Symposium on Infectious Diseases

Assessment of fever in the returning traveller

ABSTRACT

Evaluation of people returning from trips abroad with fever is an important skill for all general physicians given the increasing trend in foreign travel. This evaluation should comprise a detailed travel history, thorough clinical examination, appropriate initial tests and a knowledge of when to ask for further advice. An understanding of the incubation periods of common imported infections and a syndromic approach to patients' symptoms is helpful in order to narrow down the likely diagnosis. The need to implement relevant infection control precautions has been highlighted by the recent Middle East respiratory syndrome coronavirus and Ebola virus disease outbreaks.

UK residents are making more and more trips overseas with 65.7 million visits abroad in 2015 (Office for National Statistics, 2015). Medical complaints among travellers are common, with 22–64% reporting a period of illness related to their trip (Steffen et al, 2003), but most are self-limiting. Approximately 8% of returning travellers, however, will be unwell enough to seek medical attention (Freedman et al, 2006). GeoSentinel is a worldwide network of tropical medicine clinics and two large analyses of their patients were published in 2013, one using data for 82 825 returning travellers with acute illnesses (Jensenius et al, 2013) and the second using data from 42 173 patients (Leder et al, 2013). The former found 91% of these patients had fever.

A systematic approach to diagnosing fever in returning travellers is therefore a key part of a general physician's role. The differential diagnosis is broad – most people have acquired common illnesses that are not necessarily specific to the place they have returned from. Once diagnosed, most tropical infections can be treated, although some are potentially fatal (Johnston et al, 2009). Certain infections should be reported to Public Health England or the equivalent to help prevent potential outbreaks (Public Health England, 2010). Knowledge of prompt infection control measures has been highlighted by the recent epidemics of Middle East respiratory syndrome coronavirus and Ebola virus disease which demonstrate secondary spread within hospitals. This article outlines the salient points in the history and diagnosis, common causes of fever in the returning traveller and an overview of necessary infection control measures.

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History

The history should narrow down the differential diagnosis by assessing the onset of illness in relation to the dates of travel, taking a thorough travel history and details of any pre-travel precautions. This will direct initial tests and management and inform any infection control measures that need to be taken.

It is vital to ascertain the interval between potential exposure and symptom onset. Many infections have defined incubation periods (*Table 1*); most febrile travellers present within 1 month of return and many infections can be excluded if they present later (Bottieau et al, 2006). *Table 2* summarizes the 'red flags' in the history which indicate the need for a risk assessment and urgent infection prevention against viral haemorrhagic fevers, Middle East respiratory syndrome coronavirus and avian influenza. Risk assessments for these can be found at the Public Health England website (Public Health England, 2015, 2017, 2018). Over time more emerging infections are likely to be encountered, so it is important to access the latest information and advice; *Table 3* details suggested resources.

A thorough travel history should cover countries and exact locations visited (including stopovers or airport transfers), length of stay and relevant exposures. Febrile travellers returning from sub-Saharan Africa, for example, are more likely to have malaria, whereas those returning from central and south America are more likely to have dengue (Leder et al, 2013). The exact location is relevant as many diseases are localized to certain regions only. *Table 3* includes resources for up-to-date information on country-specific risks and outbreaks. The length of stay will naturally increase the risk of certain diseases (Phillips-Howard et al, 1990). The reason for travel is relevant; people returning to their country of origin to visit friends and relatives, for example, are less likely to obtain pre-travel advice and more likely to have serious

illnesses than people visiting new countries. One survey found that 15.5% of patients were visiting friends and relatives but these made up 62.1% of cases of falciparum malaria (Leder et al, 2013).

Any illnesses during the trip should be recorded and any relevant exposures; the type of accommodation used, whether in rural or urban settings, type of food and water consumed, activities such as freshwater swimming and caving, any new sexual partners, any contact with others who were unwell (Johnston et al, 2009), close contact with animals and any insect bites, particularly from mosquitoes, ticks and tsetse flies (Fink et al, 2018) and whether mosquito bites were obtained during the day or night. The *Anopheles* mosquito transmits malaria and tends to bite humans at dawn or dusk (Milali et al, 2017).

Whether a patient sought and followed pre-travel advice affects his/her chance of developing certain diseases; one survey found that only 40.5% of patients attended a pre-travel consultation (Leder et al, 2013). Malaria prophylaxis is not 100% effective but does significantly reduce the risk of developing the disease. A vaccination history should be recorded along with knowledge of their effectiveness. Most are highly efficacious, but the typhoid vaccine is only around 60% effective. A travel history checklist is summarized in *Table 4*.

