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PRACTICE

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CLINICAL UPDATES

Fever in the returning traveller

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What you need to know

- Malaria is the most common specific diagnosis in febrile returning travellers and must be excluded using peripheral blood smear testing for the malarial parasite
- To protect yourself and prevent an outbreak, always ask yourself, "Does this patient need to be isolated?"
- Consider the possibility of antimicrobial resistance if a patient with fever has recently travelled to Africa, Asia, or the Middle East, particularly if they were hospitalised

Sources and selection criteria

We searched the Medline database (1994–2017) using the terms "fever," "travel," and "travel medicine." The search was limited to English language articles. Given the absence of randomised controlled trials in this field, we focused on observational studies in adult travellers (>16 years). Studies of infection in endemic populations were excluded. Appropriate publications were selected from the abstract list by two authors, with additional relevant articles included from their references. We have reviewed guidelines from the World Health Organization, Centers for Disease Control and Prevention, Public Health England, and the European Society for Clinical Microbiology and Infectious Diseases, and have compiled key recommendations from these.

International travel is increasingly common. The United Nations World Tourism Organisation estimates that by 2030, nearly 2 billion people will travel internationally each year, most of them to emerging economies.[1] In the UK alone, there were more than 70 million visits abroad by UK residents in 2016, and 37 million overseas residents visiting the UK.[2]

Illness associated with travel is common (Boxed Text on page 1box 1). Most infections are mild or self limiting, however their non-specific presentations make them challenging to distinguish from life threatening infections such as malaria.[17]

Box 1 How common is fever in the returning traveller?

- Between 10% and 42% of travellers to any destination[3 4] and 15%-70% of travellers to tropical settings experience ill health, either while abroad or on returning home [5-9]
- Immigrants who are visiting friends and relatives in their country of origin are at high risk of infections.[10] More than 70% of malaria cases in the US and UK, and up to 90% of enteric fever diagnoses in the UK are attributable to people who travelled to their country of origin[11-13]
- Gastrointestinal and respiratory symptoms are the commonest presentations with fever.[5-14] Most illnesses are self-limiting; however, between 12% and 54% of patients are ill enough to seek medical attention, and 1%-6% are hospitalised.[4-14] The presence of fever is associated with both severity of illness and hospital admission[15 16]

Studies from the UK indicate that a post-travel risk assessment is recorded in only 5%-20% of potentially eligible patients presenting to a hospital with fever.[18 19] This can result in delayed diagnosis, increased morbidity and mortality,[10] and an increased risk of onward transmission. This clinical update provides a framework for the timely evaluation and initial management of febrile returning travellers.

What are the causes of fever in returning travellers?

The causes of fever in returning travellers are largely derived from studies of patients presenting to specialist centres and national mandatory reporting of specific travel associated infections.[20 21] The GeoSentinel network represents the most extensive global real time surveillance database of travel related morbidity encompassing more than 60 travel medicine clinics.[22]

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Patients presenting to specialist centres most likely reflect the severe end of the illness spectrum.[5] Patients accessing primary care or general hospitals, or with a self limiting illness, are under-represented in the literature.

Approximately one third of febrile travellers presenting to the GeoSentinel network have confirmed gastrointestinal, respiratory tract, or genitourinary infections, and a further third have a systemic febrile illness attributable to a specific diagnosis, such as malaria.[15] Bacteraemia has been reported in 5%-10% of returning travellers managed in secondary care.[23 24] A substantial proportion of patients remain undiagnosed (21%-40%), possibly because relevant diagnostic tests were not performed on presentation or these patients had a self limiting illness that was not further investigated.[21-26]

Malaria is the commonest specific diagnosis made in febrile returned travellers, accounting for 5%-29% of all individuals presenting to specialist clinics[26-28] and 26%-75% of patients hospitalised with a systemic febrile illness.[25 29] Most patients with malaria are infected with *Plasmodium falciparum*, a life threatening infection that accounts for 25%-55% of deaths in febrile returned travellers.[15-30] After malaria, dengue, enteric fever, and rickettsial infections are the commonest specific diagnoses made.[15 26] However, a wide range of low frequency, potentially life threatening infections should also be considered in the differential diagnosis (⇓, ⇓, ⇓).

