁶

Factors that influence the risk of acquiring a travel-related illness include the geographic location of travel and the duration as well as the type of travel. Children who travel with caregivers who are visiting friends and relatives (VFR) are at the highest risk of travel related illness.^{7,8}

The main cause of fever among returned travelers is Malaria. Other specific etiologies seen in returned travelers include Dengue fever, mononucleosis, *Salmonella*

serotypes Typhi, and Paratyphi and rickettsial infections.⁹ However, no specific cause may be identified in 40% of returned travelers. Clinicians should always be aware of ongoing or emerging epidemics such as Ebola epidemics in Africa, Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) in the Arabian Peninsula, Zika and Chikungunya viruses in Latin and South America. The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic that started in December 2019 and still ongoing has changed the landscape of travel worldwide.¹⁰ Currently all travelers regardless of clinical status should be evaluated for the risk of coronavirus disease 2019 (COVID-19). In addition, the emergence of multidrug resistant pathogens such as extended spectrum beta lactamase (ESBL) producing Gram negative bacteria, carbapenemase resistant Enterobacteriaceae (CRE), and *Candida*

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auris need to be taken into consideration when evaluating travelers.^{11,12}

The focus of initial evaluation should be on excluding treatable and transmissible infections as well as infections that are likely to cause complications including death. In stable patients, treatment may be delayed while awaiting work up. However, empiric treatment in toxic children should be initiated as appropriate.^{6,9}

Initial Evaluation

Seriously ill children should be managed immediately according to pediatric advanced life support guidelines. An infectious diseases consultation should be obtained to facilitate expedited evaluation and management. Keys to etiology include exposure history to potential infectious agents, mode of exposure, the incubation period of the pathogen, and its relation to the arrival date as well as pre-travel vaccination and prophylaxis.^{6,9,13} A comprehensive medical and travel history should be obtained along with a detailed physical examination with focus on the elements detailed in the following sections.

Travelers Visiting Friends and Families (VFR) Abroad

Travelers who are visiting friends and relatives are referred to as VFR travelers and include persons who maintain familial or other social links to a country that is different from their current citizenship or residence.⁷ The most common reason of travel among the pediatric population is VFR. VFR travelers have a higher risk of travel related infections and other associated morbidities. This is likely related to familial, social, and cultural connections to the destination country. VFR travelers are more likely than business travelers or tourists to travel for longer duration and have closer contact with local people.^{6,7} They are more likely to consume locally prepared foods and drinks. In addition, VFR travels are less likely to seek pre-travel medical advice and to receive prophylactic medications and vaccines. VFR travel among children has been found to be associated with systemic febrile illness, particularly with malaria.¹⁴ Among VFRs, children younger than 5 years may be particularly at higher risk of travel related illnesses than older children and adults.^{7,15,16}

Travel Dates and Destination

By obtaining exact travel dates, the medical practitioner may be able to exclude certain infections by their incubation periods (Table 1). For example, malaria may be

excluded if symptoms occur less than 7 days of suspected exposure. Similarly, dengue fever can be excluded if symptoms start more than 14 days after departure from travel area.^{5,6,17} History of travel to different destinations during the last 12 months should be obtained to evaluate infections that are prevalent in the specific geographical areas. In addition, the risk of a certain infection may vary from 1 area to the other in the same country such as urban and rural regions and high or low altitudes. Travel season is another consideration. Examples of seasonal variation include malaria acquisition during the rainy season in tropical areas and meningococcal disease during the dry season in sub-Saharan Africa.⁶

Table 2 summarizes common infections associated with specific geographical areas. For example, the most common infection in a returned traveler from Sub-Saharan and West Africa is malaria due to *Plasmodium falciparum*.¹⁸ Other important causes of fever after travel to sub-Saharan Africa include schistosomiasis, amebiasis, rickettsiosis, meningococcal disease, and viral hemorrhagic fever (VHF).^{3,19,20} Rickettsial infections are encountered in travelers to South Africa. Important causes after to travel to Asia include dengue, typhoid fever, and chikungunya.⁶ Dengue fever and coccidioidomycosis should be considered in travelers to the South America and the Caribbean. Brucellosis is considered among travelers to the Middle East.^{21,22} Ongoing outbreak should be considered during assessment. Consultation with online resources such as CDC website may be helpful in this regard. In the era of climate change, unusual infections may be unexpectedly encountered in certain geographic area. For example, during the last decade dengue and Chikungunya viruses have been detected in European countries such as Italy and France.^{23,24} Chikungunya was first detected in the Caribbean in 2013 and since then spread in Central and South America.²⁵

Travel Activities

Certain activities practiced at a travel destination can be associated with specific infections. For example, exposure to fresh water is associated with risk of acquiring schistosomiasis and leptospirosis in certain destinations.²⁶ In addition, children are more likely than adults to get in contact with animals placing them at particularly high risk of zoonosis. Camping and living close to local population are associated with increased risk of malaria, meningococcal disease, and typhus.⁶ The risk of infections associated with food and water consumption depends on hygiene and preparation. For example, consumption of undercooked food and contaminated water is associated with risk of typhoid fever,

Table 1. Incubation Periods of Different Travel Associated Infections.

Incubation period	Infection	Usual incubation period
<14 days	SARS CoV-2 (COVID-19)	2-14 days
	Influenza	1-3 days
	Arbovirus encephalitis (JE virus, WN virus)	3-14 days
	Chikungunya	2-4 days
	Zika virus	3-14 days
	Dengue fever	4-8 days
	Acute HIV	7-21 days
	Typhoid/paratyphoid fever	7-18 days
	Leptospirosis	7-12 days
	Malaria:	
<i>P. falciparum</i>	6-30 days	
<i>P. vivax</i>	8 days-12 months	
Spotted fever rickettsiosis	3 days-3 weeks	
14 days to 6 weeks	Amebic liver abscess	Weeks-months
	Hepatitis A	28-30 days
	Hepatitis E	26-42 days
	Acute schistosomiasis (Katayama fever)	28-60 days
>6 weeks	Hepatitis B	60-160 days
	Visceral leishmaniasis	2-10 months
	Tuberculosis	Weeks for primary infection

Abbreviations: COVID-19, coronavirus diseases-2019; JE, Japanese encephalitis virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WN, West Nile.

