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REVIEW

Fever in returned travellers presenting in the United Kingdom: Recommendations for investigation and initial management

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Summary International travel is increasing. Most physicians and general practitioners will encounter returned travellers with fever and the majority of travel-related infection is associated with travel to the tropics. In those returning from the tropics malaria must always be excluded, and HIV considered, from all settings. Common causes of non-malarial fever include from Africa rickettsial diseases, amoebic liver abscess and Katayama syndrome; from South and South East Asia, enteric fever and arboviral infection; from

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the Middle East, brucellosis and from the Horn of Africa visceral leishmaniasis. Other rare but important diseases from particular geographical areas include leptospirosis, trypanosomiasis and viral haemorrhagic fever. North and South America, Europe and Australia also have infections which are geographically concentrated. Empirical treatment may have to be started based on epidemiological probability of infection whilst waiting for results to return. The evidence base for much of the management of tropical infections is limited. These recommendations provide a pragmatic approach to the initial diagnosis and management of fever in returned travellers, based on evidence where it is available and on consensus of expert opinion where it is not. With early diagnosis and treatment the majority of patients with a potentially fatal infection related to travel will make a rapid and full recovery.

Introduction

Travel, especially to developing countries, is associated with an increased risk of infection. The number of visits abroad made by UK residents continues to rise with 9.7 million visits in 2006 to countries other than Europe or North America.[1] Up to 70% of travellers to developing countries report health problems, the majority of which are self-limiting; 8—15% of travellers are ill enough to seek medical care either while abroad or on returning home.[2—4] Fever is a common symptom of illness in returning travellers.[5,6] The evaluation of fever in returning travellers requires an understanding of the geographical distribution of infections, risk factors for acquisition, incubation periods, clinical presentation and appropriate laboratory investigations. Most travellers with fever have self-limiting illnesses they could have acquired in Europe, but an important minority has tropical infections which are potentially life-threatening (such as falciparum malaria) or are of public health importance (such as typhoid). Almost all tropical infections are easily treated if identified early enough.

The aim of these recommendations is to provide the hospital physician with a practical approach to the diagnosis and initial management of adult returning travellers with fever. While the main focus concerns travellers returning from tropical countries, mention is also made of travellers returning from North America, Europe and northern Australia where certain infections are endemic yet rarely encountered in the UK. These recommendations are based on evidence where available and expert opinion where evidence is lacking. Infectious disease departments and specialist tropical disease centres in the UK can be contacted for advice on specific patients (contact details see Box 2: Sources of additional information).

Initial assessment and management of returning travellers with fever

Travel history

The aim of a travel history is to assess an individual's risk of having acquired a specific infection establishing, where possible, an epidemiological link. A detailed geographical history and the time of onset and duration of symptoms are essential. Most tropical infections become symptomatic within 21 days of exposure (Table 3) and the majority of febrile returning travellers present within one month of leaving endemic areas.[6,7]

The risk of acquiring specific infections varies according to *destination*, *setting*, including whether rural or urban and type of accommodation, and *activities* undertaken (Tables 1 and 2 and Appendix A).[5,8—11] Individuals visiting family in developing countries are at greater risk than tourists, especially of malaria, typhoid, tuberculosis, hepatitis A and sexually transmitted infections. [9,10,12—18] The travel history should include details of visits to game parks, farms, caves, and health facilities, consumption of exotic foods, activities involving fresh or salt water exposure, and sexual activity. A history of contact with unwell individuals can be helpful, particularly for localised epidemics (e.g. legionella), emerging infections (e.g. SARS) or risk assessment for viral haemorrhagic fever.

The risk of viral haemorrhagic fevers should be considered in all febrile travellers with epidemiological risk factors, particularly those for whom no diagnosis has been made and who become symptomatic within 21 days of leaving rural areas of sub-Saharan Africa. Those thought to be at risk should still undergo local testing for malaria and have other tests important for their immediate management performed as required (with appropriate laboratory management of samples) (Box 1; Table 1).

Whilst serious these haemorrhagic fever infections are rare. Approximately one case of Lassa fever is diagnosed every two years in travellers returning to the UK. Most patients acquired their infection in rural areas in Sierra Leone or Nigeria. Updated guidelines on management of suspected viral haemorrhagic fever are due to be published in 2009. If in doubt, clinicians are advised to avoid taking non-essential blood tests prior to consulting with infectious disease or microbiology services. Further details and current guidelines are available on the HPA and CDC websites.

Clinical assessment

Patients may present with undifferentiated fever, or fever with localising symptoms which may give a clue as to the underlying diagnosis. Examination findings such as rash, eschar, hepatosplenomegaly, lymphadenopathy or jaundice may aid in the differential diagnosis, and important syndromic presentations are laid out in Tables 4—7.

Initial investigations (Box 1)

Box 1. Recommended initial investigations in returning travellers presenting with (undifferentiated) fever[a]

Investigation	Interpretation
Malaria film and dipstick antigen test (RDT)	• Perform in all patients who have visited a tropical country within 1 year of presentation • The sensitivity of a thick film read by an expert is equivalent to that of an RDT, however, blood films are necessary for speciation and parasite count • Three thick films/RDTs over 72 h (as an outpatient if appropriate) should be performed to exclude malaria with confidence • Positive blood films (thick and thin) should be sent to the reference lab for confirmation
FBC	• Lymphopaenia: common in viral infection (dengue, HIV) and typhoid • Eosinophilia ($>0.45 \times 10^9$/L): incidental or indicative of infectious (e.g parasitic, fungal) or non-infectious cause — Table 7 • Thromobocytopaenia: malaria, dengue, acute HIV, typhoid, also seen in severe sepsis
Blood cultures	• Two sets should be taken prior to any antibiotic therapy • Sensitivity of up to 80% in typhoid
U&E, LFTs	See Table 5
Serum save[b]	• HIV testing should be offered to all patients with pneumonia, aseptic meningitis/encephalitis, diarrhoea, viral hepatitis, mononucleosis-like syndrome, unexplained lymphadenopathy, fever or blood dyscrasia • Other, e.g. arboviral, brucella serology if indicated
EDTA sample for PCR[b]	• Consider if other features suggestive of arboviral infection, VHF
Urinalysis	• Proteinuria and haematuria in leptospirosis • Haemoglobinuria in malaria (rare)
CXR and liver U/S	

[a] In patients at high risk of VHF avoid taking unessential blood tests prior to 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, e.g. dengue and other arbovirus. These are available on the HPA website.

Box 2. Sources of additional information.