Infections for which vaccines are available, eg, enteric fever, hepatitis A, and influenza, are identified in a minority (~3%) of febrile returned travellers presenting to specialist clinics.[15] The burden of influenza is likely to be higher, as patients are likely to have self limiting illness or access non-specialist centres for care.

How is it diagnosed?

Assess all returning travellers with a fever for signs of life threatening infection, notably malaria, which might require immediate referral to a hospital. Obtain a detailed travel history to identify exposure to potential risks, and evaluate the need for isolation. (infographic)

Identify life threatening infection

Note the patient's general appearance and mental status, and record vital parameters to determine severity of infection.[31] The quick sequential organ function assessment (qSOFA) (Boxed Text on page 2box 2) is a clinical tool that identifies individuals with suspected infection who are at high risk of mortality.[32] It has been validated in emergency department settings,[33 34] but not specifically in returning travellers. Expedited treatment and intensive care should be considered if the qSOFA score is 2 or greater.[35]

Box 2qSOFA score
http://www.qsofa.org

One point for each of

Low blood pressure (sBP≤100 mm Hg)

High respiratory rate (RR≥22 breaths/min)

Altered mentation (Glasgow Coma Scale score<15)

≥2 qSOFA points near the onset of infection is associated with a greater risk of death or prolonged stay in intensive care unit

Assess patients for factors that increase the risk of sepsis related mortality, as these individuals might benefit from inpatient care.[31] Between 18% and 26% of travel clinic attendees in Europe and North America have pre-existing medical conditions, such as lung disease or diabetes mellitus, and between 1% and 4% are immunocompromised secondary to conditions such as cancer, HIV, and transplanted organs.[36 37] Live vaccines are often contraindicated in immunocompromised patients and response to inactivated vaccines can be impaired, making them more vulnerable to infections.[36-39]

Need for isolation

Assess early the need for isolation to prevent onwards spread of highly transmissible infections. See Boxed Text on page 2box 3/infographic for infection control measures that might be required.

Box 3Infection control and isolation measures

Observe contact precautions for any febrile patient with

- diarrhoea or vomiting
- acute respiratory symptoms
- rash
- wound or skin infections
- travel to a region where viral haemorrhagic fever is endemic in the last 21 days
- recent hospitalisation overseas

Precautions include

- Use of personal protective equipment (PPE; gloves and apron) by healthcare providers and carers, and where available, private room isolation[40]
- Surgical face masks should be worn for all acute respiratory infections, such as seasonal influenza[41]
- Negative pressure single room isolation and FFP3 respirators are recommended for suspected acute respiratory infections with pandemic potential, such as severe acute respiratory syndrome coronavirus (SARS-CoV), novel influenza viruses (eg, avian influenza), and other novel infections, such as Middle East respiratory syndrome coronavirus (MERS-CoV)[41]
- If viral haemorrhagic fever is suspected, isolate the patient in a single room. Staff must use enhanced PPE to include head, foot, and eye protection.[42 43] Inform laboratory services regarding precautions while handling samples. Confirmed cases are transferred to high level isolation units

Patients with a severe respiratory illness who have recently returned from the Middle East (risk: contact with camels or hospitals) or Asia (risk: contact with chickens) should be assessed for the possibility of MERS-CoV and avian influenza, respectively.

In febrile patients with travel to a region endemic for viral haemorrhagic fevers, ask for specific exposure such as animal contact (bats, primates), cave or mine exposure, tick bites, and known outbreaks[43 44] (⇓). The risk of viral haemorrhagic fevers in returning travellers is low (<1 diagnosis per million travellers), however, the public health implications of missing a case are considerable.