Table 2. Common Causes of Fever in Tropical Areas Based on Geography.

Geographic area	Common infections causing fever
Caribbean	Chikungunya, acute histoplasmosis, dengue fever, Zika virus, cholera, leptospirosis, malaria (mainly Haiti: <i>P. falciparum</i> malaria)
Central America	Chikungunya, dengue fever, malaria (primarily <i>P. vivax</i>), Zika, acute histoplasmosis, coccidioidomycosis, tuberculosis
South America	Dengue fever, malaria (primarily <i>P. vivax</i>), Zika, chikungunya
South Central Asia	Dengue, Typhoid fever, malaria (primarily non falciparum)
Southeast Asia	Dengue, malaria (primarily non- falciparum), Chikungunya, yellow fever, Japanese encephalitis virus
Sub-Saharan Africa	Malaria (primarily <i>P. falciparum</i>), rickettsioses, acute schistosomiasis, dengue, meningococcus, yellow fever

hepatitis A and E, traveler's diarrhea, and fascioliasis.^{3,6,9,13} Unpasteurized dairy products are associated with *Salmonella*, *Brucella* and *Listeria* infections.^{22,27} Specific risk taking behavior such as sexual activity should be discussed with adolescents who may be at risk of human Immunodeficiency virus (HIV) acquisition.²⁸ Examples of travel-related disease association with certain exposures and activities are in listed in Table 3.

Prophylaxis and Vaccines

Details of malaria chemoprophylaxis should be obtained from travelers to malaria endemic areas including compliance with regimen. Mefloquine is taken weekly until 4 weeks after last exposure, while atovaquone/proguanil

is taking daily until 7 days after departing endemic area.²⁹ History of mosquito bites, the use of mosquito nets, long sleeved clothing, and mosquito repellents should be obtained to determine potential risk of mosquito borne illnesses.⁶

Vaccination history should be obtained; certain vaccines are highly protective against travel related illnesses such as hepatitis A and yellow fever. However, others are less protective such as typhoid fever vaccine.^{6,30}

Past Medical History

Details of past medical history, medication use, and potential contact with ill individuals should be obtained from all travelers. Underlying medical conditions such

Table 3. Differential Diagnosis According to Exposure and Activity.

Exposure/activity	Disease
Undercooked food	Nontyphoidal salmonellosis, Trichinosis, typhoid fever
Untreated water	Amebiasis, hepatitis A and E, Cholera, nontyphoidal salmonellosis, typhoid fever, other parasites: <i>Cryptosporidium</i> , <i>Cyclospora</i> , <i>Giardia</i>
Contact with fresh water	Acute schistosomiasis, leptospirosis, free living amebiasis
Unpasteurized dairy products	Brucellosis
Sexual contact	Chancroid, gonorrhea, hepatitis B, syphilis, HIV
Contact with animals	Brucellosis, plague, Q-fever, rabies, tularemia, avian influenza
Contact with ill persons	Meningococcal disease, TB, viral hemorrhagic fevers, MERS-CoV, COVID-19
Caves	Histoplasmosis, rabies
Arthropods	
Mosquitos	Dengue fever, malaria, yellow fever, Chikungunya, Zika virus, JE virus, WN virus
Ticks	Rickettsial disease, tularemia, Lyme disease, babesiosis
Fleas	Murine typhus, plague
Lice	Epidemic typhus, relapsing fever
Mites	Scrub typhus (<i>Orientia tsutsugamushi</i>)

Abbreviations: COVID-19, coronavirus disease-2019; MERS-CoV, Middle East respiratory syndrome-coronavirus; TB, tuberculosis.

as immunosuppression predispose travelers to infections. Patients with splenic dysfunction are at higher risk of acquiring malaria and pneumococcal invasive disease.^{31,32} Medication history should be obtained as noncompliance with prescribed antimicrobial regimens or use of un-prescribed antimicrobials may be associated with partially treated infections.⁶

Clinical Presentation

A detailed medical history should be obtained including the duration and pattern of fever. A complete physical examination should also be performed. In some instances, associated symptoms such as abdominal pain, cough, diarrhea or skin rash may help narrow the differential diagnosis, or localize the site of infection. For example, petechial lesions and fever may indicate meningococcal disease, rickettsiosis, and viral hemorrhagic fever.⁶

However, it is not uncommon to have no focal findings in different infections such as malaria, typhoid fever, or dengue fever.^{9,17} Localized symptoms may be early presentation of a systemic infection. For example, children with malaria may present with fever and gastrointestinal symptoms leading to instances of misdiagnosis as gastroenteritis.³³ In addition, certain findings such as skin rash may represent a manifestation of a systemic illness. Examples of clinical presentations of selected travel related infections are in Table 4.

Infection Control Considerations

Institutional infection control screening questions may be used to identify febrile returning child travelers. Such

patients should be managed in a separate room with universal precautions.⁶ Further infection control measures will depend on history as well as presenting signs and symptoms. Laboratory personnel may need to be notified for certain suspected infections. It is essential to be aware of potential VHF which are endemic in different parts of the world especially in Africa.¹⁷ VHF should be suspected in a returning traveler from endemic area within 21 days especially if bleeding manifestations are present on physical examination. Because of the high contagiousness, high mortality, and difficult diagnosis, patient with suspected or confirmed VHF are typically managed in specially designated units with the highest level of personal protective equipment use.³⁴

Laboratory Evaluation of the Febrile Returning Traveler

Table 5 includes investigations that should be initially considered in a febrile returning child traveler. Of particular importance are malaria blood smears, blood culture, stool culture, and chest radiography.⁴ Further investigations such as specific serological tests or PCR panels will depend on the initial work up, clinical presentation, and travel destination. With the ongoing COVID-19 pandemic, nasopharyngeal specimen for SARS-CoV-2 PCR should be obtained for all travelers. Consultation with local microbiologists, infectious disease specialists and local public health experts may be needed to determine further testing, empiric therapy of seriously ill children, and specific infection control measures.⁴

The complete blood count (CBC) and white blood count differential may provide helpful clues in the

Table 4. Findings and Possible Etiologies of Fever in Returning Travelers.

