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# Assessment of returning travellers with fever

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## Abstract

Millions of people travel to the tropics each year and a significant minority of them become ill, either during their stay, or shortly after their return. Most have mild, self-limiting illnesses, but a few will have a life-threatening condition. This article outlines how to evaluate fever in the returning traveller and discusses important infection control and public health measures. A detailed travel history, which takes into account travel destinations, specific activities and risk factors in relation to the onset of symptoms, is essential for constructing a comprehensive list of differential diagnoses and guiding appropriate investigations. Importantly, all travellers returning from the tropics with a fever should be investigated for malaria, even if their return was 3 months ago or longer.

**Keywords** fever aetiology; fever assessment; fever diagnosis; imported fever; travel; traveller

**Malaria**

A 26-year-old woman visited her GP with a 3-day history of flu-like symptoms. She had returned from a 2-week holiday to The Gambia 3 weeks previously but did not volunteer this information and the GP did not ask about travel. She was apyrexial with no abnormal findings on examination. The GP diagnosed a viral illness and recommended paracetamol and plenty of fluid. Three days later, she presented to her local emergency department. She was febrile, confused, tachycardic and dehydrated. Her respiratory rate was 24 breaths per minute but her chest was clear. A travel history was elicited from her family. An urgent blood film showed *Plasmodium falciparum* with a parasitaemia of 15.2%. In addition to cerebral malaria there was evidence of renal failure with a serum creatinine of 312 micromol/litre. She was given intravenous quinine and transferred to intensive care in a regional infectious diseases unit where she received intravenous artesunate. Fortunately, she made a complete recovery.

**Learning points**

- Patients often do not volunteer their travel history
- The initial presenting symptoms and signs of many tropically acquired infections are often non-specific
- Any delay in the diagnosis of falciparum malaria can lead to serious and sometimes fatal consequences
- Nearly all patients with malaria give a history of fever but approximately half are afebrile on presentation[15]

**Box 1**

## Why is this topic important?

In 2012, UK residents made 8.9 million visits to countries other than Europe and North America.[1] Up to 70% of those travelling to developing countries report health problems and 8–15% are unwell enough to seek medical attention, with fever a common complaint.[2,3] Whilst many of these patients will have self-limiting illnesses, an important minority will have a more serious tropical infection which, if missed, could become life-threatening (as with malaria – Box 1) or have significant public health implications (as with typhoid - Box 2). The difficulty is in identifying these low-frequency events.

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## Factors influencing risk of infection

- ***Travel destination***: the risk of acquiring an infection whilst travelling varies according to the country visited (Table 1 ), the local environs (urban or rural) and the activities or exposures encountered.[4–6] Malaria is the most important cause of fever in travellers returning from sub-Saharan Africa (see Malaria on pages 100–106 of this issue).[4,7] Even when rural exposure in West Africa within 21 days of symptom onset raises the possibility of viral haemorrhagic fever (VHF), malaria remains far more likely and should always be excluded (Table 1). If in doubt, isolate the patient whilst advice is sought from an infectious diseases specialist (see 'Whom to ask for help?'). Among travellers returning from Asia or the Caribbean, dengue is a more probable diagnosis, whereas enteric fever is more likely in travellers from south central Asia.[4] It is often worth asking the patient whether they are aware of any local outbreaks whilst travelling (e.g. Ebola, severe acute respiratory syndrome (SARS) – see also Emerging infectious diseases *MEDICINE* 2014: **42**(1): 60–63) or local areas of particularly high endemic risk (e.g. schistosomiasis).
- ***Purpose and duration of travel***: travellers visiting friends and relatives (VFR), expatriates, overseas healthcare workers and backpackers often stay for longer

