Emerging and Re-emerging Infections in Travellers

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Preface

Welcome to the world of emerging infections among travellers. As editors, we present a comprehensive collection of chapters, written by authors from different corners of the globe, each offering their unique insights and experiences.

In an increasingly interconnected world, the movement of people across continents has become an integral part of our lives. Travel has the potential for encountering unfamiliar pathogens and the risk of new infections not present in our home countries.

The chapters in this book cover a vast spectrum of infectious diseases, ranging from well-known infections such as dengue, influenza, and malaria, to emerging threats like Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Alkhurma Haemorrhagic Fever. Each chapter covers current knowledge, clinical manifestations, diagnostic approaches, treatment options, and prevention strategies.

The book explores the intersection between travel and infectious diseases in unique contexts such as mass gatherings, health tourism, and humanitarian aid work. It also examines the challenges posed by the emergence and spread of resistant microorganisms, as well as the crucial aspects of preparedness and response in the face of emerging infectious diseases.

As editors, we have had the privilege of collaborating with esteemed authors from diverse backgrounds, whose expertise spans continents. By bringing together this wealth of knowledge, we aim to provide a comprehensive resource for healthcare professionals, researchers, and policymakers alike.

We extend our heartfelt gratitude to all the authors who have shared their expertise and experiences, enriching this book with their invaluable insights. We would also like to express our appreciation to the publishers, who have worked tirelessly to transform this vision into a reality.

Finally, we extend our deepest gratitude to you, the readers. It is our sincere hope that *Emerging and Re-emerging Infections in Travellers* will serve as a source of inspiration, knowledge, and guidance, empowering you to navigate the uncharted territory of emerging infections and contribute to global efforts in safeguarding the health of travellers worldwide.

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Liverpool, UK — Nick Beeching
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Contents

Approach to Fever in the Returning Traveller

1

Sofia R. Valdoleiros and Eskild Petersen

Abstract

Fever is common in the ill returned traveller, with high hospitalization rates. A risk-based clinical approach to fever in the returning traveller is recommended, with initial priority given to recognizing and treating life-threatening causes of fever and identifying any infections with a high risk of transmission. Subsequently, the risk assessment should be established based on the geographic distribution of infections, risk factors for acquisition, incubation periods, and clinical findings.

Globalization and the marked increase in international travel in the last decades have increased the potential for the dissemination of infectious agents and vectors [1]. The number of travellers at a higher risk of developing infections is also growing, accompanying the rise in the immunosuppressed population (HIV infection, transplant recipients, autoimmune diseases, and other inflammatory diseases treated with immunomodulators). The likelihood of multidrug resistance is also rising and the possibility that an emerging pathogen can cause fever in the returning traveller is an additional challenge [2].

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Fever occurs in 2–3% of European or American travellers returning to their home countries [3] and may be the only symptom of a severe or life-threatening illness [4]. In the ill returned traveller, fever is common and frequently leads to hospitalization [1, 5]. Although mortality is low (1 per 100,000) in the small proportion of patients who develop a travel-associated illness and seek medical care, the associated morbidity is significant, with high hospitalization rates [6].

Travel, especially to low-income regions, is associated with an increased risk of infections not typically seen in high-income countries, such as malaria, enteric fever, dengue, chikungunya, Zika, and schistosomiasis. As this will change the clinical approach, all febrile patients should be asked about travelling [7].

The possible causes of fever in the returning traveller are plentiful. A specific diagnosis is often difficult to establish because diagnostic tests for many diseases either perform poorly or are unavailable locally [8]. In approximately 25% or more of returned travellers, the cause for fever may not be identified [9].

For this reason, a risk-based approach is recommended, with initial priority given to recognizing and treating life-threatening causes of fever and identifying any infections that threaten public health, with a high risk of transmission [8–10]. Subsequently, the risk assessment should be established based on the knowledge of the geographic distribution of infections, risk factors for acquisition, incubation periods, and clinical findings [8–10].

1.1 Initial Evaluation

1.1.1 Does the Patient Have a Travel History?

This is the key question to be asked to all patients and especially patients with fever. A travel history opens up exposure to infections not present where the patient lives and this information is key for the healthcare professional to properly understand the situation. The evaluation is summarized in Table 1.1.

1.1.2 Is the Patient Seriously Ill?

As for all emergency admissions, it should be assessed if the patient is seriously ill. Glasgow Coma Scale, blood pressure, pulse, temperature, respiratory rate, and peripheral oxygen saturation are essential parameters in the initial evaluation, in order to evaluate whether the patient may be a candidate for intensive care.

1.1.3 Medical Emergencies and Life-threatening Diseases

Malaria is the most common life-threatening tropical disease associated with fever in returned travellers [9]. As so, fever in a traveller returning from a malaria-endemic country must be evaluated immediately.

