Travel medicine II

Assessment of travellers who return home ill

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Every year, millions of people travel abroad, exposing themselves to various diseases. Advice on risk avoidance and on self-medication is not always successful; sometimes travellers return home ill or become unwell soon afterwards. There are many possible causes for such illnesses, and physicians should try to establish whether the disease is specifically associated with the recent journey. The approach to assessment of the ill traveller should make use not only of signs and symptoms, but also of geography and epidemiology. Travellers with fever need immediate attention to rule out serious and potentially life-threatening conditions. Faced with a difficult diagnosis, physicians should consult with experts in tropical and travel medicine.

The popularity of international travel continues to grow,[1,2] and physicians increasingly need to understand diseases of travel as people visit more exotic and remote parts of the world. Exposure to diseases that are rare in the developed world is rising, especially instances in which the traveller's behaviour or special epidemiological characteristics of the country visited play a part. Furthermore, travellers can introduce these diseases into their community on return. Data from the 1980s and 1990s suggest that for 100 000 travellers to the less-developed world for 1 month: 50 000 will have a health problem during their trip, 8000 will seek medical care, 5000 will be bedridden, 1100 will be incapacitated in their work either abroad or on return, 300 will be admitted to hospital during the trip or on return, 50 will have to be air evacuated, and one will die.[3,4]

Travellers who are well on their return rarely need assessment. However, when a traveller returns ill from a journey abroad it can be difficult to decipher whether the condition is the result of a disease directly related to travel, especially in the case of tropical disease, or whether a routine cosmopolitan disease was acquired while travelling; statistically, routine illness is more likely than exotic disease (panel 1). For the purpose of this review, travel refers to a short visit from a developed to a tropical or subtropical country rather than, for example, emigration or long stays for work purposes.

Approach

In the assessment of a returning traveller, the physician should consider geographical, seasonal, environmental, and cultural factors. He or she should establish which potential ailments carry the greatest morbidity and mortality, and work backwards from there—seeking to find those that are treatable and those that could pose public-health risks. Clinical presentations in short-term travellers (less than 4 weeks) might be very different to those in patients living in endemic areas, because the visitor will be immunologically naive. Compared with the local population in the country visited, the traveller might undergo more severe disease from an infection with fewer organisms, and this can easily decrease diagnostic sensitivity.[5] An algorithm can be a guide, but physicians should not depend on it completely or be restricted by it when assessing the ill returned traveller (figure).

History and physical examination

A detailed travel history is essential (panel 2), and an atlas should be part of every medical library. Countries vary greatly in disease patterns, and within countries there can be great differences based on altitude, climate, urbanisation, local vectors, economy, and other factors. The physician needs to know the duration of travel and the incubation periods of potential infections (panel 3). Several diseases are restricted to specific geographical areas (see figures 1 and 2 in part one of this series; *Lancet* 2003; **361:** 1368–81). However, the presence or absence of a disease can change rapidly, and keeping up to date requires effort. Furthermore, specific exposures can help predict travel-related infection (panel 4), and the possibility of an infection acquired on a flight or on a cruise ship should not be forgotten.[6–9] The relative risk of disease can be estimated by taking into account these factors and, combined with careful assessment of the timing of signs and symptoms, should help physicians estimate the urgency of assessment and choose tests to further identify the cause of illness.

Often, distinctive physical findings are not seen in returning travellers. However, findings that do point to travel-acquired disease as opposed to common diseases are summarised in panel 5, examples being lymphadenopathy with plague, HIV infection, rickettsioses, brucellosis, and leishmaniasis and liver and spleen enlargement with malaria. A comercially-available diagnostic program, GIDEON (http://www.gideon.com) can help in tabulating findings and providing differential diagnoses.