Finding	Possible etiologies
Systemic febrile illness	Malaria, Enteric (typhoid/paratyphoid) fever, Dengue fever, spotted fever rickettsiosis, Chikungunya, Zika virus, acute HIV, leptospirosis, infectious mononucleosis, respiratory virus infections (Influenza, SARS-CoV-2, pneumonia)
Abdominal pain	Enteric fever, amebic liver abscess
Diarrhea	Bacterial (<i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>E. coli</i>), Parasitic (<i>Giardia</i> , <i>Entamoeba histolytica</i> , <i>Cryptosporidium</i>), viral
Pulmonary infiltrates	Common bacterial/viral pathogens, Katayama fever, Legionella, Q fever, leptospirosis
Jaundice	Viral hepatitis (A, B, C, E), malaria, leptospirosis (Weil's disease), yellow fever, viral hemorrhagic fever
Hemorrhagic manifestations	Dengue fever, meningococemia, other viral hemorrhagic fever, leptospirosis
Conjunctivitis	Leptospirosis, Zika
Splenomegaly/hepatomegaly	Malaria, infectious mononucleosis, dengue, viral hepatitis, visceral leishmaniasis, amebic liver abscess
Skin rash	Dengue, Zika, Chikungunya, measles, rickettsial spotted fevers, typhoid fever, Katayama fever, acute HIV
Arthralgia/myalgia	Chikungunya, dengue fever, Zika
Altered mental status	Bacterial meningitis, cerebral malaria, viral meningoencephalitis (Japanese encephalitis, West Nile, tick-borne), typhoid fever, rickettsia, leptospirosis

Table 5. Initial Work Up of the Febrile Returning Traveler.

Complete blood count with differential
Serum biochemistry including liver enzymes
NP swab for SARS-CoV-2 PCR
Malaria thin and thick blood smear, rapid tests
Blood culture, stool studies: ova and parasites, culture
Urinalysis and urine culture
Save serum for paired serology if needed
EDTA blood sample for PCR tests: if arbovirus or VHF is suspected
Chest radiograph and liver ultrasound: in some cases, other imaging as indicated
Bone marrow microscopy and culture: some cases with fever of unknown origin

Abbreviations: EDTA, ethylenediamine tetraacetic acid; NP, nasopharyngeal; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

diagnosis of a febrile returning traveler. For example, neutrophilia is often seen in bacterial infections but may also be noted in patients with amoebic liver abscess.³⁵ Lymphopenia may be seen in viral infection such as dengue fever and in typhoid fever. Lymphocytosis is seen in Epstein-Barr virus or cytomegalovirus mononucleosis and in *Toxoplasma* infections.⁴ Thrombocytopenia is seen in patients with malaria, viral infections such as dengue fever and HIV and patients with severe sepsis.^{4,36,37} Thrombocytopenia, anemia, and hypoglycemia are associated with malaria. Leukopenia and thrombocytopenia are associated with dengue.^{36,37}

Eosinophilia is a common finding in the returning travelers. Eosinophilia is seen in parasitic diseases, especially helminthic infections such as schistosomiasis, fascioliasis, and echinococcosis.^{4,38,39} Evaluation of

eosinophilia largely depends on the destination of travel because some helminths have distinct geographical distribution.³⁹ However, it is not noted in protozoa infections except for *Toxoplasma* and *Isospora*. Eosinophilia may also be seen in certain viral infections such as HIV, fungal infections, and occasionally in tuberculosis.^{4,38}

Thick and thin blood smears should be performed in all travelers to endemic areas within 12 months of return regardless of clinical presentation or chemoprophylaxis which is not 100% effective.^{29,40}

Biochemical studies that may provide clues to diagnosis include bilirubin and liver enzymes. Unconjugated hyperbilirubinemia may indicate hemolysis due to malaria or babesiosis.^{4,35} Conjugated hyperbilirubinemia may indicate viral hepatitis, leptospirosis, viral hemorrhagic fever, and bacterial sepsis.⁴ Elevation of

alkaline phosphatase is seen in hepatitis, cholangitis, and amoebic liver abscess.^{4,35}

Blood cultures should be part of the initial work up of a febrile returning traveler. Specialized culture bottles may be needed for certain bacterial, mycobacterial, and fungal infections. Infections seen in tropical areas such as those caused by *Brucella*, *Salmonella* serotype Typhi or Paratyphi, and *Burkholderia pseudomallei* may be detected in blood cultures.⁴ Medical providers should inform the laboratory of any suspected infections that need the staff to handle specimens safely or provide special culture requirements. If bacterial, mycobacterial, or fungal infections are suspected and cultures are negative, specimen may be sent for 16s ribosomal DNA detection for bacteria, 18s ribosomal DNA for fungi, or for *M. tuberculosis* PCR.⁴

It is important during the initial evaluation of the sick returning traveler to consider the risk of VHF because of the implications on infection control and handling of laboratory specimens.³⁴ If a patient is suspected of having VHF, only essential blood tests should be done such as malaria smear while other urgent investigations for VHF are pending.⁴

Major Tropical Causes of Fever

Malaria

Malaria is a major international public health problem. Transmission of malaria occurs in most parts of Africa, Latin America, parts of the Caribbean, and Asia. Malaria may be reintroduced in areas where it was previously eliminated if infected people return, and the mosquito vector is still present as has occurred recently in Jamaica, Greece, and the Bahamas.²⁹ There are approximately 1700 cases of Malaria per year in the United States are almost all are imported.⁴¹ According to CDC data in 2015, 85% of cases were acquired in Africa, 9% in Asia, 5% in the Caribbean and the Americas, and 1% in Oceania or the Middle East.⁴¹ The majority of imported cases of malaria in the USA and European countries occur among immigrants and VFR travelers.^{7,8} Children account for 11% to 23% of cases of imported malaria and the majority were associated with travel to Sub-Saharan Africa.⁷ VFR children have 4 times higher risk of getting malaria than tourists. Children born in non-malaria endemic countries who acquire malaria develop a higher level of parasitemia than recent immigrants.⁷ The risk of malaria acquisition may also be related to the low rates of adequate chemoprophylaxis (0%-30%) in these children.⁷ The risk of malaria in a specific country can change rapidly depending on the season and mosquito activity. Thus, up to date information on

transmission can be obtained from WHO website www.who.int or the CDC website at www.cdc.gov/malaria.