Table 1.1 Initial evaluation of the febrile returned traveller

Medical emergencies	Hemodynamic instability (monitor blood pressure) Respiratory distress (respiratory rate and peripheral oxygen saturation) Haemorrhagic manifestations (petechiae, ecchymosis, conjunctiva) Neurologic manifestations such as altered mental status (Glasgow Coma Scale), neck stiffness, or focal deficits
Isolation measures	Implement transmission-based precautions based on the clinical presentation and likely pathogens
Localizing symptoms	Associated symptoms Date of illness onset and temporal relation to the trip Previous received healthcare (such as medications or hospitalizations)
Host factors	Age and sex Comorbidities and chronic diseases, including immunosuppressive conditions Pregnancy Immunization status, including pretravel vaccines Routine medications Over-the-counter medications Recent antimicrobials Herbal, complementary, and alternative medicines
Pretravel advice	Adherence to effective insect measures, such as repellent and bed nets Adherence to malaria chemoprophylaxis
Travel history[a]	Destination, itinerary and visited areas Travel purpose (tourism, visiting friends or relatives, business, research, education, missionary/volunteer work, providing medical care or receiving medical care) Duration of travel and date of return from travel Type of environment Type of accommodation Recreational activities (safari, hiking, ocean exposure, freshwater exposure, swimming pools and hot tubs, rafting/boating and other adventure activities) Exposures (type of eaten foods, source of drinking water, animal or insect bites, stings, or scratches, sexual activities, tattoos or piercings received while travelling)

[a] Should go back at least a year, but may go back several years (for instance if TB, HIV or schistosomiasis are suspected)

Other life-threatening diseases include avian (H5N1) influenza, Middle East respiratory syndrome coronavirus (MERS-CoV), viral haemorrhagic fevers (yellow fever, severe dengue, Ebola, Lassa, Marburg, and Crimean-Congo haemorrhagic fevers), Japanese encephalitis, Rift Valley fever, rabies, anthrax, enteric fever, leptospirosis, relapsing fever, melioidosis, Oroya fever, scrub typhus, rickettsioses, plague, and East African sleeping sickness [8].

1.1.4 Isolation

In the initial evaluation of the febrile returning traveller, risk assessment for highly transmissible pathogens is a critical first step. If viral haemorrhagic fevers such as

Ebola, Marburg, Lassa, and Crimean-Congo are considered (according to the patient's travel itinerary and symptoms) or infections with airborne transmission, for instance pulmonary tuberculosis, isolation should be implemented to prevent nosocomial outbreaks [8]. Infections with a risk of airborne transmission are shown in Table 1.2.

Transmission-based precautions must be applied based on the clinical presentation and likely pathogens [11]. Certain clinical syndromes carry a sufficiently high risk to warrant their use empirically while awaiting confirmatory tests (Table 1.3).

Table 1.2 Type of precautions recommended for selected infections

Disease	Type of isolation precaution[a]
Colonization or infection with multidrug-resistant microorganisms (e.g. methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Enterobacteriaceae*)	Contact
COVID-19, MERS-CoV, and SARS	Airborne + Contact
Diphtheria	
Cutaneous	Contact
Pharyngeal	Droplet
Ebola, Marburg, Lassa, Crimean-Congo, and Chapare haemorrhagic fevers	Airborne + Contact
Influenza	Droplet
Measles	Airborne
Meningococcal infections	Droplet
Mpox	Airborne + Contact
Pneumonic plague	Droplet
Poliomyelitis	Contact
Tuberculosis	
Pulmonary or laryngeal	Airborne
Extrapulmonary, draining lesion	Airborne + Contact

Contact precautions: A single-patient room is preferred. Healthcare personnel wear a gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment

Droplet precautions: A single-patient room is preferred, but special air handling and ventilation are not required. Healthcare personnel wear a surgical face mask (a respirator, for instance N95, is not necessary) for close contact with the patient. If the patient is transported outside of the room, a mask should be worn and respiratory hygiene/cough etiquette followed

Airborne precautions: The preferred placement of the patient is in an airborne infection isolation room, a single-patient room that is equipped with special air handling and ventilation capacity. Healthcare personnel wear a respirator (for instance N95 or equivalent). Whenever possible, non-immune healthcare worker (HCWs) should not care for patients with vaccine-preventable airborne diseases (e.g. measles, chickenpox, and smallpox)

COVID-19 Coronavirus disease 2019, *MERS-CoV* Middle East respiratory syndrome coronavirus, *SARS* Severe acute respiratory syndrome

[a] Standard precautions should always be applied

Table 1.3 Clinical syndromes warranting empiric transmission-based precautions

Clinical syndrome in addition to fever	Potential pathogens	Type of isolation precaution[a]
Acute diarrhoea with a likely infectious cause	Enteric pathogens	Contact if incontinent or diapered patient
Cough and weight loss	*M. tuberculosis*	Airborne
Cough/fever/pulmonary infiltrate in any lung location in a patient with a history of recent travel to countries with active outbreaks of SARS	SARS-CoV-1	Airborne + Contact
Cough/fever/pulmonary infiltrate in any lung location in a patient with a history of recent travel to countries with active outbreaks of MERS-CoV	MERS-CoV	Airborne + Contact
Meningitis	*N. meningitidis* *M. tuberculosis*	Droplet if *N. meningitidis* is a possibility Airborne if *M. tuberculosis* is a possibility, in the presence of pulmonary infiltrate
Rash, macular, papular, vesicular or pustular	Mpox	Airborne + Contact if Mpox is a possibility
Rash, maculopapular with cough and coryza	Measles	Airborne + Contact if measles is a possibility
Rash, petechial/ecchymotic	*N. meningitidis* Viral haemorrhagic fevers (Ebola, Lassa, Marburg viruses)	Droplet if *N. meningitidis* is a possibility Airborne + Contact if viral haemorrhagic fever is a possibility

Contact precautions: A single-patient room is preferred. Healthcare personnel wear a gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment

Droplet precautions: A single-patient room is preferred, but special air handling and ventilation are not required. Healthcare personnel wear a surgical face mask (a respirator is not necessary) for close contact with the patient. If the patient is transported outside of the room, a mask should be worn and respiratory hygiene/cough etiquette followed

Airborne precautions: The preferred placement of the patient is in an airborne infection isolation room, a single-patient room that is equipped with special air handling and ventilation capacity. Healthcare personnel wear a respirator, for instance N95 or equivalent. Whenever possible, nonimmune HCWs should not care for patients with vaccine-preventable airborne diseases (e.g. measles, chickenpox, and smallpox)

[a] Standard precautions should always be applied

If implemented when the patient arrives at the healthcare facility, these measures reduce transmission opportunities [11].