Assess the risk of antimicrobial resistance, as it is associated with higher mortality and can influence choice of empiric antibiotics. Travel to Africa, Asia, and the Middle East, particularly if the patient is hospitalised, can pose a risk for infection with resistant pathogens. Seventy five per cent of all travellers returning to northern Europe from South Asia acquire extended spectrum β lactamase enzyme producing bacteria, while carbapenem-resistant organisms have been detected in 3% to 5% of returning travellers.[45 46] European and US guidelines recommend testing by rectal swab for carbapenem resistant organisms in any patients requiring hospital admission and with

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travel to regions of high prevalence of antimicrobial resistance irrespective of fever status.[47 48] Contact precautions should be implemented while awaiting test results (Boxed Text on page 2box 3).

Travel history (see infographic)

Where did you travel? (□)

Some infections have a global distribution, while others are endemic in discrete geographical regions, eg, tick borne encephalitis in eastern Europe. The commonest diagnosis in febrile travellers from sub-Saharan Africa is *P. falciparum*.[49] More than 90% of *P. falciparum* cases diagnosed in the UK are acquired in sub-Saharan Africa, with 73% diagnosed in travellers from west Africa, a region with high malaria endemicity.[50] Rickettsial infection is a common diagnosis in febrile travellers from southern Africa. Dengue is common in travellers from South East Asia, Latin America, and the Caribbean, and enteric fever often in febrile travellers from South Central Asia.[15 26] Seventy five per cent of confirmed cases of enteric fever diagnosed in the UK in 2015 were acquired in South Asia.[51]

For each travel destination, the risk of exposure to an infection varies according to seasonal variations in endemicity, as seen with malaria, or according to outbreaks. Ask the patient if they were aware of any outbreaks during their travels and consult online resources such as ProMED for details of current outbreaks.[52] Climate change has also resulted in some vector borne infections emerging in subtropical regions, for example, outbreaks of dengue and chikungunya have been reported in Italy, France, and the Caribbean.[53 54]

When did you travel?

Two thirds of unwell travellers present within four to six weeks of travel. The timing of presentation varies according to the incubation period of the underlying infection[15] (⇓). Infections with a short incubation period, for example arboviruses and rickettsial infections, present within the first one to two weeks of return.[55 56] Nearly 80% of *P. falciparum* cases present within one month of travel.[57] By contrast, nearly one fifth of *P. vivax* diagnoses are made more than one year after returning from endemic regions.[57]

What risk factors were you exposed to? (□)

Specific activities can lead to an increased risk of certain infections. For example, travel to game parks in sub-Saharan Africa is associated with African tick bite fever,[58] a rickettsial infection transmitted by ticks, and with trypanosomiasis (sleeping sickness), caused by a parasite transmitted by the tsetse fly.[59]

A study of travellers returning with systemic febrile illness who had visited friends or relatives, when compared with tourists, identified a nearly threefold increased risk of being diagnosed with a systemic febrile illness, fourfold increased risk of malaria, and approximately sevenfold increased risk of typhoid and of influenza.[10] This possibly reflects the travel patterns of travellers visiting friends and relatives, who tend to travel for longer, visit rural areas, live in close proximity to the local population, and eat local food.[10 60] In addition, this subgroup of travellers is less likely to seek pre-travel health advice, or take malaria chemoprophylaxis and appropriate vaccinations.[10-62] Immigrants travelling to their home country might be less likely than tourists to experience acute hepatitis A or acute schistosomiasis (Katayama fever) because of previous exposure to these infections.[63-65] However, immigrants living in non-endemic settings rapidly lose their immunity to malaria and are at high risk of symptomatic infection on re-exposure. The associated mortality is nearly 10 times less than tourists, suggesting that some protective immunity is retained.[61]