Search strategy

I used PubMed and the Cochrane Library (a disappointing source for travel medicine references) and my personal collection of *The Lancet*, *Transactions of the Royal Society of Tropical Medicine*, *Journal of Travel Medicine*, *American Journal of Tropical Medicine* and *Hygiene*, *Clinical Infectious Diseases*, *Journal of Infectious Diseases*, *New England Journal of Medicine*, *Undersea and Hyperbaric Medicine Journal*, and *Journal of Wilderness Medicine*, which dates back to 1992. I also have the abstract reviews from the annual meetings of the American Society of Tropical Medicine and Hygiene and those from the biannual meetings of the International Society of Tropical Medicine for the past 10 years.

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Panel 1: **Relative risks for travellers**

Risk	Illness
High	Acute viral gastroenteritis, *E coli* enteritis, upper respiratory infection
Moderate	Salmonella, shigella, campylobacter, giardia, hepatitis A, gonorrhoea, chlamydia, herpes simplex, dengue, Epstein-Barr, malaria (without chemoprophylaxis)
Low	Malaria (with chemoprophylaxis), amoebiasis, leptospirosis, typhoid, cholera, HIV, HBV, syphilis, chancroid, Lyme, schistosomiasis, tuberculosis, ascariasis, enterobiasis, strongyloidiasis, trichuriasis, rubella, rubeola, rickettsioses, borreliosis, tropical sprue
Very low	Yellow fever, rabies, anthrax, plague, trypanosomiasis, viral haemorrhagic fevers, filariasis, flukes, toxocariasis, diphtheria, legionella, tularaemia, melioidosis, poliomyelitis, echinococcosis, trichinosis, gnathostomiasis, anisakiasis, yaws, pinta, LGV

LGV=lymphogranuloma venereum. HBV=hepatitis B virus. Risk modified by behaviour of traveller, season, preventive measures, and duration of exposure. Adapted from: Steffen R. Travel medicine: prevention based on epidemiological data. *Trans R Soc Trop Med Hyg* 1991; **85:** 156–62. Steffen R, Rickenbach M, Wilhem U, et al. Health problems after travel to developing countries. *J Infect Dis* 1987; **156:** 84–91. WHO. International travel and health. Geneva: World Health Organization, 2002. Centers for Disease Control and Prevention. Health information for international travel 2001–2002. Atlanta: Department of Health and Human Services, 2001. Abdullah ASM, McGhee SM, Hedley AJ. Health risks during travel: a population-based study amongst the Hong Kong Chinese. *Ann Trop Med Parasit* 2001; **95:** 105–10. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Trav Med* 2000; **7:** 259–66.