Websites

- British Infection Society UK guidelines: www.britishinfectionsociety.org
- WHO outbreak data: www.who.int/csr/don/en/
- Health Protection Agency (HPA): www.hpa.org.uk
- Centers for Disease Control and Prevention: www.cdc.gov
- NaTHNaC (travel advice): www.nathnac.org
- Promed: www.promedmail.org
- Fever Travel (diagnostic website): www.fevertravel.ch
- Gideon (diagnostic website; subscription only): www.GIDEONonline.com

UK Specialist tropical disease units (24 h specialist telephone advice):

- Hospital for Tropical Diseases, London
  Tel.: (24 h: ask for tropical/ infectious diseases physician on call) +44 (0)845 155 5000.
  www.thehtd.org

- Liverpool School of Tropical Medicine
  Tel.: (0900–1700 h) +44 (0) 151 705 3100.
  Tel.: (24 h: ask for tropical/infectious diseases physician on call) +44 (0) 151 706 2000.
  www.liv.ac.uk/lstm/index.htm
- Oxford Centre for Clinical Vaccinology and Tropical Medicine, Oxford
  Tel.: (24 h: ask for infectious diseases consultant on call) +44 (0)1865 741 841.
  www.ccvtm.ox.ac.uk

UK high-security infectious diseases units (Viral Haemorrhagic Fever)

- Royal Free Hampstead NHS Trust, London
  Tel.: (24 h: ask for infectious diseases physician on call) +44 (0) 20 7794 0500 or 0844 8480700 (local rate number when calling from outside London)
  www.royalfree.nhs.uk
- The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle
  Tel.: (24 h: ask for infectious diseases physician on call) +44 (0)191 233 6161.
  www.newcastle-hospitals.org.uk

Common causes of undifferentiated fever

Malaria

Malaria should be excluded in all patients with a history of fever returning from the tropics. It is the most important potentially fatal cause of febrile illness in travellers returning to Europe from the tropics, especially sub-Saharan Africa.[7,19–21]

Incubation period

A minimum incubation period of 6 days means that the majority of short-term travellers with malaria develop their first symptoms following return home.[22,23] Most *Plasmodium falciparum* cases present within 1 month of return, but may present over 6 months later.[23] *Plasmodium vivax* and *ovale*, due to the presence of hypnozoites and *Plasmodium malariae* due to long persistence in blood with no symptoms, can present up to a year or longer following return.[24]

Distribution

Throughout tropics.

Mode of transmission

Anopheles mosquito biting between dusk and dawn.

Clinical presentation

There are no specific symptoms but the majority of patients give a history of fever, headache, myalgia, arthralgia and malaise. Some patients describe gastrointestinal or respiratory symptoms, e.g. jaundice or cough. Roughly half of malaria patients are afebrile on presentation (although almost all have a history of fever) and in most cases there is no specific fever pattern.[25] Complications can develop, particularly in *P. falciparum* cases; confusion, seizures or a reduction in Glasgow coma scale may indicate cerebral malaria or hypoglycaemia; hypoxia, tachypnoea and signs of pulmonary oedema may indicate respiratory complications.

Investigations

All febrile patients returning from malarious areas of the tropics (within a year) should have an urgent blood film and/or rapid diagnostic tests (RDTs) for malaria performed regardless of whether or not malaria prophylaxis has been taken. A significant number of travellers to malaria endemic countries do not take malaria prophylaxis, or take it inadequately.[12,14,26] When taken, malaria prophylaxis may delay onset of symptoms and obscure microscopic diagnosis.[27] All chemoprophylaxis should be stopped whilst a patient is being investigated for malaria. The best RDT's are almost as sensitive as expert malaria microscopy for falciparum malaria, but less sensitive for non-falciparum malaria. They cannot give additional information such as parasite count, maturity, or the presence of mixed species so should be seen as an adjunct to, rather than replacement for, malaria microscopy. Patients with a high *P. malariae* parasite count who have returned from Asia (particularly Malaysia) should have *P. knowlesi* excluded using PCR. This is a potentially lethal form of primate malaria which occurs as a zoonosis in humans.[28]

Treatment

See UK malaria treatment guidelines (www.britishinfectionsociety.org)

Enteric fever (typhoid and paratyphoid fever)

Having excluded malaria, enteric fever is the commonest serious tropical disease requiring treatment in travellers returning from Asia; it is relatively uncommon in Africa.

Incubation period

Seven to 18 days (range: 3–60 days).

Distribution

Worldwide distribution in developing countries; the highest incidence is found in south central Asia and South East Asia (>100 cases per 100,000 person years).[29] Enteric fever is

Table 1 Summary of diagnostic tools and empirical therapy by geographical area of travel and clinical presentation.

Undifferentiated fever

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments / empirical Rx
Amoebic liver abscess						Serology (>92% sensitive at presentation); U/S abdomen	Empirical tinidazole / metronidazole if suggestive clinical and travel history with abscess on U/S. Serology is positive in 25% of asymtomatic individuals in endemic areas
Brucellosis						Extended BC, serology	Suspect if contact with livestock / unpasteurised milk. Discuss treatment with ID unit
Chikungunya						PCR (1-4 d) or IgM (>5 days)	Manage symptomatically as an outpatient
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)	Manage symptomatically as outpatient with daily FBC unless high risk of shock (high haematocrit, falling platelets). Supportive management but avoid aspirin. Vaccination (YF, JE, TBE) history required to interpret results.
Enteric fever (typhoid / paratyphoid)						BC (up to 80% sensitive in 1st wk)	If clinically unstable Rx empirically with ceftriaxone. If travelled from SSA ciprofloxacin remains an alternative. If confirmed sensitive switch to ciprofloxacin; if resistant use azithromycin empirically as oral follow-on agent. Rx 2 wks.
HIV						HIV (antigen and antibody)	Many rapid tests do not pick up seroconversion illness
Leptospirosis						CSF + BC <5 days EIA IgM >5 days	Rx on suspicion doxycycline / penicillin (may not be helpful after jaundice developed). Transfer BC at room temp to reference lab
Rickettsiae						Acute phase + 3-6 wk serum	Consider empirical Rx doxycycline if exposure to ticks in game park, headache, fever +/- rash/eschar
Schistosomiasis, acute						Not helpful	Empirical Rx praziquantel if appropriate presentation and exposure 4-8 wks previous. Consider steroids.

Fever with rash

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments / empirical Rx
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)	Manage symptomatically as outpatient with daily FBC unless high risk of shock (high haematocrit, falling platelets). Supportive management but avoid aspirin. Vaccination (YF, JE, TBE) history required to interpret results.
HIV						HIV (antigen and antibody)	Many rapid tests do not pick up seroconversion illness
Rickettsiae						Acute phase + 3-6 wk serum	Consider empirical Rx doxycycline if exposure to ticks in game park, headache, fever +/- rash/eschar
Schistosomiasis, acute						Not helpful	Empirical Rx praziquantel if appropriate presentation and exposure 4-8 wks previous. Consider steroids
VHF						PCR to ref lab	**Always** contact regional centre. VHF are also endemic in South America (arenaviruses) and Europe / Asia (Congo-Crimean haemorrhagic fever), however are rarely encountered in travellers

Fever with jaundice

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments / empirical Rx
Leptospirosis						CSF + BC < 5days EIA IgM >5 days	Rx on suspicion doxycycline / penicillin (may not be helpful after jaundice has developed). Transfer BC at room temp to reference lab
Viral Hepatitis						Anti-HAV IgM, HBsAg, anti-HEV IgM	Acute hepatitis C should also be considered in homosexual men
VHF						PCR to ref lab	**Always** contact regional centre.VHF are also endemic in South America (arenaviruses) and Europe / Asia (Congo-Crimean haemorrhagic fever), however are rarely encountered in travellers
Yellow fever						EDTA (blood) +/- CSF for PCR; IgG / IgM serology	Require confirmation of YF vaccine history

