



THEME

Travel medicine



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Assessment of febrile illness in the returned traveller

BACKGROUND

Fever is among the most frequently reported problems in returning travellers.

OBJECTIVE

This article provides an overview of the general approach to fever in the returned traveller, including identification of common causes and management.

DISCUSSION

The returned traveller may present with fever and it is important to exclude life threatening conditions such as malaria that may be related to the travel. A complete risk assessment should be undertaken, including a complete travel history, examination and further investigations, to help to narrow the differential diagnosis. Common tropical diseases found include malaria, dengue, enteric fever, rickettsial infections and respiratory infections. General practitioners should be alert to the public health implications of travel related diseases.

Fever is an important and relatively common presentation of infections in returning travellers. The most common infections diagnosed in febrile returning travellers are malaria, dengue, mononucleosis, rickettsial infections and typhoid and paratyphoid, but many remain undiagnosed (Table 1).¹ These conditions are reflected in an Australian study of hospital admissions of febrile returning travellers, although they were in different proportions.² A significant proportion of travellers may have infections that are also common in nontravellers, which can be a source of confusion. The initial evaluation of these travellers should focus on infections that are life threatening, treatable, or pose a risk to public health. If an infection is thought to be one of those that pose a risk to public health, often listed as a notifiable disease, then the general practitioner should liaise with public health authorities immediately.

Assessment

History

A history of travel is the most important question, and some patients will volunteer that they have travelled

recently, particularly due to promotional campaigns by immigration authorities. An accurate history will assist in developing an appropriate differential diagnosis and help guide initial investigations. Ask about:

- specific presenting symptoms
- medical history (including medication/drug history)
- possible exposure to infectious diseases, and
- details of travel history. This is often easiest by way of a travel checklist, which could be used for any returned traveller (Table 2).

Vaccination is generally very effective against a wide range of national schedule diseases and travel related diseases. However, some vaccinations, such as typhoid vaccination, are not 100% protective. Many travellers do not seek pre-travel health advice and may not be current for routine national schedule or relevant travel related vaccines, or may be immigrants or travellers from overseas that may not be immunised. The travel history will be important for determining the approximate incubation period for the presenting illness (Table 3). In many cases, this will help to eliminate several potential infections and shorten the potential differential diagnoses.

Physical examination

Physical findings in returning travellers can be nonspecific and can mimic nontravel related diseases. Certain findings can be helpful (Table 4). For example, a cyclic fever may indicate malaria; a maculopapular rash may be seen in several diseases such as dengue, rickettsial infections, leptospirosis, or human immunodeficiency syndrome (HIV); and an eschar, a painless ulcer with a blackened centre, may indicate a rickettsial disease such as scrub typhus (Table 2).

Investigations

Initial laboratory investigations may include:

- a full blood count with differential
- thick and thin blood malaria films (where indicated by the travel history)
- liver function tests
- cultures of blood and stool
- urine analysis with urine culture, and
- serological tests for arboviral or rickettsial infections (where indicated by the travel history).

Additional tests may be requested based on the history and finding of physical examination. Eosinophilia is associated with Katayama fever due to acute schistosomiasis, however, it may be unrelated to the febrile illness and be associated with a coexisting helminthic infection.³ Finally, it may be useful for the laboratory to store a tube of 'acute' serum for retrospective antibody detection with a paired convalescent specimen.

Common tropical diseases

Malaria

Malaria is a global tropical parasitic disease with more than 300 million cases and 3 million deaths each year.⁴ On average, over 600 cases of imported malaria are notified in Australia each year.^{5,6} Malaria in humans is normally caused by one or more of four species, *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Worldwide, malaria due to *P. falciparum* and *P. vivax* account for most of the recorded malaria. Malaria due to *P. falciparum* accounted for about one-third of recorded cases in Australia during the period 1991–1997;⁷ however a recent study of 482 cases of imported malaria in Western Australia from 1990–2001 indicated that the proportion of *P. falciparum* cases during 1996–2001 had increased to about 44%.⁸ In Australia, fatalities are occasionally reported, predominantly from *P. falciparum*.⁹ Of those admitted with malaria to a specialist infectious disease hospital in Australia, only 56% had reportedly been taking malaria chemoprophylaxis.¹⁰

Malaria is a common finding of hospital presentations of febrile travellers in Australia.² Malaria caused by *P. falciparum* generally presents within the first month or so of exposure,

Table 1. Summary of main causes of fever presenting at GeoSentinel Clinics, June 1996–August 2004¹