***Salmonella typhi***

A 34-year-old man returned to the UK after spending 4 weeks visiting his family in Bangladesh. His travel vaccinations, including typhoid and Hepatitis A, had been updated beforehand. One week before his return he had developed a febrile illness and was treated for malaria with no improvement. After further blood tests, was told he had typhoid and was treated with ciprofloxacin. On arrival home, he presented to hospital with fever, headache and a dry cough. He had a temperature of 39.0°C and a respiratory rate of 28 breaths per minute. Although tachycardic, he had an adequate blood pressure. His chest was clear and he had 2-cm hepatomegaly. Investigations revealed a normal differential white count, normal renal function, mildly raised transaminases and a clear chest radiograph. A provisional diagnosis of enteric fever was made and his antibiotic was changed to intravenous ceftriaxone. He gradually improved. Two sets of blood cultures taken before changing the antibiotic were sterile and so a bone marrow aspirate was performed. Bone marrow cultures confirmed the presence of *Salmonella typhi*, resistant to ciprofloxacin. Following 3 days of intravenous ceftriaxone, treatment was changed to oral azithromycin. He completed 14 days of effective therapy.

**Learning points**

- Enteric fever is an uncommon but important cause of fever, particularly in returning travellers from Asia
- Vaccination provides incomplete protection against *Salmonella typhi* and none against *S. paratyphi*
- Many resource-limited settings lack facilities for blood culture and so use serology (Widal's test) instead. In most settings this lacks sensitivity and specificity and is often positive in individuals who have previously been vaccinated. It is not recommended
- Blood cultures have a sensitivity of >80% with their highest yield within the first week of symptoms.[16] Stool and urine cultures become positive after the first week of illness. Although invasive, a bone marrow aspirate has a higher sensitivity than blood culture and should be considered in patients who have already taken antibiotics[16]
- More than three-quarters of isolates imported into the UK from Asia are resistant to fluoroquinolones, but remain sensitive to ceftriaxone. This is therefore the recommended first-line agent, particularly for severe disease[17–19]
- Ciprofloxacin remains the most effective treatment option if the isolate is proven to be sensitive
- Azithromycin is an alternative for uncomplicated infection. Although azithromycin sensitivity testing is not readily available, recent data from Public Health England suggest that resistance is infrequent but increasing[17,19]
- Regardless of which antibiotic is used, fever takes several days to respond. If the isolate is known to be sensitive, failure to defervesce is not a reason to change antibiotics

**Box 2**

periods than tourists and may have closer contact with local populations. They are therefore at greater risk of acquiring malaria, typhoid, tuberculosis, Hepatitis A and sexually-transmitted infections, including HIV.[8–12] Military personnel and travellers to isolated geographical locations under primitive conditions may come into close contact with specific vectors that put them at high risk of infections such as rickettsial disease and leishmaniasis.

- ***Specific activities:*** fresh-water exposure, safaris and sexual exposure put individuals at risk of specific infections (Table 2 ). For example, a diagnosis of African trypanosomiasis should be considered in febrile travellers who recall painful bites whilst on safari in East/Central Africa.
- ***Immune status:*** travellers with HIV or malignancy and those taking long-term corticosteroids or other immunomodulatory drugs are at increased risk of opportunistic infections (Table 2). In contrast, migrants returning to their country of origin may be immune to certain infections (e.g. Hepatitis A, Katayama fever (acute schistosomiasis)).
- ***Preventative measures***: no vaccination, chemoprophylaxis or insect repellent is 100% effective but most interventions reduce the risk of acquiring infection and sometimes the severity of the resulting illness. Malaria prophylaxis is often taken inadequately, particularly by VFRs who may falsely consider themselves immune to malaria; this can delay symptom onset and lead to initial blood films being falsely negative.[8,13]

## Incubation periods and risk of infection

Knowledge of incubation periods for common travel-related infections, together with dates of travel and/or risk exposures, facilitates an appropriate differential diagnosis (Table 3 ). Whilst most travellers present within a month of returning from the tropics, some infections such as malaria, acute schistosomiasis, Hepatitis A and E can present weeks to months later.[14]

## Initial investigations

Recommended initial investigations for evaluating returning travellers with undifferentiated fever are listed in Table 4.