Routine non-travel related pathogens and non-infectious causes of fever such as autoimmune diseases, malignancies or medications should be considered (Dewitt et al, 2017).

Examination

This should comprise an assessment of how unwell the patient is along with a physical examination for any localizing features which may point to a diagnosis such as jaundice, rash, skin lesions, lymphadenopathy, retinal or conjunctival changes, hepatosplenomegaly or neurological findings. The examination should include looking for genital lesions and a thorough examination for eschars (pointing to rickettsial disease) as these are often found in 'hard to assess' places such as the natal cleft and under the breasts (Johnston et al, 2009). Patients with respiratory distress, hypotension or shock, haemorrhage, confusion, meningism or other neurological findings should be urgently investigated (Centers for Disease Control and Prevention (CDC), 1995) and those fitting local criteria for sepsis started on broad spectrum antibiotics.

Table 1. Incubation periods for common tropical diseases

Cause	Short incubation (<10 days)	Intermediate incubation (<1 month)	Long incubation (>3 months)
Bacterial	Anthrax Brucellosis Diptheria *Legionella* Leptospirosis Rickettsial diseases Lyme disease Melioidosis Meningococcal infection Typhoid and paratyphoid fever Plague Psittacosis Relapsing fever Tularaemia	Brucellosis	Bartonellosis Brucellosis Lyme disease Melioidosis Tuberculosis Syphilis
Viral	Chikungunya virus Dengue fever Hantavirus Acute HIV Influenza Japanese encephalitis Lassa virus Ebola/Marburg virus Crimean-Congo haemorrhagic fever Q fever Rabies Measles Tickborne encephalitis Yellow fever	Cytomegalovirus Hepatitis A, C, E HIV Rubella	Cytomegalovirus Hepatitis B and C HIV Rabies
Protozoal	Malaria Toxoplasmosis Trichinosis	Visceral leishmaniasis Acute schistosomiasis Toxoplasmosis Trypanosomiasis Amoebic liver abscess Clonorchiasis Fascioliasis Malaria	Clonorchiasis Fascioliasis Visceral leishmaniasis Amoebic liver abscess Filariasis Malaria Gnathostomiasis Visceral larva migrans Trypanosomiasis
Fungal	Acute histoplasmosis	Coccidiodomycosis	Histoplasmosis *Penicillium marneffei*

Adapted from Wilson and Pearson (2005)

Initial diagnostic tests

Table 5 summarizes the minimum initial diagnostic tests.

A malaria rapid diagnostic test and three malaria thick films for microscopy should be performed over 72 hours for anyone who has travelled to a malaria region in the past year. Rapid diagnostic tests are as sensitive for diagnosing falciparum malaria as thick films which is useful in centres with less malaria experience, but microscopy remains the gold standard for speciation and parasite count (Johnston et al, 2009). In severe falciparum infection, parasites may not be visible in peripheral blood films so films should be repeated (Winters and Murray, 1992; Svenson et al, 1995). Three negative films, however, make the diagnosis of malaria much less likely.

Table 2. Red flags requiring further infection prevention measures

Risk of viral haemorrhagic fever	Fever in the past 24 hours and travel to viral haemorrhagic fever endemic country in the past 21 days plus any of the following: ■ Travel to area with known current viral haemorrhagic fever outbreak ■ Living in basic rural conditions in Lassa endemic area ■ Visited caves or mines or had contact with oreaten primates, antelopes or bats in area with Ebola or Marburg outbreak ■ Had tick bite or contact with animal slaughter in an area with Crimean-Congo haemorrhagic fever ■ Contact with known or strongly suspected case of viral haemorrhagic fever in the past 21 days
Risk of Middle East respiratory syndrome coronavirus	Severe respiratory infection requiring hospitalization and fever and clinical or radiological evidence of pneumonia plus any of the following: ■ Travel to area with known Middle East respiratory syndrome coronavirus outbreak in the past 14 days ■ Contact with confirmed case of Middle East respiratory syndrome coronavirus in the past 14 days ■ Contact with camels or consumption of camel products in area with Middle East respiratory syndrome coronavirus in the past 14 days
Risk of avian influenza	Fever and clinical or radiological evidence of pneumonia or other severe illness suggestive of infectious process plus one of the following: ■ Travel to China in the past 10 days or ■ Contact with known case of avian influenza in the past 10 days

Adapted from Public Health England (2015, 2017, 2018)