	Number	%
Specific pathogen or cause reported	594	59.4
Malaria	352	35.2
Dengue	104	10.4
Mononucleosis (due to Epstein-Barr virus or cytomegalovirus)	32	3.2
Rickettsial infection	31	3.1
<i>Salmonella typhi</i> or <i>S. paratyphi</i> infection	29	2.9
No specific cause reported	406	40.6
Total	1000	100
(n=3907)		

as its incubation period is the shortest of the *Plasmodium* species, although onset may be delayed by suppressive antimalarial drugs.¹⁰ In contrast, malaria caused by *P. vivax* may present many months or years after exposure. No signs or symptoms are specific to malaria, although fever is almost always present so a high index of suspicion is required for any traveller returning from a malarial area. Complicated malaria, such as HIV, is a great mimicker and the diagnosis should be considered in anyone returning from a malarious area, until proven otherwise.

Malaria is diagnosed by:

- detecting the parasite in a blood film, or
- detecting circulating malarial antigen.

Laboratories with experience in detecting malarial parasites should be used. Initial blood films may be negative, and repeat films should be taken every 6–12 hours for 36–48 hours before malaria can be confidently excluded,¹¹ especially during typical cyclic spikes of fever, if present.

Malaria due to *P. falciparum* is particularly dangerous, as untreated complicated falciparum malaria can be fatal within 24–48 hours of presentation, particularly in young children. Patients with falciparum malaria require hospital admission until the patient has recovered and complications have been excluded. Complications may include renal failure, respiratory distress, altered consciousness, seizures, shock, or severe anaemia.

As patterns of resistance evolve, current guidelines for treatment of malaria should be consulted. In Australia these are given in *Therapeutic guidelines: antibiotic*.¹² Severe malaria, particularly due to *P. falciparum*, may require intravenous treatment. If eradication treatment with primaquine is considered, then glucose-6-phosphate dehydrogenase (G6PD) deficiency should be tested for before the drug is administered. Specialist advice should be sought if the patient does not improve or relapsing disease becomes problematic.

Dengue

Dengue is a flavivirus transmitted by the largely urban dwelling *Aedes aegypti* species of mosquito. It is a major global public health problem and is increasingly common in returning travellers.¹ There are four serotypes of the dengue virus that affect humans. Unfortunately, exposure and immunity to one serotype does not seem to confer protection to other serotypes; in fact, subsequent infection with another serotype can be more severe.³

Onset of disease can be rapid with an incubation period as short as 4–7 days. Infection may range from subclinical disease to influenza-like illness, including fever, headache, and myalgia; often with lymphadenopathy, erythema and/or a rash; or complicated by haemorrhagic diatheses or shock syndromes which can be fatal.

Dengue is usually diagnosed clinically and diagnosis depends on virus isolation in the laboratory from blood, amplification of viral nucleic acid or serological results (dengue IgM or IgG seroconversion).

Supportive treatment is all that can be offered and severe cases, especially those with evidence of complications, need to be managed in hospital. Spontaneous resolution is usual in uncomplicated dengue.

Dengue has important public health implications. The rapid spread of disease is possible in a receptive area such as Queensland (Australia). Numerous outbreaks of dengue in northern Queensland can be attributed to travellers returning with the disease from the tropics, including southeast Asia, where the disease is widely endemic. If dengue is suspected clinically, public health authorities should be informed, particularly in jurisdictions where the disease is notifiable.

Enteric fever (typhoid and paratyphoid)

Enteric fever is caused by *Salmonella typhi* (typhoid); however a similar syndrome is caused by *S. paratyphi* and other salmonella species. Infection is the clinical syndrome caused by *S. typhi* or 'paratyphi' salmonella species. Transmission is usually faecal-oral in nature and the disease is widespread, particularly in tropical areas.

Enteric fever has an incubation period of 3–60 days and can present with a remittent fever pattern together with headache. Gastrointestinal symptoms may be present, possibly constipation early and diarrhoea later,³ although this may vary in children.^{3,11} A history of recent typhoid vaccination does not rule out a diagnosis of typhoid as the vaccine is only about 70% protective against *S. typhi*.¹³

Diagnosis depends on laboratory culture, as serological testing is unreliable, particularly if typhoid vaccination has been undertaken previously. Once malaria has been excluded, empiric therapy for enteric fever may be

considered for those with prolonged fever. As patterns of resistance evolve, current guidelines for the treatment of typhoid should be consulted.¹²

Complications may include gastrointestinal perforation, haemorrhage, severe toxæmia, haemolytic anaemia, renal disease, or typhoid abscess.