There are 5 *Plasmodium* species that cause infection in humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae* and *P. knowlesi*. Travelers acquire infection via the bite of an infective female Anopheles mosquito. *P. vivax* and *P. falciparum* are the most prevalent species worldwide. *P. vivax* malaria is prevalent on the Indian subcontinent and in Central America.^{29,41} *P. falciparum* malaria is prevalent in different parts of the world including Africa, Papua New Guinea.^{29,41} Patients may develop symptoms as early as 7 days after mosquito bite but most within 2 months of infection. Other Plasmodium species may present as late as several months or more after exposure.^{29,41}

Malaria is characterized by fever and non-specific influenza-like symptoms, abdominal pain, vomiting, diarrhea, and cough.^{3,9,17} Malaria is often initially misdiagnosed in children. Headache, myalgias, and rigors are less common in children than adults.²⁹ Clinical findings may include jaundice, pallor, and hepatosplenomegaly. Severe malaria is frequently associated with *P. falciparum* species. Young children are at high risk of severe disease including anemia and cerebral malaria.³⁷ Suspected or confirmed *P. falciparum* malaria is a medical emergency that requires urgent intervention. Severe malaria in children may include one of the following clinical syndromes, all of which can be fatal if untreated: Cerebral malaria; hypoglycemia; renal failure due to acute tubular necrosis; respiratory failure; metabolic acidosis; severe anemia due to high parasitemia, hemolysis with hypersplenism and shock.^{29,37,41} Relapses may occur in *P. vivax* and *P. ovale* infections because of a persistent hepatic (hypnozoite) stage of infection.²⁹

Diagnosis is mainly by blood smear microscopy which can provide immediate information about the presence of parasites, the species, and the density of the infection.⁴¹ Thin and thick blood films should be repeated as needed and analyzed by experienced laboratory personnel to avoid false negative results. Three smears should be performed every 12 to 24 hours if clinical suspicion of malaria remains.^{29,41} Rapid diagnostic tests (RDTs) for malaria detect antigens derived from malaria parasites and can be a useful alternative when reliable microscopy is not immediately available. The Food and Drug Administration (FDA) has approved an RDT (the BinaxNOW Malaria test) for hospital and commercial laboratory use. However, RDTs have limitations including low sensitivity compared to expert microscopy, and PCR and inability to distinguish between different malaria species.^{41,42} RDTs may remain positive for days or weeks after successful treatment. Positive or negative RDT results

should always be followed by microscopy as soon as possible.⁴¹ Malaria PCR tests are also available and are more sensitive than microscopy.⁴³ PCR is recommended to confirm the species and detect mixed infections.^{41,44} However, the clinical utility of the test may be limited because it is not readily available. In the USA, mandatory reporting of malaria disease to local health departments is required.

Delay and misdiagnosis of malaria are associated with increased mortality and morbidity.^{29,37} Specific treatment options depend on the species of malaria, the severity of infection, and the likelihood of drug resistance. Severe malaria, usually caused by *P. falciparum* is defined as any 1 or more of the following: parasitemia greater than 5% of red blood cells infected, signs of central nervous system or other end-organ involvement, shock, acidosis, thrombocytopenia, and/or hypoglycemia.²⁹ Patients with severe malaria require intensive care and parenteral antimalarial therapy. The CDC⁴¹ recommends that all patients with severe malaria, regardless of infecting species, should be treated with intravenous (IV) artesunate. For uncomplicated *P. falciparum* infections acquired in areas with chloroquine resistance, 4 treatment options are available. These include artemether-lumefantrine (preferred) if readily available, and atovaquone-proguanil.^{41,45} Quinine sulfate with doxycycline, tetracycline, or clindamycin are also other treatment options. The fourth option is mefloquine.⁴¹ However, potentially severe neuropsychiatric reactions with mefloquine make it a less preferred option.⁴⁶ CDC⁴¹ recommendations for malaria treatment can be found at www.cdc.gov/malaria/diagnosis_treatment/treatment.html.

Typhoid Fever

Typhoid fever is a systemic illness caused by the bacterium *Salmonella enterica* serotype Typhi. Most cases diagnosed in the USA and Western Europe are among international travelers, with the greatest proportion from travel to the Indian subcontinent.⁴⁷ Typhoid fever is a less common cause of illness than malaria in febrile returning children. Without antibiotic treatment, the mortality rate is 12% to 30%.⁴⁸

Typhoid is transmitted via consumption of contaminated food and water as well as via person-to-person contact. Humans are the only host of serotype Typhi.⁴⁷ Vaccination is recommended for people traveling to endemic areas.⁴⁹ However, typhoid fever vaccines are 50% to 80% effective and do not protect against paratyphoid fever.⁴⁸ Travelers are advised to practice safe eating and drinking habits to prevent infection.⁴⁸

Symptoms of typhoid fever include fever, headache, abdominal pain, constipation or diarrhea, malaise, chills,

and myalgias. Other findings include hepatomegaly, splenomegaly, and rose spots in 30% of patients.⁴⁷ Relative bradycardia, which indicates slower heart rate than is expected with degree of fever is a common finding in adults but is not seen in children with typhoid fever.⁴⁷ Clinical presentation may resemble other febrile infectious diseases; thus, a high index of suspicion should be maintained. Severe typhoid fever can be complicated by bacteremia with sepsis or shock.^{47,50} Other systemic complications in the second week can include gastrointestinal manifestations such as intestinal perforation, peritonitis and intestinal hemorrhage, hepatitis, and abnormal neurologic findings such as encephalopathy. Myocarditis and endocarditis occur rarely.⁴⁷