Public health officials should be alerted as per local guidelines, considering the possibility that the traveller may be infected with a pathogen of public health importance at the origin or destination and the possibility that the traveller may have been contagious.

1.1.5 Presenting Symptoms and Physical Examination

Fever should be characterized by measured temperature, pattern (sustained, intermittent, biphasic, or relapsing), and response to antipyretics. Associated symptoms, such as nausea, vomiting, diarrhoea, rash, respiratory symptoms, genitourinary symptoms, localized pain, and neurologic manifestations, should be thoroughly explored.

A complete physical examination that includes vital signs, neurologic examination, haemorrhagic manifestations, rash or other skin lesions, jaundice, retinal or conjunctival changes, organomegaly, lymphadenopathy, and genital lesions should be conducted.

1.1.6 Host Factors

Baseline history should include comorbidities (including immunosuppression factors, such as diabetes mellitus, HIV infection and CD4+ T cell count, transplantation, malignancy, and asplenia) and medications (especially immunosuppressive therapy), as these can affect the patient's immune response to preventive vaccines and infection or predispose the individual to specific diseases. The patient's immunization status should be documented. Drug and toxin history, including antimicrobials, should be noted.

1.1.7 Pretravel Advice

The patient should be inquired about receiving pretravel advice, immunizations, adherence to recommendations, and malaria chemoprophylaxis, including compliance and duration.

1.1.8 Travel History

The travel purpose (tourism, visiting friends or relatives, business, research, education, missionary/volunteer work, providing or receiving medical care) should be addressed, as it is associated with different risks. For example, missionaries and healthcare personnel are at higher risk for contracting diseases that require prolonged or closer exposure, like tuberculosis, whereas the adventure traveller that goes to remote destinations engages in high-risk activities and is at higher risk for vector-transmitted diseases [10]. People visiting friends or relatives are a particular category of travellers, as they are less likely to seek pretravel advice and take prophylactic measures, but typically stay for more extended periods, possibly in rural environments, and have more exposure to the local population and contaminated food and water.

The travel history should be thoroughly explored and include the itinerary and visited areas, type of environment and accommodation, activities and exposures (such as eating and drinking places, recreational activities, and unprotected sexual intercourses), and the travel duration.

1.2 Differential Diagnosis

In a traveller, the probability of common diseases with a global distribution (such as respiratory tract infections or urinary tract infections) to be the cause of fever is about as high as more exotic illnesses [7, 10]. Noninfectious, travel-related diseases should also be considered (for example, deep venous thrombosis of the lower extremities in air travellers on long flights) [10].

Three main factors should be used to narrow the differential diagnosis: (1) clinical findings, (2) locations of exposure, and (3) the incubation period.

1.2.1 Clinical Findings

In association with fever, certain signs, symptoms, or laboratory findings can suggest specific infections (Table 1.4) [9].

Table 1.4 Clinical syndrome or findings and infectious diseases to consider

Clinical syndrome or findings	Infections to consider
Fever and rash	Dengue Zika Chikungunya Rickettsial infections Acute schistosomiasis Enteric fever Meningococcemia Acute HIV infection Measles Varicella Mpox
Fever and haemorrhage	Viral haemorrhagic fevers (such as dengue, yellow fever, Ebola, Lassa, Marburg, and Crimean-Congo haemorrhagic fevers) Meningococcemia Leptospirosis Rickettsial infections
Fever and diarrhoea	Traveller's diarrhoea (Enterotoxigenic *E. coli*, norovirus, *Giardia*, *Cryptosporidium*, *Campylobacter*, *Shigella*, nontyphoidal *Salmonella*) Intestinal amebiasis Cholera (persistent, voluminous diarrhoea)

(continued)

Table 1.4 (continued)

Clinical syndrome or findings	Infections to consider
Fever and abdominal pain (without diarrhoea)	Enteric fever Amebic or pyogenic liver abscess Non-travel-related causes (appendicitis, urinary tract infection, cholecystitis, cholangitis, pancreatitis)
Fever and arthralgia or myalgia (sometimes persistent)	Chikungunya Dengue Zika Ross River virus Muscular sarcocystosis Trichinellosis
Fever and eosinophilia	Acute schistosomiasis Drug hypersensitivity reaction Fascioliasis Filariasis Sarcocystosis Trichinellosis Angiostrongyliasis Other parasitic infections (Helminths)
Fever and respiratory symptoms/pulmonary infiltrates	Influenza and other common bacterial and viral pathogens Legionellosis Tuberculosis Acute schistosomiasis Q fever Leptospirosis COVID-19, MERS-CoV, and SARS-CoV-2 Acute histoplasmosis Coccidioidomycosis Psittacosis Melioidosis Pneumonic plague (rare)
Fever and altered mental status/ central nervous system involvement	Cerebral malaria Arboviral encephalitides (for example, Japanese encephalitis, West Nile virus) Meningococcal meningitis Pneumococcal meningitis Rabies African trypanosomiasis Scrub typhus Angiostrongyliasis Tick-borne encephalitis (TBE)
Flaccid paralysis of recent onset	Poliomyelitis
Fever and jaundice	Acute viral hepatitis (A, B, C, E) Yellow fever, severe dengue and other viral haemorrhagic fevers Severe malaria Leptospirosis Liver flukes Acute cholangitis (non-travel related)