(*continued on next page*)

Table 1 (*continued*)

Fever with hepato (and/or) splenomegally

	SSA	SEA	SCA	ME/NA	SA	Diagnostics	Comments / empirical Rx
Amoebic liver abscess						Serology (>92% sensitive at presentation) U/S abdomen	Empirical tinidazole / metronidazole if suggestive clinical and travel history with abscess on U/S. Serology is positive in 25% individuals in endemic areas
Brucellosis						Extended BC, serology	Suspect if contact with livestock / unpasteurised milk. Discuss treatment with ID unit
Leptospirosis						CSF + BC <5 days EIA IgM >5 days	Rx on suspicion doxycycline / penicillin (may not be helpful after jaundice has developed). Transfer BC at room temp to reference lab
Trypanosomiasis						Blood film	Travel to game parks in SSA; discuss with tropical centre
Visceral leishmaniasis						Leishmaniasis serology, bone marrow	Travel to Mediterranean, Horn of Africa, Bihar, Nepal, Bangladesh, Brazil

Serious / very common	
Common	
Rare	

SSA, sub-Saharan Africa ; SEA, South East Asia; SCA, South Central Asia; ME/NA, Middle East, Mediterranean, North Africa; SA, South America, Caribbean

YF, Yellow fever; JE, Japanese encephalitis; TBE, tick borne encephalitis; VHF, viral haemorrhagic fever; BC, Blood culture; CSF, cerebrospinal fluid; Rx, treatment

This table applies to patients in whom MALARIA has been excluded.
Diseases that present commonly in non-travellers with fever are omitted – respiratory tract infections, diarrhoea, EBV, lymphoma, etc.

a common cause of fever in returning travellers from these areas, particularly in those visiting friends and relatives.[5,9,15]

Clinical presentation

Fever is almost invariable. Other symptoms and signs are non-specific, and include any or none of headache, constipation/diarrhoea and dry cough. Meningism and other misleading symptoms may occur. Full blood count and liver function tests may be normal or deranged in almost any pattern. Complications such as gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy occur in 10–15% of patients and are more likely if the duration of illness is >2 weeks. Vaccination provides incomplete protection against typhoid fever and does not protect from paratyphoid.

Investigations

Blood cultures have the highest yield within a week of symptoms onset.[30] Stool and urine cultures become positive after the first week. The sensitivity for blood cultures is reported as 40–80% (but modern methods may well be higher), urine culture 0–58% and stool culture 35–65%.[30–33] Bone marrow cultures have a higher sensitivity than blood culture.[30,32,33] When testing isolates for antibiotic sensitivity the use of ciprofloxacin discs to determine *Salmonella typhi* and *Salmonella paratyphi* sensitivity is unreliable. Only if the organisms is also sensitive on disc testing to nalidixic acid should the isolate be considered sensitive to fluroquinolones. The serological Widal test lacks sensitivity and specificity and is not recommended. Newer rapid serological tests detecting IgM against specific *S. typhi* antigens (e.g. Typhidot®, Typhidot-M®, Tubex®) have been developed, but so far have shown mixed results.

Treatment and practice points

Where there is a strong suspicion of enteric fever and the patient's clinical condition is unstable, treatment should be started empirically pending blood culture results. In patients returned from Asia there are increasing reports of fluroquinolone resistant isolates[34,35] and intravenous ceftriaxone is now preferred as a first-line agent. More than 70% of isolates of *S .typhi* and *S. paratyphi* imported into the UK are resistant to fluroquinolones; all isolates reported to the HPA in 2006 were sensitive to ceftriaxone.[36] In patients returning from Africa fluroquinolone resistance remains rare (~4% of isolates) and ciprofloxacin may still be considered as empirical therapy.[34]

If fluroquinolone resistance is confirmed azithromycin is a suitable oral alternative for uncomplicated disease. Azithromycin sensitivity testing is not readily available, however, resistance is currently rare in the UK.[36] Cefixime, when used as an alternative oral first-line agent has reported treatment failure rates of 4–37.6%.[37] In sensitive isolates fluroquinolones remain the most effective treatment option with an average fever clearance time of <4 days, cure rates >96% and low rates of faecal carriage. Ceftriaxone and azithromycin have longer average fever clearance times, 6.2 days and 4.4 days, respectively.[38] Regardless of which antibiotic is used fever takes some time to respond; failure to defervesce is not a reason to change antibiotics where the isolate is known to be sensitive. Relapse rates for fluroquinolones are reported as <3%, ceftriaxone <8% and azithromycin <3%.[38] To reduce risk of relapse treatment should be continued for 14 days. The addition of steroids may be helpful in severe cases.[39]

Rickettsiae

Rikettsial infection is common, especially in travellers visiting game parks in southern Africa. The majority of travel-associated cases are caused by *Rickettsia africae* (African tick bite fever) or *Rickettsia conorii* (Mediterranean spotted or tick bite fever) although *Rickettsia typhi* (murine typhus) and *Orientia tsutsugamushi* (scrub typhus from Asia) are reported.

Incubation period

Five to 7 days (up to 10 days).

Distribution and mode of transmission

R. africae, transmitted by cattle ticks is endemic throughout rural areas of sub-Saharan Africa and the eastern Caribbean and is a common cause of fever in travellers returning from safaris in southern Africa. *R. conorii* is transmitted by dog ticks, predominantly in urban and suburban areas of the Mediterranean and Caspian littorals, the Middle East, Indian subcontinent and Africa. *R. typhi*, transmitted by rat fleas, is found throughout tropical and subtropical areas, particularly port cities and coastal regions where the rodent population is dense. *O. tsutsugamushi*, transmitted by the bites of a mite is a significant cause of fever in some populations in rural south Asia (especially Laos), South East Asia and western Pacific, but is infrequently reported in travellers.

Clinical presentation

More than 80% of patients with *R. africae* or *R. conorii* report fever, headaches and myalgia with the classic signs of an inoculation eschar, rash, and lymphadenitis seen in <50%.[40] Retrospective cohorts report higher rates of eschars (53–100%), rash (15–46%) and regional lymphadenitis (43–100%).[41–44] Complications of African tick bite fever are rare although reactive arthritis can occur. Murine typhus and scrub typhus present with similar symptoms and in the majority of cases are mild. Complications, however, occur more frequently with Mediterranean spotted fever, murine typhus and scrub typhus.[44–46] Mediterranean spotted fever and murine typhus can be fatal with reported mortality rates of up to 32% and 4%, respectively.[45,47,48] Scrub typhus, particularly if left untreated, will commonly progress to develop pneumonitis, meningoencephalitis, disseminated intravascular coagulation or renal failure with fatality rates up to 17%.[49,50]

Other rare but serious causes of fever and a skin lesion which may resemble an eschar are anthrax and African trypanosomiasis. In trypanosomiasis, a chancre occurs at the site of the tsetse fly bite. Consider this in febrile patients with a history of receiving painful bites while in the game parks of East or Central Africa.