## Infection control and notifiable infections

Source isolation, ranging from standard barrier nursing to respiratory isolation or high-level protection, may be required during the initial assessment and following confirmation of the illness. This is particularly necessary where VHF is suspected but should also be considered in any traveller suspected of having a notifiable disease, or with an unexplained fever and respiratory illness or rash. It is a statutory requirement that certain infections (suspected or confirmed) are notified to the local public health team in order to implement appropriate public health measures and prevent outbreaks (Table 5 ). ◆

## Common causes of fever associated with geographical area of travel

| Destination | Common | Occasional | Rare but important |
|---|---|---|---|
| Sub-Saharan Africa | Malaria, rickettsial infection (tick typhus) | Amoebic liver abscess, brucellosis, dengue, enteric fever, Katayama fever, HIV seroconversion, meningococcus | Other arbovirus (West Nile, Rift Valley etc.), histoplasmosis, trypanosomiasis, viral haemorrhagic fever (Lassa, Ebola, Marburg, CCHF), visceral leishmaniasis |
| North Africa, Middle East, Mediterranean | | Brucellosis, Q fever, Toscana (sandfly fever) | Visceral leishmaniasis |
| Eastern Europe and Scandinavia | | Lyme disease | Hantavirus, tick-borne encephalitis, tularaemia |
| South and central Asia | Dengue, enteric fever, malaria | Chikungunya, visceral leishmaniasis | CCHF, other arbovirus (Japanese encephalitis, Nipah), rickettsial infections |
| South East Asia | Dengue, enteric fever, malaria | Chikungunya, leptospirosis | Other arbovirus (Japanese encephalitis, Nipah, Hantavirus), melioidosis, penicilliosis, rickettsial infection (scrub typhus) |
| North Australia | | Dengue, Murray Valley fever, Q fever, rickettsial infection, Ross river fever | Other arbovirus (Barmah forest), melioidosis |
| Latin America and Caribbean | Dengue, enteric fever, malaria | Coccidioidomycosis, histoplasmosis, leptospirosis | Acute Chagas' disease (American trypanosomiasis), other arboviruses (Hantavirus, yellow fever), paracoccidioidomycosis |
| North America | | Coccidioidomycosis, histoplasmosis, Lyme disease, Rocky Mountain spotted fever | Arbovirus (Eastern and Western equine encephalitis, West Nile fever), babesiosis, ehrlichiosis |

CCHF; Crimean–Congo haemorrhagic fever.

Adapted from British Infection Society recommendations. See: Johnston V, Stockley JM, Dockrell D, et al. Fever in returning travellers presenting in the United Kingdom: recommendations for investigation and initial management. *J Infect* 2009; **59:** 1–18.

**Table 1**

## Common causes of fever associated with specific risk activities

| Risk activities | Common | Occasional | Rare but important |
|---|---|---|---|
| ***Bites*** | | | |
| Tick | Lyme disease, tick typhus | Q fever | Other borreliosis (tick bite fever, relapsing fever), CCHF, ehrlichiosis, tick-borne encephalitis, tularaemia, |
| Tsetse fly | | Trypanosomiasis | |
| Animal | Cellulitis | Q fever, tularaemia | Anthrax, rabies, rat bite fever |
| Dust exposure (e.g. caves, mines, deserts) | Coccidioidomycosis, histoplasmosis | | Rabies (caves) |
| Cruise ships/resorts | *Legionella*, norovirus | | |
| Farms | Brucella, Q fever | | |
| Fresh-water exposure | Katayama fever (acute schistosomiasis), leptospirosis | | Acanthamoeba |
| Game parks | Tick typhus | | Anthrax, trypanosomiasis |
| ***Ingestion*** | | | |
| Faecal-contaminated water | Amoebiasis, enteric fever, gastroenteritis (bacterial or viral), hepatitis A/E | | Poliomyelitis |
| Unpasteurized milk | *Listeria, Salmonella, Shigella* | *Brucella* | |
| Undercooked/raw food | Bacterial gastroenteritis, amoebiasis | | Trichinosis |
| Sexual exposure | HIV, hepatitis A/B/C, syphilis, gonorrhoea, reactive arthritis, pelvic inflammatory disease | | |
| ***Host factors*** | | | |
| Immunocompromized | Amoebiasis, non-typhoid salmonella, tuberculosis | Visceral leishmaniasis, STI (e.g. syphilis) | Blastomyces dermatitides, coccidioidomycosis, histoplasmosis, penicilliosis |