Table 3. Potential resources for up to date information on outbreaks

Promed – http://www.promedmail.org/
Travax – http://www.travax.nhs.uk/
Public Health England – https://www.gov.uk/government/organisations/public-health-england
World Health Organization Disease Outbreak News – http://www.who.int/csr/don/en/
Travel Health Pro – http://travelhealthpro.org.uk/outbreaks
Centres for Disease Prevention and Control – https://cdc.gov

Table 4. Travel history checklist

Exact dates of travel	
Exact location(s) travelled to, including stopovers	
Purpose of travel	
History of illness while travelling	
Relevant exposures	■ Rural or urban area? ■ Type of accommodation? ■ Type of food and water consumed? ■ Activities? (such as freshwater swimming and caving) ■ Any unwell contacts? ■ New sexual partners? ■ Close contact with animals? ■ Insect bites? (especially mosquito, tsetse and tick bites)
Preventative measures	■ Pretravel consultation? ■ Use of malaria prophylaxis? ■ Travel vaccines obtained?

Table 5. Suggested minimum initial diagnostic tests

Three malaria thick films and a rapid diagnostic test
Full blood count
Urea and electrolytes
Liver function tests
C-reactive protein
Blood cultures
Serum save
Chest X-ray
HIV antibody screen
Urinalysis

HIV testing should be offered to any febrile returning traveller (Johnston et al, 2009).

Undifferentiated fever

A systemic febrile illness without localizing signs is a common presentation as found in 35% of 24 940 travellers attending GeoSentinel sites (Wilson et al, 2007). Most of these present within 2 weeks of return (Gautret et al, 2009) and the commonest cause is malaria, particularly travellers returning from sub-Saharan Africa. Other causes include dengue (particularly travellers returning from south east Asia), typhoid or paratyphoid fever, and rickettsia (Wilson et al, 2007). Malaria is the most important potentially fatal disease to diagnose (Johnston et al, 2009). Other infections such as HIV, mononucleosis, leptospirosis, schistosomiasis, amoebic liver abscess, brucellosis and toxoplasmosis should be considered and advice from infectious diseases units is advised unless the cause is quickly apparent.

Fever and respiratory symptoms

Of 42 173 travellers returning to GeoSentinel sites, respiratory tract infections were diagnosed in 10%. Most of these were caused by pathogens with a worldwide distribution such as influenza and those which commonly cause pneumonia (Leder et al, 2013).

Upper respiratory infections are usually viral or caused by bacteria such as *Streptococcus* and *Haemophilus* as found in the UK. Viral and bacterial throat swabs should be sent. As well as these bacteria, causes of lower respiratory tract infections include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* and respiratory syncytial virus. Less prevalent pathogens such as *Staphylococcus aureus*, avian influenza viruses and Middle East respiratory syndrome coronavirus must be considered, as well as other pathogens that do not usually cause pneumonia, such as malaria (Rello et al, 2016). Pulmonary oedema is a complication of severe malaria (Johnston et al, 2009) and cautious fluid rehydration is needed in patients suspected of having malaria who have respiratory symptoms.

Influenza A and B was diagnosed in 8% of returning travellers with respiratory symptoms and should be considered in patients who have returned less than 7 days ago from an endemic area (Johnston et al, 2009). Note that transmission is year-round in the tropics (Leder et al, 2013). Avian influenza should be considered in anyone who has had contact with birds in an area with an epidemic, most recently China (Public Health England, 2017).

Patients with fever and evidence of pneumonia and return within 14 days from the Arabian peninsula should be considered as potentially infected with Middle East respiratory syndrome coronavirus (Leblebicioglu et al, 2016). Camels are a host and human to human transmission occurs (Rello et al, 2016).

Fever and CNS symptoms

Specific neurological diagnoses in the returning traveller are rare (Freedman et al, 2006). There is considerable overlap, however, with other diagnostic categories as neurological symptoms such as headache are caused by systemic infections (particularly malaria, dengue and chikungunya infection and rickettsial diseases). Malaria and meningitis are the commonest treatable causes of fever and CNS symptoms and must always be excluded first (Johnston et al, 2009).

Cerebral malaria caused by *Plasmodium falciparum* can present with headache, confusion, seizures or reduced consciousness. Any patient with neurological symptoms and a history of travel to a malaria region should be urgently investigated. Other causes of fever and encephalopathy include bacterial infections (typhoid, Lyme disease, leptospirosis) and HIV seroconversion (Johnston et al, 2009).

In patients with meningism, common viral and bacterial causes should be considered as in the UK (Johnston et al, 2009). Meningitis is more common in the meningitis belt of sub-Saharan Africa and outbreaks have occurred in those travelling to Mecca (Goodman et al, 2014).