Table 1.4 (continued)

Clinical syndrome or findings	Infections to consider
Mononucleosis syndrome	Epstein-Barr virus infection Cytomegalovirus infection Acute toxoplasmosis Acute HIV infection
Fever persisting >2 weeks	Malaria Enteric fever Epstein-Barr virus infection Cytomegalovirus infection Toxoplasmosis Acute HIV infection Acute schistosomiasis Brucellosis Tuberculosis Q fever Visceral leishmaniasis Abscess Noninfectious causes

COVID-19 Coronavirus disease 2019, *MERS* Middle East respiratory syndrome coronavirus, *SARS* Severe acute respiratory syndrome

1.2.2 Locations of Exposure

In the febrile returning traveller, the destination is one of the strongest diagnostic predictors for tropical diseases [12], since specific diseases are limited to or are more prevalent in certain locations, even within the same country [10]. Hence, the geographic area of travel determines the relative likelihood of major causes of fever [7, 9, 13] (Table 1.5). As previously discussed, specific activities may constitute additional risk factors, and preparation before travel (such as vaccinations and malaria prophylaxis) reduces the probability of some infections.

After travelling to sub-Saharan Africa and other tropical areas, malaria is the most common cause of acute undifferentiated fever [9]. Dengue is the most common cause of febrile illness after travelling to Latin America or Asia [9]. Other arboviral infections are causes of fever in travellers, such as chikungunya and Zika viruses. Viral haemorrhagic fevers other than dengue and yellow fever (such as Ebola, Lassa, Marburg, and Crimean-Congo haemorrhagic fevers) are essential to identify but rare in travellers. Some bacterial infections, like leptospirosis, meningococcemia, and rickettsial infections, can also cause fever and haemorrhage and should be considered in order to institute prompt treatment. Especially among travellers hospitalized abroad, infection or colonization with drug-resistant pathogens is possible. Special attention should also be taken to current outbreaks in the traveller's destination.

Table 1.5 Common causes of fever by geographic area

Geographic area	Common diseases	Other rare infections
North Africa, Europe, Mediterranean Middle East	Brucellosis MERS-CoV Q fever Toscana (sandfly fever) West Nile fever	Visceral leishmaniasis
Africa, Sub-Saharan	Acute schistosomiasis Dengue HIV infection Malaria (primarily *P. falciparum*) Rickettsiae (main cause of fever in southern Africa)	African trypanosomiasis Amebic liver abscess Brucellosis Chikungunya Dengue Zika Enteric fever Meningococcal meningitis Other arboviruses (e.g. Rift Valley fever, West Nile fever) Viral haemorrhagic fever (Lassa, Ebola, Marburg, Crimean-Congo haemorrhagic fever, yellow fever) Visceral leishmaniasis
America, Latin Caribbean	Chikungunya Dengue Enteric fever Malaria (primarily *P. vivax*) Zika	Bartonellosis Brucellosis Chagas disease Coccidioidomycosis Hantavirus Histoplasmosis Leishmaniasis Leptospirosis Paracoccidioidomycosis Yellow fever
America, North	–	Babesiosis Coccidioidomycosis Ehrlichiosis Histoplasmosis Lyme disease Rocky Mountain Spotted fever West Nile fever
Asia, South and Central	Dengue Enteric fever Malaria (primarily non-*falciparum*)	Chikungunya Crimean-Congo haemorrhagic fever Japanese encephalitis Other arboviruses (Nipah virus, Kyasanur Forest disease) Q fever Rickettsiae Sandfly fever Scrub typhus Visceral and cutaneous leishmaniasis

Table 1.5 (continued)

Geographic area	Common diseases	Other rare infections
Asia, Southeast	Chikungunya Dengue Enteric fever Malaria (primarily non-*falciparum*) Zika (emerging)	Hantavirus Japanese encephalitis Leptospirosis Melioidosis Other arboviruses (Nipah virus) Paragonimiasis Scrub typhus Talaromycosis
Australia	–	Barmah Forest virus infection Dengue Melioidosis Murray Valley encephalitis Q fever Rickettsiae Ross River fever
Europe, Eastern Scandinavia	Lyme disease	Hantavirus Tick-borne encephalitis Tularemia

1.2.3 Incubation Period

Since each infection has a characteristic incubation period (although the range is extensive in some diseases), the onset of symptoms and its relation to the trip should be determined, in order to establish the likely incubation period. The incubation period will allow the clinician to narrow the differential diagnosis (Table 1.6).

Although most common travel-related infections have a short incubation period and the majority of ill travellers will seek medical care within one month of return from their destination [9], it should be noted that some infections can manifest months or even years after initial infection.