Categorical assessment

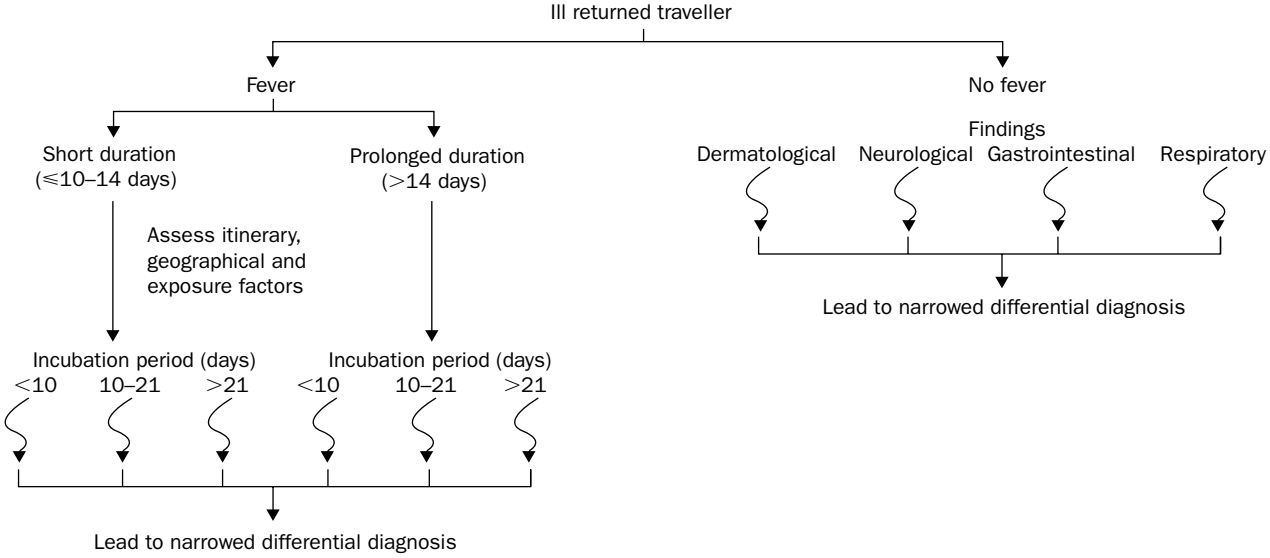
Fever

Fever in the returned traveller can represent many illnesses, but the most important causes are malaria, enteric fever, hepatitis, amoebic liver abscess, arbovirus infections, rickettsial infection, septicaemia, and meningitis. The old advice that any fever in a returning traveller must be considered as malaria until proven otherwise is still relevant, but other causes must be considered in differential diagnosis (panel 6). A useful approach is to categorise fever as acute (<14 days) or chronic and then to assess associated findings. Acute fever with anaemia suggests malaria, babesiosis, bartonellosis, or infection in a patient who has sickle-cell anaemia, thalassaemia, or glucose-6-phosphate dehydrogenase deficiency. Chronic fevers can be subcategorised on the basis of blood-cell counts. A leucocytosis could point to deep abscess, amoebic liver abscess, cholangitis, or relapsing fevers, whereas a chronic fever with eosinophilia might be due to invasive *Schistosoma mansoni* or *Schistosoma japonicum*, invasive *Fasciola hepatica*, lymphangitis exacerbations secondary to microfilariae, or viscera larvae migrans. Chronic fevers with neutropenia can arise from malaria, disseminated tuberculosis (often with a negative tuberculin skin test), visceral leishmaniasis, brucellosis, or HIV infection. A normal white blood cell count could be due to localised tuberculosis, brucellosis, secondary syphilis, trypanosomiasis, toxoplasmosis (having a normal sedimentation rate as well), subacute bacterial endocarditis, systemic lupus erythematosus, chronic meningococcal septicaemia, or melioidosis; whereas variable white cell counts could result from tumours or drug reactions. Relapsing fevers are typically due to malaria, *Borrelia* spp, visceral leishmaniasis, trypanosomiasis, filariasis, or cholangitis.

The potentially most dangerous (and increasingly common) causes of fever in returning travellers are malaria, typhoid, leptospirosis, dengue, and other arbovirus infections, and rickettsial infection, and these merit separate discussion. Those illnesses associated with diarrhoea, respiratory, and neurological complaints will also be addressed, followed by septicaemia (but only briefly since this topic was reviewed in 1998).[10] Physicians need to remember that non-exotic problems are more common than exotic ones in returned travellers, but remain open to the possibility of either.

Malaria

Malaria is an increasing risk for travellers to the less-developed world. Of the four species of plasmodia that



An algorithm to guide assessment

Panel 2: **Important questions for history taking**

- Travel departure and return dates
- Countries visited, including stopovers
- Destinations within the countries; rural or urban
- Climatic conditions, season
- Exposure to bites: insect, arachnid, reptile, mammal
- Exposure to animals, including bites and licks
- Exposure to ill people
- Unprotected intercourse and partners
- Type of food and liquids consumed, how and where prepared
- Vaccination history: review certificate and compliance
- Type of travel
- Quality of travel
- Medications (specific for trip and routine)
- Injuries or illnesses (how and where treated; injections given, blood taken, blood transfused, surgery; sterility of equipment and supplies)*
- Timing and sequence of symptoms

*In one study, 64% of those who travelled to developing countries became ill, of who 8% sought medical care—of those, 17% received injections. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Trav Med* 2000; **7:** 259–66.