CCHF, Crimean–Congo haemorrhagic fever; STI, sexually-transmitted infection.

**Table 2**

## Incubation periods

| Incubation period | Infection |
|---|---|
| Short (<10 days) | Acute gastroenteritis (bacterial, viral)<br>Arboviral infections (e.g. dengue, chikungunya)<br>Meningitis (bacterial, viral)<br>Relapsing fever (*Borrelia* spp.)<br>Respiratory tract infection (bacterial, viral including influenza)<br>Rickettsial infection (e.g. tick typhus, scrub typhus) |
| Medium (10–21 days) | **Bacterial**<br>• Brucellosis<br>• Enteric fever (typhoid and paratyphoid fever)<br>• Leptospirosis<br>• Q fever<br>**Fungal**<br>• Coccidioidomycosis<br>• Histoplasmosis (can be as short as 3 days)<br>**Protozoal**<br>• Chagas' disease (acute)<br>• Malaria (*Plasmodium falciparum*)<br>• East African trypanosomiasis (*Trypanosoma brucei rhodesiense*)<br>**Viral**<br>• CMV, EBV, HIV, viral haemorrhagic fevers |
| Long (>21 days) | **Bacterial**<br>• Brucellosis<br>• Tuberculosis<br>**Fluke**<br>• Schistosomiasis, acute (Katayama fever)<br>**Protozoal**<br>• Amoebic liver abscess<br>• Malaria (including *Plasmodium falciparum)*<br>• West African trypanosomiasis (*Trypanosoma brucei gambiense*)<br>• Visceral leishmaniasis<br>**Viral**<br>• HIV<br>• Viral hepatitis (A–E) |

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus.

Adapted from British Infection Society recommendations. See: Johnston V, Stockley JM, Dockrell D, et al. Fever in returning travellers presenting in the United Kingdom: recommendations for investigation and initial management. *J Infect* 2009; 59: 1–18.

**Table 3**

## Recommended initial investigations in returning travellers presenting with (undifferentiated) fever[a]

| Investigation | Interpretation |
|---|---|
| Malaria film ± antigen test (RDT) | • Perform in all patients who have visited a tropical country within one year of presentation<br>• The sensitivity of a thick film read by an expert is equivalent to that of an RDT, but blood films are necessary for speciation and parasite count and should be sent to the reference laboratory for confirmation.<br>• Three thick films/RDTs over 72 hours (as an outpatient if appropriate) should be performed to exclude malaria with confidence |
| FBC | • Lymphopenia: common in viral infection (dengue, HIV) and typhoid<br>• Eosinophilia (>0.45 × $10^6$/litre): may be indicative of infectious cause (e.g. parasitic, fungal)<br>• Thrombocytopenia: malaria, dengue, acute HIV, typhoid, also seen in severe sepsis |
| Blood cultures | • Two sets should be taken prior to antibiotics |
| U&E, LFTs | • High transaminases consistent with a viral hepatitis, but low level transaminitis common in many infections<br>• Isolated high alkaline phosphatase is often found in amoebic lever abscess |
| Serum save[b] | • HIV testing should be offered to all patients, but particularly those with pneumonia, aseptic meningitis/encephalitis, prolonged diarrhoea, viral hepatitis, mononucleosis-like syndrome, unexplained lymphadenopathy, fever or blood dyscrasia<br>• Other (e.g. arboviral, brucella serology) if indicated |
| EDTA for PCR[b] | • Consider if other features suggestive of arboviral infection, VHF |
| Urinalysis | • Proteinuria and haematuria in leptospirosis<br>• Haemoglobinuria in malaria (rare) |
| CXR ± liver U/S | |