Table 1.6 Travel-associated infections by incubation period

Disease	Usual incubation period (range)
Incubation period ≤14 days	
Anthrax[a]	1–7 days (can be >2 weeks)
Bartonellosis[a]	1–3 weeks
Brucellosis[a]	2–4 weeks (5 days to 5 months)
Chagas disease (acute), vector-borne exposure	1–2 weeks
Chapare haemorrhagic fever (CHHF)[a]	4–21 days
Chikungunya	2–4 days (1–14 days)
Coccidioidomycosis[a]	1–3 weeks
COVID-19	4–5 days (1–14 days)
Crimean-Congo haemorrhagic fever	1–13 days (1–3 days after a tick bite; 3–7 days following contact with blood and body fluids)
Dengue	4–8 days (3–14 days)
Diphtheria	2–5 days (1–10 days)
Ebola virus disease[a]	6–12 days (2–21 days)
Enteric fever (typhoid and paratyphoid fevers)[a]	7–18 days (6–45 days)
Hantavirus infection[a]	Haemorrhagic fever with renal syndrome (HFRS): 2–4 weeks (few days to 2 months) Hantavirus pulmonary syndrome (HPS): 2 weeks (few days to 2 weeks)
Histoplasmosis (acute)[a]	10–14 days (3–25 days)
HIV infection (acute)[a]	10–28 days (10 days to 6 weeks)
Influenza	2 days (1–4 days)
Japanese encephalitis[a]	5–15 days
Lassa fever[a]	1–3 weeks
Legionellosis	5–6 days (2–12 days)
Leptospirosis[a]	7–12 days (2–26 days)
Lyme disease[a]	7–12 days for erythema migrans; longer for other manifestations
Malaria, *P. falciparum*[a]	6–30 days (98% onset within 3 months of travel)
Malaria, *P. vivax*[a]	8 days to months (almost half have onset >30 days after completion of travel)
Marburg fever	5–10 days
Measles[a]	10–14 days (8–21 days)
Melioidosis[a]	2 days to 3 weeks (days to months)
Meningococcal infections	3–4 days (2–10 days)
Mpox[a]	5–13 days (4–21 days)
Oropouche virus disease	4–8 days (3–12 days)
Plague	2–7 days for bubonic (1–14 days)
Poliomyelitis	4–10 days
Psittacosis[a]	7–14 days (4–28 days)
Q fever[a]	18–21 days (4–39 days)
Rabies[a]	1–2 months (4 days to years)
Relapsing fever[a]	7–8 days (2–18 days)
Rickettsial infections[a]	6–7 days (3–18 days)

Table 1.6 (continued)

Disease	Usual incubation period (range)
Scrub typhus (*Orientia* spp)[a]	8–12 days (3–21 days)
Tick-borne encephalitis[a]	8 days (4–28 days)
Toxoplasmosis[a]	1–3 weeks (5–23 days)
Trichinosis[a]	10–20 days (few days to >2 months)
Trypanosomiasis, African[a]	1–3 weeks Rhodesiense: <3 weeks Gambiense: weeks to months
Tularemia	3–5 days (1–14 days)
West Nile virus encephalitis	2–14 days
Yellow fever	1–6 days (3–14 days)
Zika virus infection	5–6 days (3–14 days)
Incubation period 14 days to 6 weeks	
Amebic liver abscess[b]	Weeks to months
Chagas disease (acute), transfusion- and transplant-associated[b]	Weeks to 4 months
Chapare haemorrhagic fever (CHHF)	4–21 days
Ebola virus disease	6–12 days (2–21 days)
Enteric fever (typhoid and paratyphoid fevers)[b]	7–18 days (6–45 days)
Hantavirus infection[b]	Haemorrhagic fever with renal syndrome (HFRS): 2–4 weeks (few days to 2 months) Hantavirus pulmonary syndrome (HPS): 2 weeks (few days to 2 weeks)
Hepatitis A[b]	28–30 days (15–50 days)
Hepatitis C[b]	6–9 weeks (2 weeks to 6 months)
Hepatitis E[b]	26–42 days (2–9 weeks)
Histoplasmosis (acute)	10–14 days (3–25 days)
HIV infection (acute)	10–28 days (10 days to 6 weeks)
Japanese encephalitis	5–15 days
Lassa fever	1–3 weeks
Leishmaniasis, visceral[b]	2–10 months (10 days to years)
Leptospirosis	7–12 days (2–26 days)
Lyme disease	7–12 days for erythema migrans; longer for other manifestations
Malaria[b]	Weeks to months
Measles[a]	10–14 days (8–21 days)
Melioidosis[b]	2 days to 3 weeks (days to months)
Mpox[a]	5–13 days (4–21 days)
Psittacosis	7–14 days (4–28 days)
Q fever	18–21 days (4–39 days)
Rabies[b]	1–2 months (4 days to years)
Relapsing fever	7–8 days (2–18 days)
Rickettsial infections	6–7 days (3–18 days)
Schistosomiasis (acute)[b]	14–84 days
Scrub typhus (*Orientia* spp)	8–12 days (3–21 days)

(continued)

Table 1.6 (continued)