Rickettsial disease

Fever, headache and myalgia, while a nonspecific triad of symptoms in returning travellers, may indicate one of a number of rickettsial diseases³ including scrub typhus, African tick bite fever and Mediterranean and Rocky Mountain spotted fever. All of these rickettsial diseases are transmitted by arthropod (mostly tick) bites, although a bite may not be reported. Rickettsial diseases are widespread

Table 2. Travel checklist

- Where did you travel?
- When did you travel:
 - departure date
 - return date?
- Did you travel in:
 - urban areas
 - rural areas?
- What was the purpose of your travel:
 - tourism
 - visiting friends or relatives
 - business
 - other?
- What special activities did you undertake:
 - mountaineering
 - scuba diving
 - caving
 - other?
- Did you experience any specific risk exposures:
 - sexual risks
 - consume poor quality water or food
 - ticks or other insect bites
 - swim in lakes
 - contact with wildlife?
- What vaccinations did you receive?
- Were you taking malaria prophylaxis?
 - If so:
 - which drug did you take
 - when did you start it
 - did you take it regularly as directed
 - are you still taking it?
- Did you become ill while away?
- Did anyone accompanying you become ill?

and are found in many parts of Australia. Rickettsial disease should be suspected in patients with fever and a rash, particularly if an eschar is present (Figure 1), who have travelled, camped and/or hiked in an endemic area.

Serological testing is available, however, acute serological testing is often negative. Empirical therapy with doxycycline is often commenced while awaiting results of tests on convalescent sera. Current guidelines for treatment of rickettsial diseases should be consulted.¹² Complications of these diseases Complications of scrub typhus include heart failure and pneumonia.

Respiratory infections

About 20–40% of travellers have respiratory symptoms while away or on return.^{1,2,14} The most common causes are allergy and viral infection of the upper respiratory

tract.¹³ Influenza is also becoming an increasing concern for returning travellers.¹⁵ Less commonly, respiratory symptoms may be present in travellers with Legionnaire disease, histoplasmosis, coccidioidomycosis, and Q fever.^{3,16} Transient migration of larval helminths (eg. hookworms) should be considered in nonspecific respiratory symptoms, particularly where there is evidence of a cough, nonspecific pulmonary infiltrates and a peripheral eosinophilia (Löffler syndrome).^{11,16}

Emerging infectious diseases

Recent concerns regarding severe acute respiratory syndrome and avian influenza and widespread influenza pandemic planning has helped raise awareness of possible emerging infectious diseases or other diseases of public health importance.¹⁹ The suite of viral haemorrhagic

Table 3. Incubation periods of travel related infections in febrile travellers⁷

Short (<10 days)	Intermediate (10–21 days)	Long (>21 days)
Malaria	Malaria	Malaria
Influenza	Viral haemorrhagic fevers	Hepatitis A, B, C, E
Arboviral infections including dengue, yellow fever	Typhoid fever	Schistosomiasis (Katayama fever)
Plague	Scrub typhus	Leishmaniasis
Enteric bacterial infections including paratyphoid fever	Q fever	Amoebic liver abscess
African tick bite fever	Relapsing fever (<i>Borrelia</i> spp.)	Tuberculosis
Spotted fever group (including Rocky Mountain spotted fever)	African trypanosomiasis	Filariasis
	Brucellosis	HIV
	Leptospirosis	

Table 4. Possible physical findings in selected tropical infections presenting in febrile travellers⁷

Physical finding	Infection or disease implicated
Rash	Dengue, typhoid, rickettsial infections, syphilis, gonorrhoea, Ebola virus, brucellosis
Jaundice	Hepatitis, malaria, yellow fever, leptospirosis, relapsing fever
Lymphadenopathy	Rickettsial infections, brucellosis, dengue, HIV, Lassa fever, visceral leishmaniasis
Hepatomegaly	Amoebiasis, malaria, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, relapsing fever, trypanosomiasis, typhoid, brucellosis, kala-azar, typhus, dengue
Eschar	Rickettsial infections, borrelia, Crimean-Congo haemorrhagic fever
Haemorrhage	Dengue, meningococcaemia, Lassa fever, Marburg or Ebola viruses, Crimean-Congo haemorrhagic fever, Rift Valley fever, yellow fever, epidemic louse borne typhus, Rocky Mountain spotted fever



Figure 1. An eschar in a returned traveller with scrub typhus

diseases, such as Lassa fever and Ebola virus, although rare in travellers, presents an ever present concern.¹⁷ Several treatable infections and viral infections (eg. dengue) of travellers can cause fever associated with haemorrhage in travellers.¹⁷ However, because of the public health implications, viral hemorrhagic fevers need to be considered in travellers who present with fever and haemorrhage returning from endemic areas, and public health authorities should be consulted.