Most Typhi infections in the USA are acquired during international travel. However, serotype Typhi can be acquired in the United States.⁵¹ Clinical manifestations of typhoid fever are typically evident within 30 days of international travel.⁴⁸ If typhoid fever is suspected, a blood culture should be obtained. Multiple blood cultures are usually needed to isolate serotype Typhi. Stool and urine cultures are sent but are less sensitive than blood culture. In patients who have received antimicrobial therapy, bone marrow cultures may be considered as they can remain positive despite treatment.^{47,48} PCR may be helpful in certain situations when blood culture is negative.⁵² Serological testing including Widal test is unreliable and is not recommended because of the high rate of false positive results.^{47,48}

The emergence of antibiotic resistance in Typhi isolates in certain parts of the world has made empiric treatment options challenging.⁵³ In 2016, a large outbreak of extensively drug-resistant (XDR) Typhi infections started in Pakistan.⁵⁴ Infections among travelers to or from Pakistan have been reported in multiple countries including the US. XDR Typhi strains are resistant to antibiotics that are generally used to treat typhoid fever such as ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole.⁵⁵ However, isolates from this outbreak remain susceptible to carbapenems and azithromycin. Another unrelated cluster of ceftriaxone resistant Typhi infections linked to Iraq has been reported in the United States and the United Kingdom.⁵⁶ Ceftriaxone remains an appropriate empiric treatment option for patients who traveled to countries other than Pakistan and Iraq. However, the CDC Health Alert Network⁵³ recommends empiric treatment with a carbapenem, azithromycin, or both for suspected typhoid fever in patients who traveled to Pakistan or Iraq as well as for those who did not travel out of the US.

Stool cultures should be obtained from all people who traveled with an index case of typhoid fever that

was acquired from overseas travel. Treatment should be initiated if stool cultures are positive and the individuals should be monitored for developing symptoms of typhoid fever.⁴⁷ An infected child who attends a child-care center should be excluded until results of 3 stool cultures obtained at least 48 hours after cessation of antimicrobial therapy are all negative.⁴⁷

Arbovirus Infections

Arboviruses are RNA viruses that are transmitted to humans by arthropod vectors such as mosquitoes and ticks. Dengue virus remains the most important virus worldwide. Most arbovirus infections are asymptomatic or are characterized by a benign febrile nonspecific illness.⁵⁷ In symptomatic patients, disease is manifested in 3 main clinical syndromes with possible overlap: (1) Hemorrhagic fever, (2) fever with a rash and arthralgia, and (3) encephalitis.¹⁷

Dengue Fever

Dengue remains an important cause of fever in travelers from tropical areas except Africa.⁵⁸ It is the second most common cause of fever in travelers from tropical areas. It remains a worldwide public health problem with a mortality rate of 2.5%, mainly among children.^{17,36} Transmission occurs in urban areas during daytime activity of *Aedes aegypti* mosquito vector and to a lesser extent by *Aedes albopictus*. This differs from malaria in which transmission is more common in rural areas during nighttime and is caused by the *Anopheles* species of mosquitoes.⁵⁸ The incidence is rising in different countries and cases have also been reported in the United States due to locally acquired infections.⁵⁷

The incubation period in human is 3 to 14 days.⁵⁹ The disease is caused by 4 antigenically distinct serotypes. Infections may be asymptomatic. However, symptomatic patients may develop hemorrhagic fever and shock. There are 3 distinct phases of the disease.⁵⁹ The first is characterized by a non-specific febrile illness associated with myalgias, headache, retro-orbital pain, and rash that appears over 3 to 7 days. The second or critical phase is characterized by plasma leak that can last 24 to 48 hours. This is followed by convalescent phase of illness. Signs indicative of progression to severe dengue include persistent vomiting, severe abdominal pain, mucosal bleeding, difficulty breathing, early signs of shock, and a rapid decline in platelet count with an increase in hematocrit.⁵⁹ In children, gallbladder wall thickening is non-specific finding that suggest capillary leakage often associated with severe dengue.⁶⁰ Repeat infections are associated with more severe disease and dengue shock syndrome.^{36,58}

Common laboratory findings include leukopenia and thrombocytopenia.^{36,58} The diagnosis is most frequently made by serology which may need to be repeated in 2 weeks.⁵⁹ Rapid tests are available. Treatment consists of supportive care and hydration. Salicylate should be avoided due to risk of bleeding. Blood products may be needed in patients with hemorrhagic shock manifestations. There are no effective antivirals.^{59,61}

A vaccine to prevent dengue (Dengvaxia[®]) has been developed and currently licensed for use in some countries for people 9 to 45 years of age. The WHO recommends that the vaccine only be given to persons with confirmed prior dengue virus infection. There is a concern that people who have not been previously infected with a dengue virus may be at risk of developing severe dengue if they get dengue infection after being vaccinated. In 2019, the vaccine was approved by the U.S. FDA for use in children 9 to 16 years old who live in an area with endemic dengue within the US territories and who had laboratory confirmed past dengue infection. However, the US Advisory Committee on Immunization Practices (ACIP) has not yet made a recommendation.⁶¹

Other Hemorrhagic Fevers

Hemorrhagic fevers are caused by different viruses. Some of these viruses are transmitted by mosquito vectors such as yellow fever viruses but others can be transmitted readily from person to person and pose a significant public health risk.¹⁷ Hemorrhagic fevers share common symptoms including fever, vascular permeability, hemorrhagic manifestations, and multiorgan dysfunction with a high mortality rate.¹⁷ The easy transmissibility of these viruses by direct contact, fomites, fluids, and droplets as well as the high associated mortality can pose challenges with infection control and require the proper use of personal protective equipment. Such patients usually require transfer to special high-level isolation units.³⁴

Infection should be suspected in any person who presents with fever within less than 3 weeks of exposure to potential vector or infected person in association with at least 2 hemorrhagic manifestations such as petechial skin lesions, purpura, hemorrhagic rash, epistaxis, hemoptysis, or gastrointestinal bleeding. Laboratory investigations can include leukopenia, thrombocytopenia, transaminitis, and coagulation abnormalities.¹⁷