infect people, *Plasmodium vivax* is the most common but *Plasmodium falciparum* is the most serious and most likely to be fatal. *P vivax* infection is seen more often in travellers returning to the USA, but in Europe falciparum malaria is more likely. The risk of contracting malaria is highest in Oceania and Africa, followed by Asia and Latin America with a greater risk of contracting the disease with longer travel (panel 7). Most large cities in South and Central America and southeast Asia are free of malaria, but this is generally not true of the Indian subcontinent or sub-Saharan Africa (apart from South Africa and the Kenyan capital, Nairobi). In a 10-year period, the rate of malaria infection in European travellers increased 6%, totalling 77 683 cases.[11] For the same period, 21 919 and 11 703 cases were reported in the UK (Bradley DJ. Data from the PHLS Malaria Reference Laboratory, 2002; personal communication) and USA, respectively.[12] From 1991–2000 alone there were 104 deaths from imported malaria into the UK (Bradley DJ. Data from the PHLS Malaria Reference Laboratory, 2002; personal communication. Panel 8). In addition to destination, risk of disease is related to exposure. Travellers most likely to be infected with malaria are expatriates visiting friends and family, followed by tourists, business travellers, missionaries, and students; subpopulations at high risk of contracting severe illness are elderly people, pregnant women, and infants.[13]

The region of travel affects the likelihood of a drug-resistant strain having been acquired and the treatment that should be offered: multiple *P falciparum* resistance to drugs such as chloroquine and mefloquine is well established in parts of the world; and *P vivax* resistance to chloroquine has been recognised since 1989, and has spread extensively from Oceania to South America.[14]

90% of travellers who contract malaria do not become ill until after they return home.[15] Most cases of falciparum malaria will become apparent within 7 days to 2 months after exposure; *P vivax*, *Plasmodium ovale*, and *Plasmodium malariae* infections are generally obvious 3–6 months after exposure, but *P ovale* and *P malariae* infections might take a year or longer to appear.[16] Tragically, most cases of malaria in travellers are due to lack of or inappropriate chemoprophylaxis, which includes stopping the regimen too soon after returning home, as well as delay in diagnosis and care.[17–19] Even when advice on mosquito avoidance and chemoprophylaxis has been followed carefully, a risk of contracting malaria remains. In fact, chemoprophylaxis can delay the onset of symptoms[20] since it does not prevent infection but suppresses disease, especially in vivax or ovale malaria because none of the generally used drugs eradicates hypnozoites dormant in the liver. Unfortunately, travellers can be deterred from using antimalarials by media and word-of-mouth stories about their adverse effects. As a result, they may take nothing or prefer a homoeopathic preparation to an established product.[21,22] Physicians should not assume that patients returned from travels will have taken antimalarials properly, or at all.

Panel 3: **Incubation periods**

Short (<10 days)

- Arboviral infections
- Viral haemorrhagic fevers
- Enteric bacterial infections (including paratyphoid)
- Enteric viral infections
- Rickettsioses: louse, flea-borne, typhus
- Plague
- Seafood poisoning
- Pneumonia
- Influenza
- Anthrax

Medium (11–21 days)

- Malaria (especially *P falciparum*)
- Leptospirosis
- Typhoid fever
- Rickettsioses: scrub typhus, spotted fever group, Q fever
- African trypanosomiasis
- Brucellosis
- Enteric protozoal infections
- Enteric hepatitis
- Strongyloides
- Lyme
- Cutaneous myiasis/tungiasis/scabies

Long (>30 days)

- Malaria
- Tuberculosis
- Viral hepatitis
- Enteric protozoal infections
- Enteric helminthic infections
- HIV
- Schistosomiasis
- Filariasis
- Amoebic liver abscess
- Leishmaniasis
- American trypanosomiasis

The typical symptoms of malaria are fever (intermittent or periodic), chills, headache, nausea, vomiting, abdominal pain, and myalgia, but other symptoms can include cough, arthralgia, or diarrhoea, which comes as a surprise to many physicians. Unfortunately, clinical findings cannot accurately predict the presence of malaria. However, rash and lymphadenopathy are not normally seen. Travellers who lack immunity to malaria are most likely to suffer severe disease, which can entail cerebral malaria (unrousable coma), renal failure, acidosis, hypoglycaemia, adult respiratory distress syndrome, shock, or repeated generalised convulsions. In severe cases—those due to *P falciparum*—superimposed bacterial