A vaccine history is important but should not be used to exclude a potential diagnosis. Vaccine efficacy is rarely 100%.[33] For example, a retrospective case control analysis of travellers from England showed only 65% vaccine efficacy for typhoid Vi vaccine.[62 66] Likewise, malaria prophylaxis, insect repellent, and bed nets are effective in preventing malaria; however, adherence to these measures is often poor.[67 68]

Examination

Many imported infections have a non-specific febrile presentation; however certain examination findings can provide clues to the underlying diagnosis. For example, an enlarged spleen might be detected in malaria and enteric fever. A rash might be seen in rickettsial infections and arboviral infections such as dengue.[69 70] In patients with a fever and rash, look for an eschar (ulcer with blackened centre) which is highly suggestive of African tick bite fever.[71]

Initial investigations

Routine investigations include a complete blood count, serum inflammatory markers, blood cultures, and imaging such as chest radiography. Request same day malaria testing in all patients with geographical risk, regardless of reported adherence to anti-malarial prophylaxis.[72 73] The sensitivity of rapid diagnostic tests is high, particularly for *P. falciparum* species. However, microscopy continues to be the gold standard for diagnosis of malaria. Thick and thin blood films should be obtained to determine parasitaemia, maturity, and species.[74]

Specific additional tests such as blood for polymerase chain reaction and serological testing should be based on initial assessment. Storage of a serum clotted sample from the patient at their initial presentation might be helpful for testing alongside convalescent serum. This is particularly true if the differential diagnosis includes diseases where a reliable diagnostic laboratory test in the early phase of illness is not available, such as most rickettsial diseases. Such tests should be supported by an infection doctor.

There are no consensus guidelines on clinical triggers for referral to secondary care. Primary care clinicians must use their clinical judgment to guide this decision. Patients with evidence of sepsis, for example those with suspected infection scoring 2 or greater on the qSOFA, should be referred urgently to hospital for inpatient management.[35] Early discussion with an infectious diseases specialist can help guide this decision where there is clinical uncertainty. If there is any possibility of viral haemorrhagic fevers or imported acute respiratory infections, such as MERS, isolate the patient pending discussions with an infection specialist.

How is it treated?

Empiric antibiotics can be started in patients with evidence of sepsis according to local guidelines and resistance patterns. ⇓ lists some conditions in which empiric antibiotics might be considered.[35] You might also consider antibiotics if a substantial lag is expected in receiving laboratory results.

Timely notification of communicable diseases to the local department of public health is also a key aspect of management. Countries differ in the range of notifiable infectious diseases.[83 84]

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Some key notifiable infections as per guidance from Public Health England are listed in Boxed Text on page 4box 4.

Box 4Key imported notifiable infectious diseases or syndromes

- Acute encephalitis (any suspected infectious cause)
- Acute infectious hepatitis (any suspected infectious cause)
- Acute meningitis (any suspected infectious cause)
- Brucellosis
- Cholera
- Diphtheria
- Enteric fever
- Infectious bloody diarrhoea (any suspected infectious cause)
- Meningococcal septicaemia
- Plague
- Rabies
- SARS
- Smallpox
- Tuberculosis
- Typhus
- Viral haemorrhagic fever
- Yellow fever

(Source: Public Health England)

Questions for future research

- What are the economic and health burdens of travel associated illness?
- What are cost effective interventions for reducing the risk of travel associated illness?
- To what extent is clinically relevant antimicrobial resistance in the community and hospitals related to travel? What is the burden of bacterial infection, including sepsis, related to travel? What strategy should we use for screening for antimicrobial resistance in travellers?
- Among travellers presenting with fever, what is the role of empiric antimicrobial treatment both in general and in specific circumstances, eg, travellers at risk of antimicrobial resistance?