Encephalitis presents with headache, fever and/or altered mental state and is most commonly caused by herpes simplex virus in middle and high income countries (Aryee and Thwaites, 2015); specialist advice should be sought in returning travellers with this presentation in order to arrange relevant tests and initial empirical therapy as the differential is broad and outside the scope of this review.

> **"Acute schistosomiasis presents 2–9 weeks after exposure during freshwater swimming... with eosinophilia..., fever, dry cough and urticarial rash."**

Fever and eosinophilia

Eosinophilia may be symptomatic or asymptomatic and has many causes. Infectious causes in returning travellers include helminth infections (particularly schistosomiasis and stronglyloides) and filarial infection. Guidelines are available on the evaluation and diagnosis of eosinophilia in returning travellers (Checkley et al, 2010) and causes of fever and eosinophilia are summarized in *Table 6*.

Acute schistosomiasis presents 2–9 weeks after exposure during freshwater swimming (Visser et al, 1995) with eosinophilia (which may be high grade), fever, dry cough and urticarial rash. A history of relevant exposure and symptoms should be sufficient to start empirical treatment as tests are not sensitive in the early stages.

Strongyloides stercoralis is a helminth found in tropical regions which can cause a hyperinfestation syndrome in immunocompromised patients, leading to gastrointestinal and pulmonary symptoms with a high mortality. If immunosuppressant drugs such as steroids are being considered for patients from tropical regions, it is important to first send serology to exclude *Strongyloides* infection (Tefferi et al, 2006).

Returning travellers with eosinophilia should be investigated with concentrated stool microscopy and *Strongyloides* serology. Terminal urine microscopy and schistosomiasis serology should also be performed in those returning from Africa. Eosinophilia can be a feature of significant non-infective conditions such as haematological malignancies, which should be considered (Tefferi et al, 2006).

Fever and dermatological complaints

Dermatological complaints in returning travellers include rashes, ulcers, bites and stings (Leder et al, 2013). The differential diagnosis is wide. For maculopapular rashes it includes dengue, rickettsial disease and mononucleosis-type syndromes including acute HIV infection; for purpuric rashes it includes dengue haemorrhagic shock, meningococcal infection, sepsis with disseminated intravascular coagulation and viral haemorrhagic fevers, and for urticarial rashes it includes acute schistosomiasis (Johnston et al, 2009).

Eschars are commonly caused by rickettsial disease such as African tick bite fever, anthrax or mistaken for a chancre

Table 6. Common causes of fever and eosinophilia, jaundice and hepatosplenomegaly

Fever and eosinophilia	Helminths	*Ascaris lumbricoides* *Fasciola hepatica* Hookworm (*Ancylostoma duodenale, Necator americanus*) Lymphatic filariasis (*Wuchereria bancrofti*) Schistosomiasis Trichinosis (*Trichinella spiralis*) Hydatid disease Strongyloidiasis hyperinfestation
	Other infections	Coccidioidomycosis, paracoccidioidomycosis HIV HTLV-1 Toxoplasmosis Tuberculosis
	Non-infectious	Allergic bronchopulmonary eosinophilia Auto-immune disorder, e.g. systemic lupus erythematosus, vasculitis Drug hypersensitivity reaction Haematological malignancy Solid organ malignancy
Fever and jaundice	Viral	Viral hepatitis A, B, C, E Cytomegalovirus Epstein–Barr virus Acute HIV Viral haemorrhagic fevers Yellow fever
	Bacterial	Typhoid and paratyphoid Leptospirosis Relapsing fever (*Borrelia*) Bacterial sepsis especially pneumococcal Typhus *Bartonella* *Mycoplasma pneumoniae*
	Protozoan/other	Malaria Amoebic liver abscess Ascariasis Sickle cell crisis with infective trigger
Fever and hepatosplenomegaly	Viral	Dengue Acute hepatitis A, B, E HIV, cytomegalovirus or Epstein–Barr virus seroconversion
	Bacterial	Brucellosis Enteric fever (typhoid and paratyphoid) Leptospirosis Q fever (*Coxiella burnetii*) Relapsing fever (*Borrelia*) Rickettsial infection
	Protozoan/other	Fascioliasis Schistosomiasis, acute (Katayama syndrome) Amoebic liver abscess Malaria (acute)a Trypanosomiasis Visceral leishmaniasis Chronic myeloid leukaemia Haemoglobinopathy Lymphoma Myelofibrosis

Adapted from Johnston et al (2009)

Table 7. Patients who require ongoing isolation with use of standard and/or respiratory precautions

General conditions	Rash Diarrhoea or vomiting Acute respiratory symptoms Wounds or skin infections Recent hospitalization abroad Symptoms of meningitis or encephalitis Pyrexia of unknown origin
Specific diagnoses	Typhoid or paratyphoid Acute viral hepatitis Influenza Measles Tuberculosis Varicella or herpes zoster Meningococcal septicaemia Mumps Pertussis Plague Diphtheria Anthrax Poliomyelitis Rabies

Adapted from Johnston et al (2009), Fink et al (2018).

caused by the tsetse fly bite in African trypanosomiasis (Johnston et al, 2009).