Investigations

Treatment should be started on strong clinical suspicion while other diagnoses are excluded. Confirmation of the diagnosis is retrospective and based on paired initial and convalescent-phase serum sample (3–6 weeks). In the case of *R. africae* seroconversion can take up to 6 weeks, and some patients, especially those treated early may not seroconvert.[51] Immunofluoresence assays (IFAs) are standard; more specific serological testing including multiple-antigen IFA, Western blot and cross-absorption assays can be performed with combined sensitivity for *R. africae* reported as 56%.[40,42]

Treatment and practice points

The combination of an illness onset within 10 days of exposure to ticks in game parks, fever and headache with or without rash is sufficient to prompt treatment with doxycycline 100 mg twice daily. The treatment duration is uncertain, but seven days or for 48 h after fever defervescence is common practice. Patients seldom need admission to hospital, and should respond within 24–48 h; if they do not, alternative diagnoses should be considered. Alternative antibiotics include fluroquinolones or azithromycin and may be useful if a wider differential is considered.[40,52]

Arbovirus infection (e.g. dengue and chikungunya)

There are over 500 arboviruses (arthropod-borne viruses), however only some cause disease in humans and most illness is self-limiting. While some arboviruses, notably dengue, are found throughout the tropics, others are restricted to specific regions (e.g. tick-borne encephalitis in central and Eastern Europe). Arboviral infections of medical importance have four main clinical presentations which may coexist:

1. Systemic febrile illness (all arboviruses), covered in these recommendations.
2. Haemorrhagic fever (e.g. dengue, yellow fever, Rift Valley fever, Congo Crimean haemorrhagic fever).
3. Encephalitis (e.g. Japanese encephalitis, West Nile, tick-borne encephalitis, Rift Valley fever).
4. Polyarthralgia or arthritis (e.g. chikungunya, Ross River, Barmah Forest, Sindbis, Eastern & Western Equine Viruses).

Currently the commonest arboviral infections in returning travellers are dengue and chikungunya.

Incubation period

Dengue 4–8 days (range: 3–14 days), chikungunya 2–3 days (range: 1–12 days).

Distribution

Dengue is found throughout the tropics but particularly Asia and South America. It has been reported from >100 countries with an annual global incidence of 50–100 million patients per year.[53] Dengue is the commonest arbovirus encountered in returning travellers and a common cause of fever in those returning from Asia.

Chikungunya was initially described in East Africa. In recent years there has been an epidemic, originating in Mauritius and spreading to large areas of south and South East Asia and in 2007 transmission was documented in Italy.[54] Chikungunya is being increasingly reported in travellers returning to Europe.[55]

Mode of transmission

Day-biting mosquitoes of the genus *Aedes*, in particular *Aedes aegypti* act as the primary vector of both dengue and chikungunya.

Clinical presentation

The spectrum of illness associated with dengue varies from (a) mild febrile illness to (b) dengue haemorrhagic fever (DHF) or (c) dengue shock syndrome. The last two are rare in travellers.[56]

(a) Classic dengue fever is characterised by a febrile illness associated with headache, retro-orbital pain, myalgia, arthralgia (in particular back pain) and rash. During the

Table 2 Common or important causes of fever associated with geographical areas and specific risk factors.

Risk factor	Common	Occasional	Rare but important
Geographical area			
Sub-Saharan Africa	HIV-associated infections (inc seroconversion) Malaria Rickettsiae	Acute schistosomiasis (Katayama) Amoebic liver abscess Brucellosis Dengue Enteric fever Meningococcus	Histoplasmosis Other arbovirus, e.g. Rift Valley, West Nile fever, Yellow fever Trypanosomiasis Viral haemorrhagic fever (Lassa, Ebola, Marburg, CCHF) Visceral leishmaniasis
North Africa, Middle East and 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 Japanese encephalitis Other arbovirus (Nipah virus) Rickettsiae
South East Asia	Chikungunya Dengue Enteric fever Malaria	Leptospirosis Melioidosis	Hantavirus Japanese encephalitis Other arbovirus (Nipah virus) Paragonomiasis Penicilliosis Scrub typhus
North Australia		Dengue Murray Valley Q fever Rickettsiae Ross River fever	Barmah Forest Melioidosis
Latin America and Caribbean	Dengue Enteric fever Malaria	Brucellosis Coccidioidomycosis Histoplasmosis Leptospirosis	Acute trypanosomiasis (Chagas') Hanta virus Yellow fever
North America		Coccidioidomycosis Histoplasmosis Lyme disease Rocky Mounted Spotted fever	Babesiosis Ehrlichiosis West Nile fever
Specific risk factors			
Game parks	Tick typhus		Anthrax Trypanosomiasis
Fresh-water exposure		Acute schistosomiasis (Katayama) Leptospirosis	
Caves		Histoplasmosis	Rabies Ebola
HIV	Amoebiasis Non-typhoid salmonella Tuberculosis	STI, e.g. syphilis Visceral leishmaniasis	Blastomycosis dermatitidis Coccidioidomycosis Histoplasmosis Penicilliosis

Abbreviations: CCHF, Congo Crimean haemorrhagic fever; STI, sexually transmitted infections.

first phase of the illness the rash is erythrodermic in nature, becoming petechial later. Bleeding gums, epistaxis and gastrointestinal haemorrhage are not in themselves indicative of DHF. Rarely hepatitis, myocarditis, encephalitis and neuropathies are encountered. The convalescent period following dengue is often characterised by desquamation and post-viral fatigue.

(b) DHF is defined as a triad of haemorrhagic manifestations, platelet count $<100 \times 10^9$/L and objective evidence of plasma leakage (>20% increase in packed cell volume during course of illness) or clinical signs of

Table 3 Incubation periods.

Incubation period	Infection
Short (<10 days)	Arboviral infections, e.g. dengue, chikungunya Gastroenteritis, acute (bacterial, viral) Melioidosis Meningitis (bacterial, viral) Relapsing fever (borrelia) Respiratory tract infection (bacterial, viral including avian influenza) Rickettsial infection, e.g. tick typhus, scrub typhus
Medium (10–21 days)	Bacterial • Brucellosis • Enteric fever (typhoid and paratyphoid fever) • Leptospirosis • Melioidosis • Q fever (*Coxiella burnetii*) Fungal • Coccidioidomycosis • Histoplasmosis (can be as short as 3 days) Protozoal • Chagas' disease, acute • Malaria (*Plasmodium falciparum*) • *Trypanosomiasis rhodesiensae* Viral • CMV, EBV, HIV, viral haemorrhagic fevers
Long (>21 days)	Bacterial • Brucellosis • Tuberculosis Fluke • Schistosomiasis, acute Protozoal • Amoebic liver abscess • Malaria (including *Plasmodium falciparum*) • *Trypanosomiasis gambiense* • Visceral leishmaniasis Viral • HIV • Viral hepatitis (A–E)

Table 4 Acute fever and rash or ulcer.