Disease	Usual incubation period (range)
Tick-borne encephalitis	8 days (4–28 days)
Toxoplasmosis	1–3 weeks (5–23 days)
Trichinosis[b]	10–20 days (few days to >2 months)
Trypanosomiasis, African	1–3 weeks Rhodesiense: <3 weeks Gambiense: weeks to months
Trypanosomiasis, African[b]	1–3 weeks Rhodesiense: <3 weeks Gambiense: weeks to months
Tuberculosis[b]	Months to years (4 weeks to decades)
Incubation period >6 weeks	
Amebic liver abscess	Weeks to months
Chagas disease (acute), transfusion- and transplant-associated	Weeks to 4 months
Enteric fever (typhoid and paratyphoid fevers)	7–18 days (6–45 days)
Fascioliasis	6–12 weeks
Hantavirus infection	Haemorrhagic fever with renal syndrome (HFRS): 2–4 weeks (few days to 2 months) Hantavirus pulmonary syndrome (HPS): 2 weeks (few days to 2 weeks)
Hepatitis A	28–30 days (15–50 days)
Hepatitis B	90 days (60–150 days)
Hepatitis C	6–9 weeks (2 weeks to 6 months)
Hepatitis E	26–42 days (2–9 weeks)
HIV infection	10 days to years before symptoms appear
Leishmaniasis, visceral	2–10 months (10 days to years)
Malaria	Weeks to months
Melioidosis	2 days to 3 weeks (days to months)
Rabies	1–2 months (4 days to years)
Schistosomiasis (acute)	14–84 days
Trichinosis	10–20 days (few days to >2 months)
Trypanosomiasis, African	1–3 weeks Rhodesiense: <3 weeks Gambiense: weeks to months
Tuberculosis	Months to years (4 weeks to decades)

[a] Incubation period may exceed 14 days
[b] Incubation period may exceed 6 weeks

1.3 Investigation

1.3.1 First-Tier Laboratory Tests

Initial laboratory tests to be performed in all patients include a complete blood cell count (including white blood cell count, thrombocytes, and haemoglobin) with differential (to analyse for leukocytosis, leukopenia, anaemia, thrombocytopenia, and

eosinophilia), liver enzyme and function tests, renal function tests, electrolytes, glycemia, pH, and bicarbonate. In the severely ill patient, lactate should be evaluated.

Urine and blood cultures should also be conducted and urine for white blood cells.

Because the most common life-threatening tropical disease associated with fever in returned travellers is malaria [9], it should always be excluded in people who have visited endemic areas in recent months. A rapid diagnostic test for dengue should also be done if relevant.

1.3.2 Second-Tier Laboratory Tests

Other laboratory tests may be warranted depending on the previous risk assessment (Table 1.7).

Table 1.7 Laboratory evaluation for fever in the returning traveller

First-tier laboratory tests	Complete blood count with differential (white blood cells, haemoglobin, haematocrit, and platelets) Liver enzyme and function tests Renal function tests Electrolytes Glycaemia pH and bicarbonate Lactate (if severely ill) Urinalysis (white blood cells, protein, nitrate) Rapid diagnostic test and blood smears for malaria (if travel to endemic area) Rapid diagnostic tests for dengue (if relevant) Blood cultures
Second-tier laboratory tests (to consider according to risk assessment)	Urine culture Stool culture and/or examination for blood, faecal leukocytes, ova, and parasites Serologic tests depending on exposure Serum PCR for dengue virus, Zika virus, Chikungunya, and yellow fever (if relevant) Examination of cerebrospinal fluid plus PCR and culture Urinary antigens for *S. pneumoniae* and *Legionella* PCR for SARS-CoV-2, SARS-CoV-1, MERS-CoV, influenza, and other respiratory virus Sputum culture Chest radiograph Abdominal ultrasonography Other imaging studies Blood smears for *Babesia*, *Borrelia*, filaria Bone marrow aspirate/biopsy Biopsy of skin lesion, lymph nodes, other masses

1.4 Conclusion

Because a history of travel will change the clinical approach to a febrile patient, all patients presenting with fever should be inquired about travelling. However, common illnesses with a worldwide distribution (such as respiratory and urinary tract infections) are as likely to be the most common source of fever in travellers as in non-travellers.

The febrile returning traveller poses a diagnostic challenge for the clinician. A risk-based approach is advisable, with initial priority given to recognizing life-threatening causes of fever and infections that may represent public health threats. The need for admission to an intensive care unit should be immediately assessed if the patient is severely ill; the need for isolation to prevent nosocomial transmission should also be evaluated at admission.

A detailed history is essential for risk assessment. Differential diagnosis should be conducted according to the geographic distribution of infections, risk factors for acquisition, incubation periods, and clinical findings. Malaria is the most common cause of fever in the international traveller and should always be excluded if the patient travelled to endemic areas.

Declaration of Conflict of Interest We declare that we have no conflicts of interest.

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Preparedness and Response for Emerging Infectious Diseases

2

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Abstract

Emerging and re-emerging infectious diseases cause a risk both to populations in which these diseases occur and to travellers. This chapter reviews the mechanisms of clinical, laboratory, and public health outbreak preparedness and response, global health security and the International Health Regulations (2005). New efforts to improve multi-disciplinary research responses during epidemics to advance knowledge into effective interventions are described, as well as challenges to effective outbreak detection and response and actions needed.

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2.1 Background

Emerging and re-emerging infectious diseases pose a risk to travellers, as well as to residents of countries who may be exposed to infections imported by returning travellers. These infectious diseases may be newly emerging or re-emerging diseases which had previously been controlled or absent in the traveller's home country. In either circumstance, imported infectious diseases may be poorly recognized by clinicians and public health systems, and delays in diagnosis, treatment, and control may lead to local transmission. This may in turn result in an outbreak or epidemic, and even in the imported disease becoming endemic, as in the cases of the introduction of chikungunya virus (CHIKV) and Zika virus (ZIKV) in the Americas where both viruses are now firmly established [1, 2].