Summary of important points

- Febrile illness is a common presenting feature in returning travellers and requires a clinical and epidemiological risk assessment.
- A complete history and examination together with initial laboratory investigation may give a clue to the diagnosis of a tropical disease; an estimate of the incubation period may narrow the differential diagnosis.
- Fever in returning travellers requires urgent investigation to exclude malaria and preventable deaths; persistence may be required in the laboratory diagnosis of malaria.
- There is an increasing concern to consider emerging infectious diseases and diseases of public health importance.

Resources

- Cohen J. Traveller's pocket medical guide and international certificate of vaccination. Available at: www.travelclinic.com.au/pocket-guide.asp
- Leggat PA, Goldsmid JM, editors. Primer of travel medicine. 3rd revised edn. Available at: www.tropmed.org
- Mills D. Travelling well. Available at: www.travellingwell.com.au
- Steffen R, DuPont HL, Wilder-Smith A. Manual of travel medicine and health. 3rd edn. Hamilton, Canada: BC Decker, 2003
- Yung A, Ruff T, Torresi J, Leder K, O'Brien D. Manual of travel medicine. 2nd edn. Melbourne: IP Communications, 2004
- Centres for Disease Control and Prevention. Health information for international travel. Available at: www.cdc.gov/travel

- Travel Health Advisory Group, Australia. Available at: www.well-togo.com.au
- World Health Organisation. International travel and health. Available at: www.who.int/ith.

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References

1. Freedman DO, Weld LH, Kozarsky PE, et al for the GeoSentinel Surveillance Network. Spectrum of disease and relation to place of exposure among ill returned travellers. *New Engl J Med* 2006;354:119–30.
2. O'Brien D, Tobin S, Brown G, Torresi J. Fever in returned travelers: review of hospital admissions for a 3 year period. *Clin Infect Dis* 2001;33:603–9.
3. Humar A, Keystone J. Evaluating fever in travellers returning from tropical countries. *BMJ* 1996;312:953–6.
4. World Health Organisation. Malaria. Available at www.who.int/mediacentre/factsheets/fs094/en/print.html [Accessed 9 February 2007].
5. Australian Bureau of Statistics. 9.25 National notifiable disease surveillance system reports 1998 to 2000. In: *Year Book Australia 2002*. Catalogue No. 1301.0-2002.
6. Australian Bureau of Statistics. 9.27 National notifiable disease surveillance system reports. In: *Year Book Australia*. Catalogue No. 1301.0-2005.
7. Harvey B. Trends in malaria in Australia, 1991–1997. *Comm Dis Intel* 1998;22:247–8.
8. Charles DM, Hart J, Davis WA, Sullivan E, Dowse GK, Davis TM. Notifications of imported malaria in Western Australia, 1990–2001: Incidence, associated factors and chemoprophylaxis. *Med J Aust* 2005;182:164–7.
9. Lewis SJ, Davidson RN, Ross EJ, Hall AP. Severity of imported malaria: Effect of taking antimalarial prophylaxis. *BMJ* 1992;305:741–3.
10. Robinson P, Jenney AW, Tachado M, Yung A, Manitta J, Taylor K, Biggs BA. Imported malaria treated in Melbourne, Australia: epidemiology and clinical features in 246 patients. *J Travel Med* 2000;8:76–81.
11. Carrol ED, Beeching NJ. Fever in children returning from abroad. *Current Paed* 2002;12:534–44.
12. Spicer J (Chair). Therapeutic guidelines: antibiotic. Version 13. North Melbourne: Therapeutic Guidelines Limited, 2006.
13. Looke DFM, Robson JMB. Infections in the returned traveller. *Med J Aust* 2002;17:212–9.
14. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Travel Med* 2000;7:259–66.
15. Steffen R, DuPont HL, Wilder-Smith A. Epidemiology of health risks in travellers. *Manual of travel medicine and health*. Hamilton, Canada: BC Decker, 2003:43–53.
16. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *New Engl J Med* 2002;347:505–16.
17. Leggat PA. Avian influenza and travel. *Annals Aust Coll Trop Med* 2006;7:16.