Panel 4: **Exposure and potential travel-related infections**

Exposure	Infection
Bites	
Mosquito	Malaria, dengue, yellow fever, encephalitis, filariasis
Tick	Borreliosis (Lyme, tick bite fever, relapsing fever), rickettsioses (typhus, Rocky Mountain spotted fever), Congo-Crimean haemorrhagic fever, Q fever, tularaemia, encephalitis, ehrlichiosis
Fly	African trypanosomiasis, onchocerciasis, leishmaniasis, bartonellosis, salmonella, myiasis
Flea	Plague, tungiasis
Triatomids (reduviids)	American trypanosomiasis (Chagas' disease)
Mammal	Rabies, sodoku (rat-bite fever), tularaemia, anthrax, Q fever, cellulitis
Ingestion	
Water (untreated)	Hepatitis A/E, cholera, Norwalk/caliciviruses, salmonella, shigella, giardia, poliomyelitis, cryptosporidium, cyclospora, dracunculiasis
Dairy (unpasteurised)	Brucella, tuberculosis, salmonella, shigella, listeria
Raw or undercooked food (meat, fish, vegetables)	Enteric bacteria (salmonella, shigella, *E coli, C jejuni,* etc); helminths (ascaris, trichinella, taenia—including cysticercosis, whipworm, capillaria, angiostrongylus; protozoa (amoebiasis, toxoplasma)
Freshwater skin contact	Leptospirosis, schistosomiasis, acanthamoeba, or naegleria
Sand/dirt/mud skin contact	Hookworm, cutaneous larva migrans, visceral larva migrans, leptospirosis
Sexual contact	HIV, hepatitis B/C, syphilis, gonorrhoea, chlamydia, herpes, papilloma virus
Ill contacts	Pneumonia, tuberculosis, Epstein-Barr, meningitis, rheumatic fever, Lassa fever

infection such as pneumonia and septicaemia are common.[23] Severe anaemia (packed-cell volume below 0·15, haemoglobin less than 50 g/L with parasitaemia) occurs in severe endemic malaria but is rare in the returned traveller. If the traveller took antimalarial chemoprophylaxis properly there may be mild clinical disease, but clinicians must not make the mistake of ruling out malaria. Although serological card tests exist that can identify antibodies to *P falciparum* and *P vivax*, they do not identify acute infection in people with some immunity or *P malariae* or *P ovale*.[24–26] Thus, microscopy is essential in making a correct diagnosis, but is reliant on the skill of the microscopist—parasites should be counted in a high power field to enable suitable decisions to be made about treatment.

Enteric fever

Caused by *Salmonella typhi* and *Salmonella paratyphi*, enteric fever is contracted from contaminated food or water. Most cases in the developed world occur in travellers who have acquired it while abroad in the less-developed world.[27] Common presentations include a slowly increasing fever in a step-ladder pattern over 1–2 weeks, headache, abdominal pain, and cough, which might be confused with malaria or leptospirosis. Diarrhoea is less common than constipation, and is more often seen in children.[28] Typhoid fever can begin with rose spots, 2–3 mm pink-red macules on the chest or abdomen that blanch with pressure but are fleeting in appearance and difficult to detect in dark-skinned individuals. The disease has a case-fatality rate of about 1·5%.[27] Commonly used febrile agglutinins or the Widal test give late and insensitive results. Cultures of blood are most useful in the first week of illness; afterwards, stool and bone-marrow cultures are more helpful in confirming the diagnosis, but use of antibiotics by the traveller during the journey will decrease sensitivity of laboratory testing.[5] Vaccination against typhoid does not exclude the possibility of disease, especially of paratyphoid fever. Resistance of salmonella to fluoroquinolones is rapidly expanding throughout the world and should be remembered when administering treatment.