RDT, rapid diagnostic test; FBC, full blood count; HIV, human immunodeficiency virus; U&E, urea and electrolytes; LFTs, liver function tests; PCR, polymerase chain reaction; VHF, viral haemorrhagic fever; CXR, chest X-ray; U/S, ultrasound.

[a] In patients at high risk of VHF avoid taking non-essential blood tests before consulting with infectious diseases or microbiology services.

[b] To ensure that the correct tests are done, an adequate travel history MUST be documented on request forms. This includes locations visited, dates of travel, dates of symptom onset and risk activities undertaken. Pathogen-specific request forms are required by reference laboratory for some infections, such as dengue and other arboviral infections. These are available on the Public Health England (PHE, previously HPA) website.

Adapted from British Infection Society recommendations. See: Johnston V, Stockley JM, Dockrell D, et al. Fever in returning travellers presenting in the United Kingdom: recommendations for investigation and initial management. *J Infect* 2009; **59:** 1—18.

**Table 4**

## Important notifiable diseases

| Bacteria | Mycobacteria | Protozoa | Syndromes | Virus |
|---|---|---|---|---|
| Anthrax | Leprosy | Malaria | Acute encephalitis | Acute infectious hepatitis |
| Botulism | Tuberculosis | | Acute meningitis | Acute poliomyelitis |
| Brucellosis | | | Food poisoning | Measles |
| Cholera | | | Haemolytic—uraemic syndrome | Mumps |
| Diphtheria | | | Infectious bloody diarrhoea | Rabies |
| Enteric fever | | | | Rubella |
| Invasive group A *Streptococcus* | | | | Severe acute respiratory syndrome |
| Legionnaire's disease | | | | Smallpox |
| Leptospirosis | | | | Viral haemorrhagic fever |
| Meningococcal septicaemia | | | | Yellow fever |
| Plague | | | | |
| Relapsing fever | | | | |
| Scarlet fever | | | | |
| Tetanus | | | | |
| Typhus | | | | |
| Whooping cough | | | | |

**Table 5**

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## Practice points

- Always remember to take a travel history in any patient presenting with a fever or history of fever
- Think why this PERSON, from this PLACE, develops these SYMPTOMS at this TIME.
- A malaria rapid diagnostic test ± malaria film should be requested in all patients returning from the tropics with a history of fever. A positive malaria result should be acted upon on the same day.

**Where to ask for help**

Useful websites:

British Infection Association (BIA), for UK recommendations and guidelines: www.britishinfection.org/

Centres for Disease Control and Prevention (CDC): www.cdc.gov/

National Travel Health Network and Centre: www.nathnac.org/

ProMED-mail (electronic reporting system for infectious diseases outbreaks): www.promedmail.org/

Public Health England (PHE, previously HPA): www.gov.uk/government/organisations/public-health-england

WHO outbreak data: www.who.int/csr/don/en/

**Telephone advice:**

Imported Fever Service, HPE, UK: +44 (0) 844 778 8990

Contact after discussion with local microbiology, virology or infectious diseases consultant.

Hospital for Tropical Diseases, UCLH, London, UK

Tel: +44 (0) 203 456 7890 and ask for the Tropical/ID physician on-call

www.thehtd.org/;www.uclh.nhs.uk/

Liverpool School of Tropical Medicine, Liverpool, UK.

Tel.: (0900–1700 h) +44 (0) 151 705 3100

Tel.: (24 h) +44 (0) 151 706 2000 and ask for the Tropical/ID physician on-call.

www.lstmliverpool.ac.uk/; http://www.rlbuht.nhs.uk/