Fever and jaundice

Table 6 summarizes common causes of fever and jaundice in the returning traveller which include malaria, typhoid, viral hepatitis, infectious mononucleosis type syndromes (Epstein–Barr virus and cytomegalovirus), leptospirosis and rarely viral haemorrhagic fevers (Johnston et al, 2009).

Fever and hepatosplenomegaly

The differential diagnoses of fever and hepatosplenomegaly are also summarized in *Table 6* and include malaria, amoebic liver abscess, brucellosis, leptospirosis, trypanosomiasis and visceral leishmaniasis (Johnston et al, 2009).

Infection control precautions

Patients with suspected tropical diseases may be infectious to others and should be placed in an isolation room with the use of standard precautions until a medical assessment is carried out. If they have been hospitalized abroad, they may be carrying drug-resistant pathogens such as meticillin-resistant *Staphylococcus aureus* and carbapenemase-producing enterobacteriaceae (Leblebicioglu et al, 2016). *Table 7* summarizes the general conditions and specific diagnoses (not an exhaustive list) which require ongoing isolation with use of standard and/or respiratory precautions.

"Patients with suspected tropical disease may be infectious to others and should be placed in an isolation room with the use of standard precautions until a medical assessment is carried out."

Patients with risk factors for Middle East respiratory syndrome coronavirus, avian influenza or transmissible viral haemorrhagic fevers as detailed in *Table 2* will need additional measures including isolation in a negative pressure room and use of full personal protective equipment and FFP3 masks or goggles (Public Health England, 2015, 2017).

Certain infections require extra infection control precautions in the laboratory; specimen request forms should include a patient's travel history, symptoms and possible diagnoses so laboratory staff can decide the appropriate level of precaution of which there are four. Infections such as typhoid and tuberculosis, for example, require level 3 precautions. Samples from patients suspected of diseases which are life-threatening and incurable such as many viral haemorrhagic fevers and Middle East respiratory syndrome coronavirus require transfer to a level 4 laboratory and the lab should be notified by telephone in advance (Johnston et al, 2009). Organisms such as malaria and acute viral hepatitis should be notified to the local public health authorities; an updated list can be found on the Public Health England website (Public Health England, 2010).

Conclusions

With worldwide travel on an upward trend and the emergence of new pathogens, assessing the febrile returning traveller is an important part of the general physician's role. A detailed travel and exposure history coupled with knowledge of incubation periods and a focus on key symptoms will help to direct initial tests and management. Malaria is a key infection to exclude in all travellers to relevant areas. Physicians should be familiar with how to access the algorithms for assessing patients with possible viral haemorrhagic fevers, Middle East respiratory syndrome coronavirus and avian influenza. Unwell returning travellers should be assessed in a side room with standard precautions and health-care staff should know when additional precautions are necessary. More detailed guidance is available in a review article published by the British Infection Association (Johnston et al, 2009). However, specialist advice should be sought promptly for any very unwell patients and those who remain undiagnosed despite initial investigations. BJHM

Conflict of interest: none.

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Symposium on Infectious Diseases

KEY POINTS

- Imported infections are increasingly common with increases in worldwide travel and migration.
- The differential diagnosis should be determined through a systematic approach using a detailed travel history, a focus on incubation periods and the presence of specific key symptoms.
- Infection control precautions are important to consider and institute on initial review, particularly if there are any 'red flags' in the history which convey a risk of viral haemorrhagic fever, Middle East respiratory syndrome coronavirus or avian influenza.
- Many people have acquired common infections that are not necessarily related to travel or may have a non-infectious cause of their illness.
- Malaria is the commonest specific diagnoses and a key infection to exclude in those returning from relevant areas, along with dengue, enteric fever and rickettsial diseases.
- Advice should be sought from local or regional infectious disease units if the diagnosis and management is not clear (after initial tests) or there is a suspicion of viral haemorrhagic fever, Middle East respiratory syndrome coronavirus or avian influenza.

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