Symptomatic patients returning from areas of ongoing outbreaks should be evaluated for hemorrhagic fever. The most important has been the Ebola outbreaks in Africa such as the 2014, Africa such as the 2016 outbreak that occurred in Liberia, Sierra Leon, and Guinea that caused 28 616 suspected cases and 11 310 deaths.⁶²

Outbreaks of yellow fever are still occurring in Africa and South America.⁶³ A yellow fever vaccine is available. However, the disease remains widespread and is transmitted by mosquitoes. The incubation period is 3 to 6 days.¹⁷ Clinical findings are characterized by fever and musculoskeletal symptoms that can be followed by jaundice, hemorrhagic fever manifestations, and renal failure. Among the 15% who developed severe disease, the case fatality rate was 20% to 60%.⁶⁴ Lassa fever is endemic in certain parts of Africa particularly in Nigeria with outbreaks occurring in neighboring countries. The virus is transmitted by human contact with rodent secretions via ingestion or inhalation.⁶⁵

Other Arboviruses

Zika and chikungunya are arboviruses that are transmitted via infected *Aedes aegypti* mosquitos and have caused epidemics in South America.⁶⁶ Like dengue, both viruses cause fever, rash, and arthralgia and share similar geographical distribution but unlike dengue they are not associated with hemorrhagic fever.⁶⁷ Zika is characterized by conjunctivitis and skin rash. However, painful arthralgias are typically seen with chikungunya.⁶⁷

The Zika virus was not associated with clinically significant concerns until the Brazil outbreak in 2015.⁶⁸ Perinatal infections with Zika and development of sequelae in affected infants were most alarming. These include microcephaly and other brain malformations.⁶⁷ Another neurological complication following Zika virus infection among returning travelers is Guillain Barre Syndrome.⁶⁹ The virus may persist for 3 months in semen after infection and can be sexually transmitted.⁷⁰ Treatment is primarily supportive at this time.

Leptospirosis

Leptospirosis is mainly caused by the spirochete *Leptospira interrogans*. Infection is predominant in tropical and subtropical areas. The disease is acquired by contact with water contaminated by urine of infected animals including dogs and rodents.⁷¹ Travel associated infections are commonly caused by recreational exposure such as swimming and rafting, while endemic infection is related to occupational exposure.⁷¹

The usual incubation period is 5 to 14 days.⁷² Most infections (90%) are characterized by a subclinical or a self-limited acute febrile and anicteric systemic illness. Icteric leptospirosis or Weils's syndrome (10% of cases) is a life-threatening illness that is characterized by jaundice, renal failure, myocarditis, pulmonary hemorrhage, and shock.⁷³ Regardless of its severity, the acute phase is characterized by a nonspecific illness that can include

fever, chills, headache, myalgia, nausea, vomiting, conjunctivitis, and a skin rash. Conjunctival suffusion and pain in the calf and lumbar regions are characteristic.⁷² In the classical biphasic presentation, the acute phase is followed by a second immune-mediated phase that may include fever, aseptic meningitis, and uveitis. The estimated case-fatality rate is 5% to 15% with severe illness and can be higher (>50%) in patients with pulmonary hemorrhage syndrome.^{72,73}

The diagnosis in most cases is made retrospectively by serological tests.⁷³ *Leptospira* organisms can be isolated from blood during the early septicemic phase (first week) of illness, or from the urine 14 days or more after symptoms onset.^{71,72} CSF culture may be obtained in patients with signs of meningitis. However, cultures require special media and prolonged incubation thus limiting their usefulness in the diagnosis of acute infection.⁷¹⁻⁷³

Empiric antimicrobial therapy should be initiated as soon as the diagnosis is suspected. Intravenous penicillin is the drug of choice for patients with severe infection requiring hospitalization. Parenteral ceftriaxone, cefotaxime, or doxycycline are also effective in treatment of severe leptospirosis.⁷² For patients with mild disease, oral doxycycline or amoxicillin can be used.⁷² In addition, severe cases require appropriate supportive care.

Schistosomiasis

Schistosomiasis is prevalent in multiple parts of the world but at least 90% of cases are present in Africa.⁷⁴ Recreational activities among travelers such as swimming and bathing in fresh water are associated with infection. In some cases, early infection can present with localized dermatitis (swimmer's itch) due to cercarial penetration.⁷⁵ There are 5 species of schistosomes that produce intestinal or genitourinary disease. Intestinal disease is caused by *S. mansoni* (prevalent in Africa, the Middle East, and the Caribbean), *S. japonicum* (prevalent in China, Philippines, and Indonesia), *S. intercalatum* (in certain parts of Africa), and *S. mekongi* (Laos and Cambodia). *S. haematobium* (in Middle East and Africa) causes mainly genitourinary tract disease. The adult forms mature in the blood and travel to the mesenteric venules and venous plexuses of the bladder with *Schistosoma haematobium* infection and the intestine with *Schistosoma mansoni* and *Schistosoma japonicum* infections where the worms lay eggs.^{76,77} The eggs of *S. mansoni* or *S. japonicum* may elicit an immune response when eggs are laid in the host causing symptoms of acute schistosomiasis or Katayama fever.⁷⁸ Patients typically present 2 to 9 weeks after freshwater swimming in

endemic area. Findings in Katayama fever include fever, respiratory symptoms such as cough, urticaria, skin rash, and eosinophilia which may high grade ($>5 \times 10^9/L$).^{39,78} Other findings include abdominal pain, diarrhea, pulmonary infiltrates, and rarely neurological manifestations.^{39,78} If Katayama fever is clinically suspected, empirical treatment should be started as laboratory studies including serology and stool and urine microscopy have low sensitivity at this stage.⁷⁸ Febrile illness is not a common presentation of chronic intestinal or genitourinary schistosomiasis. Katayama fever is treated with praziquantel 40 mg/kg given as a single dose. For *S. japonicum*, praziquantel is given as 60 mg/kg in 3 divided doses.³⁹ Treatment should be repeated in 6 to 8 weeks as eggs and immature schistosomules are relatively resistant. A short course of steroids (prednisolone for 5 days) may reduce the duration of symptoms.³⁹