Rash	Infection
Maculopapular	Arboviral infection, e.g. dengue, chikungunya ''Childhood viral illness'', e.g. measles, rubella, parvovirus Drug hypersensitivity reaction Fungal infection (papules / nodules), e.g. histoplasmosis, penicilliosis Infectious mononucleosis group, e.g. EBV, CMV, HIV seroconversion Leprosy (reaction) Rickettsial infection, e.g. tick typhus Syphilis Viral haemorrhagic fever, e.g. Ebola
Vesicular	Herpes simplex virus, disseminated Herpes zoster virus (chickenpox or disseminated zoster) Monkey pox Rickettsial infection
Erythroderma	Dengue, early Kawasaki's disease Staphylococcal or streptococcal toxin related syndromes, e.g. toxic shock syndrome, scarlet fever Sunburn *Vibrio vulnificus*
Purpuric	Dengue haemorrhagic syndrome Gonococcal infection Herpes zoster virus, haemorrhagic Meningococcal infection Plague Rickettsial infection, severe Severe sepsis and disseminated intravascular coagulation Viral haemorrhagic fever, e.g. Lassa, Ebola, Congo Crimean haemorrhagic fever, Rift Valley fever
Ulcer	Chancre: *Trypanosomiasis rhodesiensae*, *Yersinia pestis* (Bubonic plague) Eschar: African tick typhus, anthrax Genital ulcer: syphilis, herpes simplex virus Skin ulcer: anthrax, diptheria, fungal infection, super-infected bacterial ulcer, tropical ulcer, Buruli ulcer

plasma leakage (e.g. effusions or hypoproteinaemia).[57] Mortality rates can be as high as 10–20%.

(c) Dengue shock syndrome, with a mortality rate of up to 40%, is characterised by a narrow pulse pressure of <20 mmHg or a systolic BP of <90 mmHg.[57]

Chikungunya presents with very similar symptoms to classic dengue fever[58] although generalised arthralgia is a more prominent feature. Fever resolves spontaneously over 5–7 days. Between 5 and 30% may go on to exhibit chronic arthropathy with pain, stiffness and swelling persisting for months to years.[59,60]

Investigations

Acute dengue fever can be confirmed with a positive PCR or, if symptoms have been present for over 5–7 days, with a positive IgM capture ELISA. Retrospective confirmation can be provided by determining the presence of serum IgG by ELISA with convalescent serum taken at 3 weeks. Cross-reaction with other flavivirus IgG is well recognised therefore a vaccination history (yellow fever, Japanese encephalitis, tick-borne encephalitis) is useful in the interpretation of test results. Acute chikungunya is diagnosed by positive PCR early on, or IgM/IgG from 5 to 7 days.

Treatment and practice points

Once a diagnosis of dengue is suspected, the primary clinical aim is to identify those at high risk of shock. A high or rising haematocrit indicating plasma leakage from blood vessels or falling platelet count ($<100 \times 10^9$/L) are early indicators. Most patients with dengue can be managed as outpatients with daily full blood count to check haematocrit and platelet count. In dengue the use of non-steroidal anti-inflammatory

Table 5 Infectious causes of fever and jaundice.

Hepatic	EBV, CMV Enteric fever (typhoid and paratyphoid) Hepatitis A–E[a] Leptospirosis (Weil's disease) Non-typhoid salmonella plus HIV *P. falciparum* malaria, severe Relapsing fevers (*Borrelia* spp.) Septicaemia including pneumococcal sepsis Typhus Viral haemorrhagic fever
Post-hepatic	Ascending cholangitis (including occasionally helminths)
Haemolytic	Bartonellosis Haemolytic-uraemic syndrome (*Shigella* spp. *E. coli*) Malaria *Mycoplasma pneumoniae* Sickle cell crisis with infective trigger

[a] Fever and jaundice rarely present concurrently.

drugs should be avoided, however in chikungunya they may be helpful.

Katayama syndrome (acute schistosomiasis)

Incubation
Four to 6 weeks (range: 2–9 weeks).

Distribution
Africa (very occasionally South East Asia, South America, Arabian peninsula).

Mode of transmission
Fresh-water exposure (usually swimming in lakes or rivers) allows cercariae released from snails to penetrate intact skin.

Table 6 Fever and hepatomegaly, splenomegaly or hepatosplenomegaly.

Bacterial	Brucellosis Enteric fever (typhoid and paratyphoid) Leptospirosis Q fever (*Coxiella burnetii*) Relapsing fever (borreliosis) Rickettsial infection, e.g. tick typhus
Flukes	Fascioliasis Schistosomiasis, acute (Katayama syndrome)
Protozoal	Amoebic liver abscess Malaria (acute)[a] Trypanosomiasis Visceral leishmaniasis[a]
Viral	Dengue Hepatitis, acute (A, B, E) HIV, CMV or EBV seroconversion
Non-infectious	Chronic Myeloid Leukaemia[a] Haemoglobinopathy Lymphoma[a] Myelofibrosis[a]

[a] May cause massive splenomegaly.

Clinical presentation
Symptoms and signs are non-specific but include fever, lethargy, myalgia, arthralgia, cough, wheeze, headache, urticarial rash, diarrhoea, and hepatosplenomegaly.[61–63] The illness itself is thought to be secondary to an immune complex phenomenon. In most cases the illness is self-limiting over a period of a few weeks.

Investigations
Almost all patients will have an eosinophilia ($>0.45 \times 10^9$/L), however only a minority will have positive serology or ova of schistosomiasis identified on stool, semen or terminal urine sample (last amount of urine passed).[63] The mean time to seroconversion is 1.6 months (range: 0–6 months).[61,63]

Treatment and practice points
The combination of fresh-water exposure 4–8 weeks previously, fever, urticarial rash and eosinophilia makes the diagnosis likely and empiric therapy should be given. Praziquantel, 40 mg/kg, in a divided dose 4 h apart will kill mature but not immature schistosomes (*Schistosoma japonicum*: 60 mg/kg in 3 divided doses). Treatment should be given at the time of diagnosis of Katayama syndrome and repeated 6–8 weeks later as eggs and immature shistosomes are relatively resistant to treatment. A short course of steroids (oral prednisolone 20 mg/day for 5 days) may help alleviate acute symptoms with no known adverse effect on cure.[63] Other causes of eosinophilia, including helminths (eg strongyloides and filariasis) and non-infectious causes (including malignancy) should be considered. See BIS recommendations for the initial investigations of eosinophilia in travellers and migrants (for publication in 2009 www.britishinfectionsociety.org).

Leptospirosis

Incubation:
Seven to 12 days (range: 2–30 days).

Distribution
Worldwide including United Kingdom, however, >50% cases diagnosed in the United Kingdom are acquired abroad, predominantly in tropical and subtropical countries.

Mode of transmission
Leptospira spp. are excreted in the urine of infected animals, in particular rats but also dogs, cattle and other domestic and wild animals. Humans acquire the infection either through direct contact with urine or with urine-contaminated water. Risks include recreational sports, occupational animal or water exposure and flooding.