Hepatitis

Of the many forms of hepatitis to which the traveller is at risk, the most likely is viral. Hepatitis A and hepatitis E are transmitted by the faecal-oral route and have an incubation of 2–6 weeks. Although generally self-limiting, hepatitis A has a case-fatality rate of up to 2% in patients older than 40 years, and hepatitis E contracted in pregnancy has a maternal mortality rate of nearly 40%.[29] Viral hepatitis transmitted by body fluids (via sexual contact, unclean medical equipment, blood, body piercing, intravenous drug use, acupuncture) is most probably type B or C.

Panel 5: **Differential diagnosis of physical findings for some travel diseases**

Lymphadenopathy	● Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, lymphogranuloma venereum, Lassa fever
Hepatomegaly	● Malaria, leishmaniasis, amoebic liver abscess, typhoid, hepatitis, leptospirosis
Splenomegaly	● Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue
Jaundice	● Hepatitis, malaria, leptospirosis, relapsing fevers, cholelithiasis, pancreatitis
Abdominal tenderness	● *Yersinia enterocolitica*, colonic ameboma, anisakiasis, hepatitis, clonorchis or opisthorchis biliary obstruction
Petechiae/ecchymosis	● Meningococcaemia, yellow fever, dengue, rickettsioses, viral haemorrhagic fevers, envenoming
Ataxia/paresis/paraesthesia	● Rabies, toxic seafood ingestion, envenoming, neurocysticercosis, neuroschistosomiasis
Nystagmus/diplopia	● Rabies, botulinum poisoning, neurotoxic snakebite envenoming
Wheezing	● Loeffler's syndrome, Katayama fever, tropical pulmonary eosinophilia
Rash/eschars	● See panel 9
Fever	● See panel 6

Panel 6: **Frequency of fever and diagnosis in four published series of returned travellers**

	MacLean (n=587)	Doherty (n=195)	O'Brien (n=587)	Hill (n=822)
Diagnosis	**Frequency of fever (%)**			
Malaria	32	42	27	2
Unknown	25	25	9	8
Hepatitis	6	3	3	2
Respiratory*	11	2·5	24	24
Urinary tract	4	2·5	2	0
Dengue	2	6	8	1
Enteric fever	2	2	3	0
Diarrhoeal disease	4·5	6·5	14	31
Infectious mononucleosis	2	0·5	0·4	0
Pharyngitis	1	2	0	†
Rickettsia	1	0·5	2	1
Amoebic liver abscess	1	0	0	0
Tuberculosis	1	2	1	0
Meningitis	1	1	1	0
Acute HIV	0·3	1	0·4	0
Miscellaneous	6·3	5	5·2	33

*Respiratory includes upper respiratory infection, bronchitis, and pneumonia. †Included in respiratory. Adapted from: MacLean JD, Lalonde R, Ward B. Fever from the tropics. *Travel Med Advisor* 1994; **5:** 27.1–27.14. Doherty JF, Grant AD, Bryceson AD. Fever as the presenting complaint of travellers returning from the tropics. *QJM* 1995; **88:** 277–81. 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:** 603–09. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Trav Med* 2000; **7:** 259–66.

These hepatitides have incubation periods ranging from 6 weeks to 6 months and can result in a chronic carrier state with the potential for developing hepatocellular carcinoma.

Leptospirosis

Leptospirosis, an infection with a bacterial spirochete, is common in the tropics and is becoming more readily recognised as a cause of illness in travellers.[30,31] Any contact with freshwater contaminated with the urine of infected animals (rodents, dogs, cattle, people) can lead to leptospirosis. Contact can happen while bathing, swimming, or wading in freshwater creeks, lagoons, rivers, ponds, or lakes; hiking in mud; or drinking contaminated water. After exposure, there is an incubation period of 1–3 weeks, followed by fever, chills, headache, nausea, vomiting, myalgias, and conjunctival suffusion lasting up to 1 week. The fever can abate for several days and, in 5–10% of cases, a second more serious phase develops, known as Weil's disease, which can include hepatic damage with jaundice, renal failure, meningitis, adult respiratory distress syndrome, and pulmonary haemorrhage.[32] This second phase can last from a few days to 4 weeks, during which time bacteria disappear from the blood and cerebrospinal fluid. Diagnosis is made in the initial period by examining blood and cerebrospinal fluid in the first week; after 10 days, leptospires can be found in urine. The most reliable serological test is the microscopic agglutination test (MAT).[5]