As international travel and trade have increased, countries and their endemic infections have become much more interconnected. Today an infection can spread rapidly across the globe via air travel, as was seen during the SARS outbreak in 2002–2003, and to a greater extent during the COVID-19 pandemic. The emergence of CHIKV in the Indian Ocean region in 2005, followed by an expansion to the Western Hemisphere in 2013, again took the public health community by surprise [3]. This was followed by the introduction of ZIKV, thought to be introduced by travellers, which resulted in hundreds of thousands of infections in the Western Hemisphere [4]. Both emerging infectious diseases caused large outbreaks when introduced into areas with naïve populations. ZIKV was associated with congenital complications, such as microcephaly, spontaneous abortion, and neurologic complications, such as Guillain-Barre syndrome, that had not previously been identified in the limited number of cases detected during previous outbreaks [5]. The mpox outbreak in traditionally non-endemic regions in 2022, further emphasized the risk of introduction of travel-imported cases into new regions. It also emphasized the need for investment into clinical trials to identify effective treatments and prophylaxis for infectious diseases affecting populations in any region.

Vaccine-preventable diseases like measles have also caused large outbreaks in countries which previously had limited numbers of cases, to the point of threatening their elimination status. This has been due largely to increasing vaccine hesitancy among populations in these countries, the importation of cases from endemic countries [6, 7] and in some instances, the breakdown of public health systems due to war and conflict. Another concern that requires intensified focus is the emergence of antimicrobial resistance (AMR), which threatens the effective prevention and treatment of infectious diseases [8].

Finally, diseases of high consequence due to their morbidity, mortality or lack of approved effective vaccines or therapeutics, have resulted in the importation of cases by travellers into other countries, sometimes resulting in local transmission. During the 2014–2016 Ebola virus disease (EVD) outbreak in West Africa, a combination of factors, including delayed identification of cases, lack of access to timely diagnostics and resources to implement effective infection prevention and control (IPC), weak governmental and healthcare systems, and distrust between authorities and populations fuelled the spread of the disease. Thousands of people experienced EVD, including a large proportion of healthcare workers. Border screening and monitoring of returned

travellers may have mitigated the transmission to other countries [9]. The outbreak highlighted the need to integrate social sciences, health promotion and community engagement in outbreak preparedness and response, ensuring that efforts are targeted and adapted to the context of each outbreak, including the local culture and politics.

In this increasingly interconnected world, there is a need to strengthen preparedness across disciplines to improve our capacity to identify and respond to emerging infectious disease outbreaks. The COVID-19 pandemic highlighted how a new infection could rapidly spread across the globe, overwhelming healthcare and public health systems, and causing widespread disruption to societies. It illustrates the need for early detection to inform rapid and appropriate control measures. The pandemic also highlighted the need to strengthen global preparedness and capacity to develop new diagnostics, vaccines and medical countermeasures and ensure equitable access globally.

2.2 Clinical Preparedness and Response

What can clinicians do to be prepared for newly emerging and re-emerging infectious diseases? Prevention remains the mainstay of travel medicine. Immunization for pathogens known to be endemic in patients' travel destinations, as well as for routine infectious diseases, and prevention through behavioural measures to prevent food-borne, vector-borne, zoonotic, and sexually transmitted diseases remain important and cost-effective means to reduce the threat of infectious diseases among travellers [10]. Frontline clinicians should keep abreast of current outbreaks worldwide to inform the differential diagnosis of returned travellers to ensure timely identification of imported cases. Moreover, clinicians are advised to refer patients to travel and tropical medicine clinics for pre-travel consultation and post-travel evaluation for ill returned travellers when needed [2, 11]. There are many expert sources for clinicians and patients for pre-travel advice, including national and international websites that provide up-to-date information on current outbreaks globally (Box 2.1).

Box 2.1 Travel Risk Assessments

For information about travel risks consult with:

- travel or tropical medicine clinic
- local or national public health agency
- up-to-date national or international certified websites, e.g.:
  - Centers for Disease Control and Prevention (CDC)[a]
  - National Travel Health Network and Centre (NaTHNaC)[b]
  - Pro-Med International Society for Infectious Diseases[c]
  - The World Health Organization (WHO)[d]

[a] www.promedmail.org/
[b] https://travelhealthpro.org.uk/about
[c] https://wwwnc.cdc.gov/travel
[d] https://www.who.int/ith/en/

Clinicians should ask patients with syndromes suggesting infectious aetiologies about recent travel, activities, ill contacts, animal exposures and previous vaccinations and prophylactic medications in addition to their symptoms. Based on this information, clinicians should formulate a differential diagnosis, and order appropriate testing and infection control precautions. Treating clinicians should additionally notify and consult with their public health authorities if the differential diagnosis includes high-hazard or unknown pathogens, so that the appropriate response may be implemented, even before microbiologic confirmation is obtained. For high-hazard pathogens, testing may be required in reference laboratories with special collection and shipping requirements. Early notification of cases of possible imported infectious diseases to public health authorities improves the likelihood of timely detection, treatment, and public health response, by triggering appropriate actions locally, nationally, and internationally when needed [12] (Box 2.2). For emerging infectious disease outbreaks where information changes rapidly and imported diseases for which local knowledge on management may be limited, clinicians are advised to consult current clinical guidelines to guide differential diagnosis and treatment or consult with specialist travel clinics. For example, the World Health Organization (WHO) developed 'living' guidelines in response to the COVID-19 pandemic in which newly available evidence is rapidly assessed and incorporated.