Rickettsiosis

Arthropods such as mites, fleas, lice, and ticks are associated with rickettsial diseases in humans. However, ticks or the most frequent cause.¹⁷ Mediterranean spotted fever is the most common rickettsial illness acquired in southern Europe and the Middle East and is caused by *Rickettsia conorii*. In sub-Saharan Africa, the illness called African tick typhus is caused by *Rickettsia africae*. The main rickettsial disease in the US is Rocky Mountain spotted fever.⁷⁹

The incubation period is usually 5 to 14 days.¹⁷ The clinical manifestations are nonspecific and may include fever and non-localizing systemic symptoms such as malaise, headache, and myalgias.⁸⁰ Cutaneous manifestations are common and include petechial lesions involving the extremities. Occasionally, a necrotic skin papular lesion or a black eschar at site of the bite can serve as a clue of the diagnosis of rickettsiosis.⁸⁰ Severe clinical manifestations can occur in patients with Rocky Mountain spotted fever, Mediterranean spotted fever, epidemic, and scrub typhus with high mortality rate if untreated.^{17,79,80} Diagnosis is most frequently made by serology for detection of specific antibodies. Treatment of choice is doxycycline which should be started as soon as clinically suspected.^{79,80}

Fever and Gastrointestinal Illness

Traveler's diarrhea (TD) is the most common international travel-associated illness in children.⁸¹ Diarrhea in a traveler may also be a manifestation of a systemic infection such as malaria or typhoid fever.³³ Children who are VFR are at higher risk to acquire TD than

tourist children.^{7,9} The overall rate of pediatric TD is 28.6%.⁸¹ The average time to diarrhea onset is 8 days after departure.⁸² The incidence and severity of TD is highest in younger children.⁸¹ Diarrhea has been reported in up to 40% of children younger than 2 years of age during travel with 15% requiring medical care.⁸¹ TD is more severe and prolonged in infants and young children compared with older children and adults.⁸¹ A study has demonstrated that the duration of TD is highest among children <3 years (median 17.5 days) compared with other age groups (median 3-5 days).⁸² TD is rarely life threatening. The majority (80%) of diarrheal diseases are acute and last less than 2 weeks.⁸³ The source of infection is typically food and water; person-to-person transmission is unusual. Bacterial pathogens are more likely to be encountered in travelers to developing countries, whereas viral pathogens are more common with travel to industrialized states.⁸⁴

TD is most frequently caused by *E. coli* strains; enterotoxigenic *E. coli* is the most common.^{83,85} Bacterial pathogens that cause invasive diarrhea are also causes of TD particularly in Southeast Asia.⁸⁵ Patients frequently develop dysentery-like illness. These pathogens include *Campylobacter* species, *Shigella*, and non-typhoidal *Salmonella*.^{33,83,85} Invasive bacterial gastroenteritis may be complicated by sepsis and intestinal perforation. Less frequent bacterial pathogens are *Aeromonas* and cholera and non-cholera causing *Vibrio* species.^{83,85} Enterotoxigenic *E. coli* (EAEC) is another common cause of traveler's diarrhea and can be clinically indistinguishable from enterotoxigenic *E. coli*.^{83,85} However, bloody diarrhea is mainly encountered in those with Enterotoxigenic *E. coli*.³³ Enterohemorrhagic (EHEC) *E. coli* (mainly O157:H7) which can cause of hemolytic uremic syndrome (HUS) is an unusual cause of TD. However, it may be important in certain epidemic settings such as HUS outbreak in Germany in 2011 that was caused by the foodborne EHEC O104:H4.⁸⁶

Identification of bacterial pathogens requires a standard stool culture which routinely detects *Shigella*, *Salmonella*, and *Campylobacter* species. New stool multiplex PCR assays enabled the diagnosis of different pathogens from a single stool specimen with improved sensitivity and rapidity of diagnosis.⁸⁷

The most common viral causes of diarrhea in travelers are rotavirus and norovirus. Rotavirus has been one of the most common causes of diarrheal illness worldwide and the most frequent cause of mortality in infants in developing countries. However, a dramatic drop in cases of rotavirus gastroenteritis has been seen in countries that introduced rotavirus vaccines.⁸⁸ Norovirus typically causes fever, nausea, and vomiting and is associated with contaminated food and water on cruise

ships.⁸⁹ However, it has been recognized as a copathogen in traveler's diarrhea due to ETEC.⁹⁰

Other causes of TD include parasites such as *Giardia lamblia* which can be complicated by a prolonged course of protracted diarrhea and malabsorption.⁹¹ *Entamoeba histolytica* infection may present with dysentery that requires antimicrobial treatment. Extraintestinal complications including liver abscess that present with abdominal pain and hepatomegaly.⁹¹ Patients with chronic diarrhea should have stool samples tested for ova and parasites as well as antigen testing for *Giardia* and *Cryptosporidium*. Serological testing using an enzyme immunoassay for *E. histolytica* has high sensitivity (95%) in patients with extraintestinal amebiasis.⁹²

Fever and Respiratory Illness

Respiratory symptoms in children who traveled are commonly caused by cosmopolitan infections such as pharyngitis, sinusitis, and community-acquired pneumonia due to *Streptococcus pneumoniae* or *Mycoplasma*.⁶ Travel-related respiratory illnesses are also commonly due to viruses that are prevalent in the travel destination. Knowledge of the local epidemiology of respiratory viruses can be obtained through the CDC. Respiratory symptoms may be caused by non-respiratory tract infections such as Loeffler's syndrome and malaria.⁶

Mycobacterium tuberculosis (MTB) is an important cause of lower respiratory disease in different parts of the world and should be considered in traveling children with risk factors such as close contact with persons with confirmed or suspected active MTB infection or travel to endemic areas.⁶ MTB infection should be suspected in a febrile returning child presenting with chronic cough, night sweats, weight loss, and lymphadenopathy. It also should be considered in those who fail to improve with antibiotics for presumed bacterial pneumonia.⁸ Children younger than 4 years of age are at risk of disseminated infection which may manifest as miliary tuberculosis or TB meningitis. Drug-resistant MTB is an increasing problem in different parts of the world.⁹³