Clinical presentation
This varies from mild flu-like symptoms to a severe illness characterised by haemorrhage, jaundice and hepatorenal failure (Weil's disease).[64] Leptospirosis classically follows a biphasic course with an initial bacteraemic phase with 'flu-like' symptoms lasting 4–7 days, followed 1–3 days later by an immune phase characterised by fever, myalgia (especially of calves), hepatorenal syndrome and haemorrhage. Conjunctival suffusion is suggestive.[64] In mild cases

Table 7 Fever and eosinophilia.

Parasite (all rare except Katayama)	Acute infection with • *Ascaris lumbricoides* • *Fasciola hepatica* (during larval migration) • Hookworm (*Ancylostoma duodenale*, *Necator americanus*) • Lymphatic filariasis (*Wuchereria bancrofti*, *Mansonella perstans*) • Schistosomiasis (Katayama syndrome) • Trichinosis (*Trichinella spiralis*) Hydatid (leak or superinfection) Strongyloidiasis hyperinfestation
Other infections	Coccidioidomycosis, paracoccidioidomycosis HIV HTLV-1 Toxoplasmosis Tuberculosis
Non-infectious (a few of the important ones)	Allergic bronchopulmonary eosinophilia Auto-immune disorder, e.g. SLE, vasculitis Drug hypersensitivity reaction Haematological malignancy Solid organ malignancy

For a more complete list see BIS recommendations on eosinophilia.

the immune phase may pass unrecognised and in severe cases the bacteraemic and immune phases may merge. Occasionally gastrointestinal presentations (vomiting, diarrhoea, loss of appetite, jaundice, hepatomegaly) or respiratory presentations (cough, shortness of breath) are seen. Meningitis, renal failure, liver failure, myocarditis, pancreatitis and haemorrhage (purpura, ecchymoses, pulmonary and gastrointestinal haemorrhage) have all been reported.

Investigations

Initial investigations are non-specific. Urinalysis may show proteinuria and haematuria. There may be a polymorphonuclear leucocytosis, thrombocytopenia and anaemia if significant haemorrhage has occurred. Bleeding is due to capillary fragility and tests of clotting are often normal. There may be biochemical evidence of renal failure, and a high bilirubin with mild elevation of transaminases.[65,66] Confirmation of the diagnosis is most commonly serological with the earliest positives appearing 6–10 days after onset of symptoms.[67] An IgM titre >1 in 320 is considered suggestive of leptospirosis. A titre of 1 in 80 to 1 in 160 is consistent with early infection but may be due to cross-reactions. To confirm the diagnosis convalescent serology, >10 days after symptom onset should be sent for IgM ELISA and microscopic agglutination test (MAT). CSF and aerobic blood cultures (taken within the first 5 days of onset, before antibiotics) can be referred to the UK Leptospira Reference Unit. Blood cultures should be kept at room temperature prior to dispatch to the reference laboratory. Urine is not a suitable sample for the isolation of leptospira.

Treatment and practice points

Treatment should be upon suspicion given the non-specific nature of initial investigations. Early mild disease is generally self-limiting; penicillin and tetracycline antibiotics are thought to be effective during the bacteraemic phase.[64,68] Patients presenting with classical symptoms and signs of Weils disease such as jaundice can become very unwell despite therapy and may require renal or liver support. A systematic review of antibiotic effectiveness in established leptospirosis showed no benefit for antibiotic treatment based on three trials. However, pending further evidence most infectious disease specialists continue to recommend antibiotics, whilst accepting that severe disease is probably immunologically mediated.[69]

Amoebic liver abscess

Incubation

Eight to 20 weeks (up to one year reported).

Distribution

Worldwide with highest prevalence in developing countries.

Mode of transmission

Faeco-oral route.

Clinical presentation

The combination of fever and a raised right hemidiaphragm on chest X-ray should raise the possibility of amoebic liver abscess (ALA). 72–95% of patients presenting with amoebic liver abscess describe abdominal pain, in 80–95% the pain is localised, 67–98% of patients will have fever and 43–93% hepatomegaly. 20% of patients will give a past medical history of dysentery and only 10% will have diarrhoea at the time of diagnosis.[70–74]

Investigations

A neutrophil leucocytosis of $>10 \times 10^9$ /L, raised inflammatory markers and deranged liver function tests (in particular raised alkaline phosphatase) are common. Patients with these findings should have amoebic serology performed. Indirect haemagglutination has over 90% sensitivity for amoebic liver abscess.[75] Faecal microscopy is usually negative in patients with ALA. An abdominal

ultrasound should be performed in all patients. High liver lesions can be missed by ultrasound therefore consider a CT scan if the ultrasound is negative and strong clinical suspicion remains. The main differential diagnosis is a pyogenic abscess. These are more likely to be multiple and occur in older age groups.[74] If there is diagnostic uncertainty a percutaneous aspiration is warranted. In patients who have lived in the Middle East, Central Asia and Horn of Africa an incidental finding of hydatid disease or a leaking or secondarily-infected hydatid cyst should be considered. In these patients hydatid serology should be reviewed prior to attempting aspiration. Amoebic and hydatid serological testing can be expedited by direct discussion with the laboratory with initial results possible within 24 h of receipt.

Treatment and practice points

Empirical therapy with tinidazole or metronidazole should be started in patients with suggestive history, epidemiology and imaging. Metronidazole 500 mg tds orally for 7—10 days results in a cure of over 90%.[71,73,76,77] Tinidazole 2 g daily for 3 days is an alternative and will result in less nausea.[70] Most patients will respond within 72—96 h. As the main differential diagnosis of an ALA is a pyogenic abscess, patients with evidence of systemic inflammatory response syndrome require broad-spectrum antibiotics, e.g. ceftriaxone and metronidazole, until the diagnosis can be confirmed.

Surgical or percutaneous drainage is rarely required and should only be considered if there is diagnostic uncertainty, symptoms persist after 4 days of treatment, or if radiologically there is risk of imminent rupture, particularly a left-lobe abscess rupturing into critical sites (e.g. the pericardium).[78]

Once treatment with tinidazole or metronidazole is complete, all patients, even those with negative stool microscopy, should receive a luminal amoebicide as this reduces the risk of relapse; diloxanide furoate (500 mg orally tds) or paromomycin (30 mg/kg per day orally in 3 divided doses) for 10 days.

Brucellosis

Incubation

Two to 4 weeks (up to 6 months reported).

Distribution

Worldwide distribution, in particular Middle East, the former USSR, Balkan Peninsula, the Mediterranean basin and South America.[79]

Mode of transmission

The commonest route of transmission is ingestion of infected unpasteurised milk products. Farmers, veterinarians and abattoir workers may become infected through direct contact between infected animal parts (e.g. placenta) and cuts or abrasions. Laboratory workers are at risk through inhalation of infected aerosolised particles.