For unusual infections, there may be special infection prevention control (IPC) precautions to be aware of when evaluating and treating patients to reduce risk of healthcare-associated transmission. The evidence for the risk of transmission from different body fluids and even the mode of transmission may be limited at the early stages of outbreaks of emerging infectious diseases. Therefore, standard and transmission-based precautions based on the best available evidence should always be implemented, in consultation with public health authorities when needed. When initially evaluating patients and collecting and shipping diagnostic specimens, clinicians should seek advice on appropriate isolation precautions, personal protective equipment needed, sample collection and shipping requirements. Communicating with primary care clinics, care homes, hospitals, laboratory, and health authorities as appropriate is critical in these instances to avoid accidental exposures. Failing to adhere to isolation and IPC measures, may lead to unnecessary risks to staff, with risks of lengthy quarantine of staff members and risks to vulnerable patients.

Diseases transmitted person-to-person require contact tracing to ensure follow-up and management of exposed persons according to their level of risk. The responsibility for contact tracing may vary among countries. In many, a national public health institute or a local health authority is responsible for following up contacts and implementing necessary public health measures, whereas in others this may be the responsibility of the treating clinician, or a combination. Clinicians should contact their hospital infection control department and health authorities for guidance when needed.

Box 2.2 Clinical Management of Suspected Infectious Diseases in Returning Travellers

- Use IPC precautions (standard and transmission-based as indicated)
- Promptly examine the patient
- Ask about travel and vaccination history to help guide differential diagnostics
- Take samples for diagnostics
- If suspicion of an infection that is part of mandatory reporting or an emerging infection that may pose a risk of transmission, rapidly:
  - Inform your local microbiologist
  - Inform the relevant local authority/public health institute
- Ensure samples are referred to the appropriate reference laboratory and public health authorities are alerted as needed
- Consult up-to-date clinical management guidelines to inform evidence-based care
- Inform and provide advice to the patient and any accompanying contacts
- Inform your healthcare colleagues and IPC team
- Treat the patient according to best available evidence guidelines

Notify relevant local authorities promptly; do not wait for diagnosis to be confirmed.

Abbreviations: *IPC* Infection prevention and control

2.3 Laboratory Preparedness and Response

A timely and accurate diagnosis of cases is one of the main pillars for clinical and public health response to an infectious disease emergence [13]. As such, laboratory systems are recognized as one of the core capacities of the International Health Regulations (IHR, 2005) [14]. An adequate national laboratory response requires inter-epidemic preparedness activities focused on building capacity and identifying and overcoming logistical barriers to sample collection, shipping, testing, interpretation, and reporting of results, to ensure capability to respond to outbreaks [13]. In addition to national laboratory systems strengthening, international sharing of samples and knowledge is required to facilitate efficient confirmatory testing and response, as well as development of diagnostic tests and medical countermeasures.

Rapid diagnostic tests are available for several emerging infectious diseases, including COVID-19, dengue and malaria. Although not as accurate as the molecular methods, they are quick and easy-to-use and are of great help as they can be done by the patients themselves or at the point of care. The COVID-19 pandemic showed that they are an essential part of a comprehensive response strategy [15].

Building lab capacity requires compliance of diagnostic laboratories with accreditation schemes (e.g. ISO 15189), participation in training and external quality assessment (EQA) through proficiency testing and establishment of platforms for data sharing (e.g. sequence data, test validation data). National and international prioritization exercises [16] can provide focus to these inter-epidemic activities, while international laboratory preparedness networks can offer support in addressing these issues. Examples of such networks include the WHO Laboratory task force for high threat pathogens, the laboratory part of SHARP (Strengthened International Health Regulations and Preparedness) in the EU, and the European Centre for Disease Prevention and Control (ECDC) funded European expert laboratory network for emerging viral diseases (EVD-LabNet) [17–19]. EVD-LabNet supports preparedness and response in expert laboratories to strengthen diagnostic testing, surveillance and clinical and public health outbreak response (Box 2.3).

Box 2.3 EVD-LabNet[a] Laboratory Network for Emerging Viral Diseases
EVD-LabNet provides access to:

(a) essential background information on target viruses;
(b) reference diagnostics within the network;
(c) state-of-the-art European diagnostic portfolio and diagnostic capacity and capability;
(d) training courses and workshops based on needs within the network;
(e) EQA through proficiency panels and assistance with corrective actions based on panel outcomes;
(f) yearly meetings to strengthen the coherence of the network and to provide a platform for knowledge exchange.

Abbreviations: *EQA* External quality assessment
[a] https://www.evd-labnet.eu/

Laboratories should be informed when receiving clinical samples from travellers and collaborate with clinicians for the selection of the most appropriate sample types and testing methods (molecular and/or serological), as well as for the interpretation of the results taking into account patients' signs and symptoms, date of illness onset, immunocompromising conditions, vaccination and travel history including possible exposures (Table 2.1).
In cases when a high-risk pathogen is suspected, laboratories must be informed promptly to apply enhanced precaution measures (e.g. work in biosafety level 3 or 4 facilities) [20]. National reference laboratories must be prepared for diagnostics for "exotic" pathogens and be aware of the current global epidemiology which is changing over time [21]. Since the diagnosis is challenging, and several pathogens are included in the differential diagnosis, a syndromic approach is usually applied [22]. As an example, diagnostics for dengue virus, ZIKV, and CHIKV should be