The differential diagnosis of patients who present with fever and eosinophilia with concomitant respiratory symptoms include Katayama fever due to schistosomiasis, in addition to other parasitic and fungal infections.³⁹ Parasitic infections include Loeffler's syndrome in addition to other less common etiologies such as tropical pulmonary eosinophilia, pulmonary hydatid disease, and paragonimiasis.³⁹ Coccidioidomycosis and paracoccidioidomycosis are the most common pulmonary fungal infection associated with eosinophilia.⁹⁴

Loeffler's syndrome results from migration of larvae through the lungs during acute helminth infection. It

most frequently involves the nematode worms *Ascaris*, hookworm, and *Strongyloides*.³⁹ The symptoms start 1 to 2 weeks after infection depending on the species. Clinical findings include fever, urticaria, dry cough, and rarely hemoptysis. Eosinophilia is noted in complete blood counts and chest radiograph may reveal migratory pulmonary infiltrates.⁹⁵ Treatment depends on the species. However, albendazole 400 mg twice daily for 3 days is recommended when work up is negative.³⁹

Coronaviruses

There are at least 7 coronaviruses that are known to infect humans. The clinical spectrum of coronaviruses varies from asymptomatic or self-limited illness to severe disease characterized by acute respiratory distress syndrome and death.⁹⁶ During the last 2 decades 3 novel coronaviruses believed to be of zoonotic origin have emerged with significant implication on international travel. These include severe acute respiratory syndrome coronavirus (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and most recently is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is the cause of the ongoing coronavirus disease 2019 (COVID-19) pandemic. These coronaviruses have caused severe disease and death predominantly in adults with comorbid medical conditions.⁹⁶

Coronavirus Disease-2019 (COVID-19)

The pandemic of SARS-CoV-2 has rapidly spread worldwide since it was first identified in China in December 2019.⁹⁷ As of early May 2021, more than 154 million SARS-CoV-2 infections have been reported worldwide with at least 3.2 million deaths. In the USA, at least 32 million people were infected and over 573 000 deaths have been reported.⁹⁸ The incubation period is 2 to 14 days. Although SARS-CoV-2 infections are less deadly than SARS-CoV, it is transmitted much easier and faster.⁹⁹ Infections in adults are characterized by severe interstitial pneumonia, acute respiratory distress syndrome, multi-organ failure, and even death. Immune responses including a cytokine storm during coronavirus disease (COVID-19) have been shown to play an important role in the pathogenesis of multisystem involvement.^{97,100} Most COVID-19 infections in children are mild or asymptomatic.^{101,102} However, a rare multisystem inflammatory syndrome in children (MIS-C) which has resulted in critical illness and some deaths due to severe myocardial involvement has been described.¹⁰³⁻¹⁰⁶ The recently widespread UK B.1.1.7 SARS-CoV-2 variant has been reported to be more

transmissible and caused increased rates of infections in children and young adults. However, it remains unclear if it causes increased mortality and morbidity.^{107,108}

COVID-19 and Travel

International travel has been profoundly affected during the COVID-19 pandemic. Mass gatherings have been canceled or suspended.^{109,110} Different countries have placed travel restrictions in addition to passenger testing or quarantine requirements. At time of writing this review the CDC¹¹¹ recommends that all air travel passengers to the USA have a documented negative COVID-19 test result or documentation of recovery from infection prior to boarding any flight. Masks are required on planes as well as any form of public transportation and at all transportation hubs such as airports and stations.¹¹¹

During the pandemic, several Presidential proclamations were issued with the aim to suspend or limit entry into the United States of travelers who were physically present in different countries during the 14-day period preceding their entry.¹¹¹ Apart from China at the early stage of the pandemic, these restrictions typically included countries with either exceptionally high rates of new infections or with emerging variants harboring new genetic mutations.^{112,113} Examples of these variants and countries of origin include the B.1.1.7 variant that is widely circulating and has been traced to the United Kingdom; B.1.351: Initially detected in South Africa in December 2020; P.1: Initially identified in travelers from Brazil in early January 2020, and most recently B.1.617, identified in India in April 2021.^{112,113}

COVID-19 Vaccines and Travel

There are multiple vaccines that are currently in use worldwide. COVID-19 vaccines that are currently authorized for emergency use by the U.S. Food and Drug Administration are Pfizer-BioNTech, Moderna, and Johnson and Johnson (J&J)/Janssen COVID-19 vaccines.¹¹⁴ Vaccines are authorized for use in individuals 18 years and older. As of May 12, 2021, Pfizer-BioNTech is authorized for use in 12 years and older.¹¹⁴ The CDC¹¹⁵ has issued guidance on May 16, 2021 regarding public health measures as they pertain to fully vaccinated individuals defined as 2 weeks after receipt of the 2 dose vaccination series with either Pfizer-BioNTech or Moderna or the single dose Johnson (J&J)/Janssen vaccine. This guidance can also be applied to COVID-19 vaccines that have been authorized for emergency use by the World Health Organization such as AstraZeneca/Oxford vaccine. The CDC advises against international travel if not fully vaccinated. The CDC recommends that fully vaccinated people can participate

in outdoor activities and recreation without a mask, except in certain crowded settings and venues. Fully vaccinated international travelers who arrive in the US still need to get tested 3 days before travel by air into the US or show documentation of recovery from COVID-19 in the past 3 months. They should also be tested 3 to 5 days after their trip.¹¹⁵ Fully vaccinated people may also refrain from testing before leaving the USA for international travel unless required by the destination and refrain from self-quarantine after arriving back in the USA. However, being fully vaccinated should not stop any person from taking precautions in indoor public settings like wearing a well-fitted mask. In addition, it remains necessary for vaccinated persons to avoid indoor large-sized in-person gatherings and to follow CDC and health department travel requirements and recommendations.¹¹⁵

Author Contributions

NAH: Conception or design of work, data analysis and interpretation, drafting and finalizing the article. BIA: Conception or design of work, critical revision of the manuscript and contribution to intellectual content. All authors approved the final manuscript to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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