Clinical presentation

Fever is the commonest presentation; however, brucellosis can vary from an acute febrile illness associated with rigors to a chronic low grade relapsing fever.[80] On physical examination lymphadenopathy, hepatomegaly and splenomegaly may be found. Complications are common in particular osteoarticular disease, of which septic arthritis affecting the large joints (knees, hips, ankles and wrists) or sacroiliitis are most often seen.[81,82] These occur predominantly during acute infection. Spondylitis is also recognised, often affecting the lumbar spine and leading to long-term damage.[82] Other complications include epididymo-orchitis, septic abortions, neurological involvement (meningitis, encephalitis, brain abscesses, etc.) and endocarditis.[81] The latter often affects the aortic valve and requires early surgery (Table 8).

Investigations

Initial investigation often reveals a mild transaminitis and pancytopenia. Bone marrow specimen for culture has the highest sensitivity and is considered the investigation of choice. The sensitivity of blood cultures varies from 15 to 70% depending on laboratory practices.[81,83] Requests should be discussed with the laboratory as initial processing requires special precautions and prolonged culture (up to 4 weeks) is necessary. Most diagnoses of acute brucellosis are made on the basis of positive serology. Newer generation serological tests may help in interpreting results on individuals from endemic areas or those with chronic disease.[84]

Q fever caused by *Coxiella burnetti* is rarer than brucellosis, but presents from a similar demographic situation, often with non-specific symptoms; serology is key to diagnosis. Up to 90% of patients will have positive Q fever serology by the third week of illness.[85]

Treatment and practice points

Treatment is long and often not straightforward and specialist advice is recommended. A recent systematic

Table 8 Chronic fever (>14 days).

Bacterial	Brucellosis Infective endocarditis Enteric fever (typhoid and paratyphoid) Pyogenic deep seated abscess Q fever (*Coxiella burnetii*) Tuberculosis
Fungal	Coccidioidomycosis Cryptococcosis Histoplasmosis Paracoccidioidomycosis Penicilliosis
Helminth	Schistosomiasis, acute (Katayama syndrome) Strongyloides hyperinfestation syndrome
Protozoal	Amoebic liver abscess Toxoplasmosis Visceral leishmaniasis
Viral	HIV plus opportunistic infection
Non-infectious	Auto-immune disorders Drugs Malignancy Pulmonary embolus Vasculitis

review and meta-analysis of 30 randomised controlled trials suggests that a triple regimen of doxycycline and rifampicin for 6–8 weeks and an aminoglycoside, e.g. streptomycin or gentamicin, for 2 weeks.[86] Relapse rates of up to 10% in the year following infection have been described.

HIV

The possibility of acute HIV infection should be considered in all travellers presenting with fever. The prevalence of HIV in many tropical countries is high (up to a third of the sexually active population) and not restricted to defined high-risk groups. Between 5 and 51% of short-term travellers take part in casual sex while abroad with higher rates reported in long-term travellers.[87–90] Many sexually transmitted infections including HIV seroconversion, gonorrhoea and secondary syphilis can present as a febrile illness. The UK National Guidelines on HIV testing 2008[91] recommend that an HIV test should be routinely offered to all men and women who report sexual contact with individuals from high HIV prevalence countries, also to patients where HIV could enter the differential diagnosis which in this context includes: tuberculosis, pneumonia, aseptic meningitis/encephalitis, diarrhoea (salmonella, campylobacter, shigella), viral hepatitis, unexplained blood dyscrasia (leucopenia, thrombocytopenia), mononucleosis-like syndrome, macular-papular rashes, unexplained lymphadenopathy or pyrexia of unknown origin.

A number of HIV-associated opportunistic infections are more common in those returned from the tropics (eg TB, non-typhi salmonella), while others are specific to geographical area (e.g. *Penicillium marneffei* in South East Asia).[92] See Table 2.

Hepatitis

Incubation
Hepatitis A 15–50 days; acute Hepatitis B 60–110 days; and Hepatitis E 14–70 days.

Distribution
Worldwide distribution but higher prevalence in developing countries. Outbreaks of hepatitis E are more common in Asia.

Mode of transmission
Hepatitis A and E are transmitted by the faecal–oral route through contaminated water, food including shellfish, or direct contact. Hepatitis B in travellers is predominantly transmitted by sexual contact or blood.

Clinical presentation
Symptoms range from asymptomatic infection to a flu-like febrile illness followed by nausea, vomiting, abdominal pain, jaundice and tender hepatomegaly. The majority of hepatitis A and E cases are self-limiting, however fulminant hepatitis can occur and in the case of hepatitis E chronic hepatitis is described in the immunocompromised.[93,94] Hepatitis B may be self-limiting or become chronic with clearance of infection less likely in infants and older age groups.

Investigation
Acute serology during the symptomatic period should be taken to confirm diagnosis. Hepatitis A IgM may be positive 5–10 days before symptom onset and remains positive for 6–12 months. The presence of antibodies to Hepatitis B surface antigen and core IgM is indicative of acute hepatitis B. Hepatitis E IgM is positive during the symptomatic period.

Treatment and practice points
Treatment of acute hepatitis is supportive; liver transplant should be considered in fulminant cases.

Fever and respiratory symptoms

Respiratory tract infections are diagnosed in 7.2–24% of febrile returning travellers,[14,19,95] and include sinusitis, pharyngitis, tonsillitis, bronchitis, influenza, pneumonia, tuberculosis and pulmonary eosinophilia. In fact, influenza is the most common vaccine preventable infection acquired by travellers. Relatively few immune-competent patients have specifically tropical infections.

The most likely pathogens in upper respiratory tract infections remain viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae* and Group A streptococci. Consider *Corynebacterium diphtheriae* in travellers returning from former USSR, Indian subcontinent, South East Asia and South America where the infection remains endemic due to break-downs in immunisation programmes.

Common lower respiratory tract pathogens are the same as in the UK. HIV-associated disease, especially Pneumocystis pneumonia.

Influenza and in particular emerging sub-types, including H1N1 or ''swine influenza'' and H5N1 or ''avian influenza'' should be considered in travellers with respiratory symptoms developing within 7 days of visiting endemic areas, particularly where there has been direct contact with a suspected case and in the case of H5N1 contact with poultry. As the epidemiology and virulence of emerging sub-types may change during the course of an outbreak it is important that current management algorithms are followed. These, together with a list of countries with reported cases are available on the HPA website. For confirmation of suspected cases nose and throat swabs should be sent in viral transport medium for PCR. Local infection control procedures should be followed carefully.

Outbreaks of legionella infection are reported in returning travellers from cruise ships and air-conditioned hotels. Cases will geographically disperse on return home therefore a high index of suspicion and case reporting is required to identify an outbreak.[96] Urinary legionella antigen and samples for serology should be sent.

Tuberculosis is reported in returning travellers, particularly in individuals following prolonged visits to family and friends and overseas health care workers.[2,14,16] The estimated incidence of tuberculosis infection in travellers to areas of high tuberculosis endemicity is reported as 3.5 per 1000 person months of travel; active disease is uncommon, 0.6 per 1000 person months of travel.[16] Early notification facilitates contact tracing on return flights.

Patients from South East Asia who present with respiratory symptoms and upper zone infiltrates on chest X-rays

should also be investigated for melioidosis (*Burkholderia pseudomallei*), a Gram negative bacillus which can present with localised disease, particularly cavitatory pneumonia or as septicaemia. If the diagnosis is suspected the laboratory should be warned so that samples can be processed under appropriate conditions.