Additional educational resources

For healthcare professionals

Clinical advice is often available through local or national infectious diseases centres. For example, in the USA, clinical advice on the diagnosis and management of malaria is available through the Centers for Disease Control and Prevention malaria hotline (770-488-7788). In the UK, 24 hour advice on the diagnosis and management of imported infection is available through

- UK Imported Fever Service (IFS): +44(0)844 778 8990, www.gov.uk/guidance/imported-fever-service-ifs
- Hospital for Tropical Diseases, London: +44 (0)845 155 5000; www.thehtd.org
- Hospital for Tropical Diseases, Liverpool: +44 (0) 151 706 2000; www.lstmed.ac.uk/services

Online clinical support tools

- Fever Travel: www.fevertravel.ch
- Gideon (subscription only): www.GIDEONonline.com
- Centers for Disease Control and Prevention Yellow Book, Chapter 5, Fever in Returned Travelers: www.cdc.gov/travel/yellowbook

Online outbreak surveillance

- World Health Organization outbreak data: www.who.int/csr/don/en
- Programme for Monitoring Emerging Diseases (ProMED): www.promedmail.org

Reporting of notifiable diseases (UK)

- www.gov.uk/guidance/notifiable-diseases-and-causative-organisms-how-to-report

Resources for patients

- TravelHealthPro, National Travel Health Network and Centre (NaTHNaC; travel advice): www.travelhealthpro.org.uk
- NHS Scotland travel advice: www.fitfortravel.nhs.uk/home.aspx
- Foreign and Commonwealth Office travel advice: www.gov.uk/knowbeforeyougo
- Centers for Disease Control and Prevention (CDC): wwwnc.cdc.gov/travel
- Global Travel Clinic Directory: http://www.istm.org

Education into practice

- In patients presenting with fever, how often do you ask for a history of travel?
- How many returning travellers with fever have been seen at your practice in the past six months? What factors related to travel would you ask in your assessment? What proportion received pre-travel advice?
- How would you draw up a protocol for management of these patients?

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involved in all stages of preparation including detailed editing of drafts. DF is the guarantor of the article.

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Table

Table 1| Potential empirical antimicrobial treatments (These regimens should only be considered in patients returning from malaria endemic regions once malaria has been excluded as the cause of fever)

Syndrome or scenario	Likely diagnosis	Important investigations	Empiric treatment[a]
Fever and headache +/−rash or eschar within 10 days of tick exposure	*Rickettsia*	Acute and convalescent (3-6 weeks) serology	Doxycycline 100 mg orally, twice daily[75 76]
Fever, abdominal pain, and liver abscess on ultrasound weeks-months after travel in endemic regions	Amoebic liver abscess	Serology	Tinidazole 2 g or metronidazole 500 mg orally, three times daily[77]
Fever and severe bloody diarrhoea (≥4 unformed stools/day) within 3 weeks of exposure	Bacterial gastroenteritis or amoebiasis	Stool microscopy, culture, and sensitivity;[b] "hot" stool	Azithromycin 1g once daily, AND consider tinidazole 2 g once daily, or metronidazole 800 mg three times daily[78]
Undifferentiated fever within 3 weeks after arrival in enteric fever high incidence region[c]	Uncomplicated enteric fever	Blood culture[d]	Azithromycin 1 g once daily
	Complicated enteric fever (sepsis or reduced Glasgow coma scale)		Ceftriaxone 2 g twice daily[79]
Fever, urticarial rash, and eosinophilia (>0.4×10^9/L) within 4-8 weeks of fresh water exposure	Acute schistosomiasis	Investigations (serology, stool and blood culture) not helpful during acute illness as results can be misleading (often negative). Serology, concentrated stool and/or urine microscopy 3 months following exposure might help confirm diagnosis	Prednisolone 20 mg once daily and Praziquantel 20 mg/kg twice, 4-6 hours apart (will need repeat dosing 3 months following exposure)[80]
Flu-like symptoms (+/−jaundice, hepatorenal failure, or haemorrhage) within 2 weeks of fresh water exposure	Acute leptospirosis	Serum +/−paired urine for polymerase chain reaction (PCR; within 5 days symptom onset), acute and convalescent serology if >5 days after symptoms onset, culture of PCR+specimens	Ceftriaxone 1 g once daily, or[e] Doxycycline 100 mg twice daily
Sepsis[f] with antimicrobial resistance risk factors	Any cause	Blood culture, urine, stool, cerebrospinal fluid (as indicated), polymerase chain reaction (blood +/−cerebrospinal fluid) for suspected meningococcal / pneumococcal sepsis	Sepsis should be managed according to local guidelines. If there is risk of antimicrobial resistance the choice of empiric antibiotics should be discussed with local infection doctors when the risk is identified