Risk activities which result in exposure to dust or bats, particularly in travellers returning from geographically restricted areas of the Americas, raise the possibility of histoplasmosis and coccidioidomycosis.[97,98] *C. burnetti* should be considered in travellers presenting with fever, pneumonia and hepatitis who give a history of animal or farm exposure; serology is the diagnostic test of choice. Febrile patients with cough, wheeze, pulmonary infiltrates and peripheral eosinophilia should be investigated for Loefflers syndrome (ascaris, hookworm, strongyloides), Katayama syndrome (schistosomiasis) and tropical pulmonary eosinophilia (filaria). A leaking hydatid cyst, visceral larva migrans and paragonimiasis may also present with fever, respiratory symptoms and a peripheral eosinophilia. BIS eosinophilia recommendations are due for publication 2009. Other tropical infections including enteric fever and malaria may have respiratory features as part of their presentation.

Fever and gastrointestinal symptoms

Acute traveller's diarrhoea, defined as 3 episodes of loose stool in 24 h, is one of the commonest diagnoses in those returning from developing countries with a reported incidence of 222 cases per 1000 ill returned travellers.[5] Fever is self-reported in up to 30% of patients with traveller's diarrhoea.[99] The aetiology of travellers' diarrhoea varies according to destination, setting and season. Enteric bacteria, in particular *E. coli* (enterotoxigenic and increasingly enteroaggregative species), campylobacter, salmonella and shigella are common causes.[21,100–102] Norovirus and rotavirus are less likely to cause fever but should be considered in patients returning from cruise ships or resorts where outbreaks occur. In up to 50% of patients no pathogen is identified.[100–102] In addition to bacterial dysentery, amoebic colitis can cause bloody diarrhoea, often with a more indolent onset. A wet preparation of a recently passed stool specimen (within 15–30 min) looking for amoebic trophozoites can be helpful in making the diagnosis. The combination of fever and significant diarrhoea, particularly if bloody, is suggestive of invasive bacterial disease or amoebic dysentery and should prompt consideration of empiric antibiotic treatment.[103] Cephalosporins or fluoroquinolones are effective for most cases of travellers' diarrhoea. Quinolone resistance, however, is increasingly reported in campylobacter isolates from Asia and in these cases a macrolide should be considered.[104] Tinidazole or metronidazole are effective in the treatment of amobebic dysentery.

Other systemic infections causing fever (e.g. severe sepsis including meningococcal septicaemia and toxic shock syndrome, malaria, typhoid, atypical pneumonia, influenza, measles, viral haemorrhagic fever) may have diarrhoea at presentation. Fever and diarrhoea are both common in travellers, and may have separate aetiologies.

Gastrointestinal symptoms other than diarrhoea may be related to travel. Enteric fever and amoebic liver abscess should be considered in patients with fever and abdominal pain. Leaking or infected hydatid cysts, may present many years after leaving endemic countries, and are a rare but potentially serious causes of fever and abdominal pain. Exposure in the Middle East, North Africa, Turkey and Eastern Europe is suggestive and an abdominal ultrasound may be helpful. See Table 5 for infections which may present with fever and jaundice.

Fever and neurological symptoms

Neurological presentations are seen in 15 per 1000 ill returned travellers.[5] Malaria and meningitis are by far the most common treatable causes and must always be excluded first.

Encephalopathy is found in systemic infections including *P. falciparum* malaria, typhoid and HIV seroconversion. Meningism, seizures and focal signs may be manifestations of cerebral malaria in adults.

All the common causes of meningitis should be considered in returning travellers. Meningococcal meningitis has been associated with the Hajj pilgrimage to Mecca and evidence of vaccination is now mandatory before individuals can participate.[105] In cases of lymphocytic meningitis HIV seroconversion should be excluded.[106] Other causes include tuberculosis, syphilis, arbovirus, Lyme disease, leptospirosis, brucellosis, Q fever, relapsing fevers and HIV related opportunistic infection, e.g. cryptococcal meningitis. This last can be easily diagnosed by India ink staining of the cerebrospinal fluid (CSF) and cryptococcal antigen testing on serum and CSF.

Encephalitis with or without fever in a returning traveller has a wide differential diagnosis which not only includes the common causes seen in the UK (herpes simplex, varicella zoster, tuberculosis and enterovirus) but also arboviruses (Japanese encephalitis, tick-borne encephalitis), rabies, rickettsial infections, brucellosis and African trypanosomiasis. In addition non-infectious causes of encephalopathy should be considered in particular alcohol withdrawal. Discussion with a neurologist, and a virologist or reference laboratory is essential. For further advice refer to the British Infection Society encephalitis guidelines (due for publication 2010).

Trypanosomiasis (sleeping sickness) has been described in tourists who have visited game parks in East and Central Africa, including Zambia, Tanzania and Malawi.[107,108] Treatment caries the risk of significant morbidity but if untreated the disease is invariably fatal. If suspected, expert advice should be sought for diagnosis and treatment.

Protection of staff and contacts

Patient isolation

Patients with certain infections require source isolation (side room, gloves, apron, +/− mask, +/− goggles). Local hospital guidelines should be followed, however in general this includes suspected or confirmed cases of:

- anthrax, diphtheria, encephalitis, enteric fever, hepatitis (acute), infectious diarrhoea, influenza, measles, meningococcal septicaemia, meningitis, mumps, pertussis, plague, poliomyelitis, rabies, tuberculosis, travellers with respiratory illness or rash, pyrexia of unknown origin, varicella and herpes zoster, VHF.

Laboratory hazards

For some infections there is a risk of laboratory staff being infected if samples are not processed under upgraded infection control procedures. Laboratory staff therefore need to be warned if these infections are being considered. This includes enteric fever, brucella, Q fever, melioidosis, and in particular viral haemorrhagic fevers for which statutory handling arrangements apply.

Notification of infectious diseases

It is a statutory requirement that certain infections are notified to the local health protection unit in order to investigate and prevent possible outbreaks. This includes suspected or confirmed acute encephalitis, acute poliomyelitis, anthrax, avian or ''swine'' influenza, cholera, diphtheria, dysentery (bacterial or amoebic), enteric fever (typhoid or paratyphoid), food poisoning, leprosy, leptospirosis, malaria, measles, meningitis, meningococcal septicaemia, mumps, plague, rabies, relapsing fever, rubella, scarlet fever, small pox, tetanus, tuberculosis, typhus, viral haemorrhagic fever, viral hepatitis, whooping cough, yellow fever.

Conclusions

Fever in travellers returning from the tropics is common. Many will not have tropical infections but this should always be looked for. All patients with relevant travel history should have an assessment for VHF risk and up to three daily blood films to exclude malaria. A number of key diagnoses warrant empiric therapy. Advice is available for specific cases from infectious disease units, microbiologists and specialist tropical disease centres. To make the most of this advice a detailed travel history, including exact dates and place of travel and timings of onset of symptoms, is essential.

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Appendix A
Supplementary information

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2009.05.005

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