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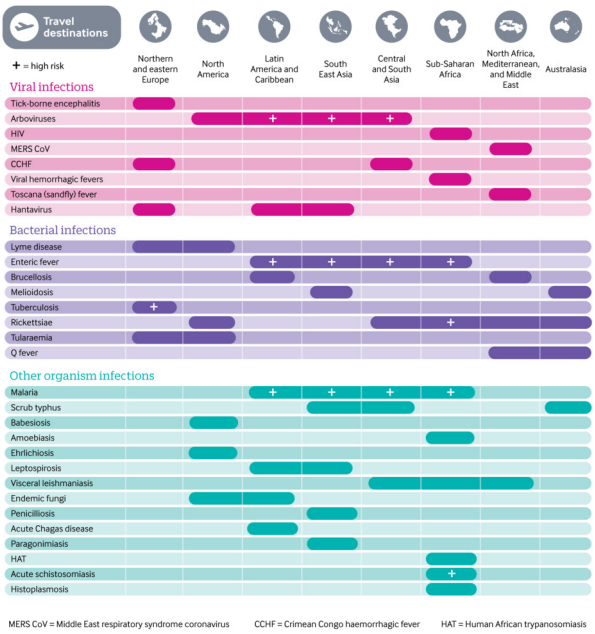
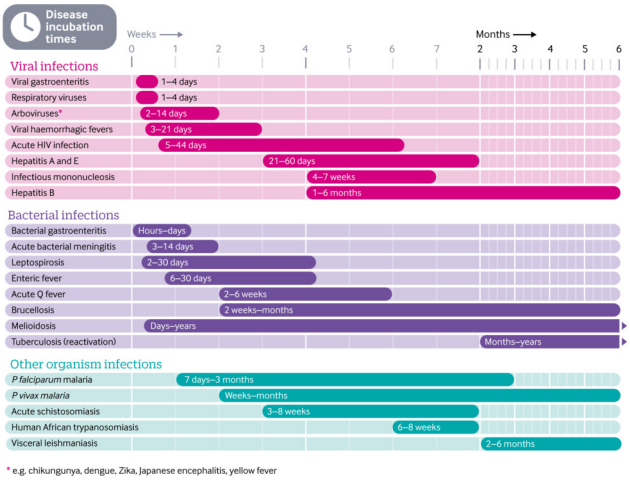
Figures



Travel destinations and associated infections



Disease incubation times

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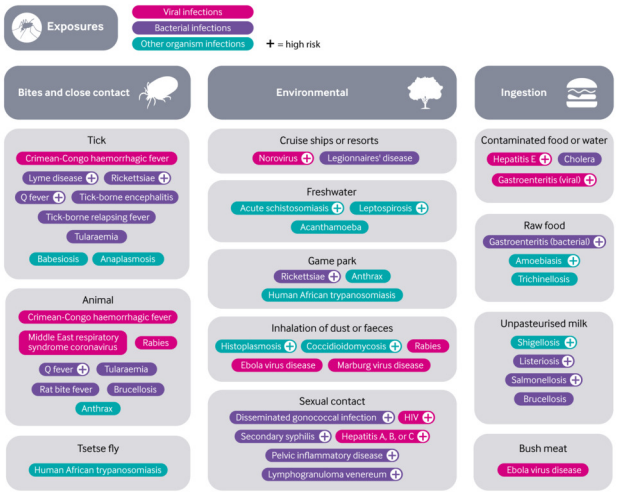

Exposure to infection

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