Dengue and other arbovirus infections

Arbovirus infections are the main cause of viral fevers in returned travellers, and tend to have short incubation periods, typically less than 2 weeks. Dengue fever, the most common such infection in travellers, is transmitted by *Aedes* mosquitoes, which tend to be urban and to bite during the day.[33–35] Dengue fever is present in and increasing throughout the tropics. Other causes of viral fevers include Chikungunya fever, West Nile virus, tick-borne encephalitis, Rift Valley fever, Japanese encephalitis, and yellow fever. Most arbovirus infections have non-specific symptoms such as fever, chills, myalgia, malaise, arthralgia, headache (notably retro-orbital as in dengue), diaphoresis, and rash. There may be a transient improvement in symptoms before a second stage sets in with exacerbation or worsening of illness; in dengue this typically happens during days 3–5, when the maculopapular rash (which may even resemble sunburn) classically arises. Dengue infection can be a worse illness on re-exposure to dengue virus, in particular if the second infection is with a different serotype, which can lead to dengue haemorrhagic fever or dengue shock syndrome. Dengue haemorrhagic fever is defined as dengue fever with haemorrhagic manifestations, thrombocytopenia (platelet count $\leqslant 100\times10^9$/L), and objective evidence of increased capillary permeability such as haemoconcentration, pleural effusions, or hypoalbuminaemia; in addition, dengue shock syndrome causes hypotension or a narrowed pulse pressure.[36] These illnesses are unlikely in first-time travellers, and are typically most severe in children. Diagnosis is made clinically and confirmed with virus isolation, dengue virus antigens, increased antidengue IgM antibodies, or a four-fold increase in IgG from paired acute and convalescent serum samples.[5]

Several other viral infections can lead to haemorrhagic conditions, such as Ebola and Marburg, but these are rare in travellers. Lassa fever, Rift Valley fever, and Congo-Crimean haemorrhagic fever have been acquired by

Panel 7: **Malaria risk for 1 month of travel without chemoprophylaxis**

Oceania	1:5
Africa	1:50
South Asia	1:250
Southeast Asia	1:2500
South America	1:5000
Mexico and Central America	1:10 000

Adapted from: Steffen R, Lobel HO. Epidemiological basis for the practice of travel medicine. *J Wilderness Med* 1994; **1:** 56–66. Steffen R, Jong EC. Travelers' and immigrants' health. In: Guerrant RL, Walker DH, Wyler PF, eds. Tropical infectious diseases: principles, pathogens and practice. Philadelphia: Churchill-Livingstone, 1999: 106–14. Hill DR, Behrens RH, Bradley DJ. The risk of malaria in travellers to Thailand. *Trans R Soc Trop Med Hyg* 1996; **90:** 680–81. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared to doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 963–72.

Panel 8: **Malaria imported into UK 1991–2000**

Year	Total cases	Falciparum	Non-falciparum	Deaths
1991	2332	1314	1018	12
1992	1629	935	694	11
1993	1922	1048	874	5
1994	1887	1178	709	11
1995	2055	1112	943	4
1996	2500	1283	1217	11
1997	2364	1401	963	13
1998	2073	1388	685	7
1999	2045	1504	541	14
2000	2069	1576	493	16
Total	20 876	10 559	10 317	104

Source: Bradley DJ. Data from the PHLS Malaria Reference Laboratory, 2002 (personal communication).

travellers to Africa and the Middle East.[37–42] There have been several cases of yellow fever in tourists; lack of vaccination was common to all.[43–45]

Rickettsial infections

Several rickettsial infections can affect travellers and can be divided into three general categories: the spotted-fever group, the typhus group, and Q fever. In the spotted-fever group are tick-borne typhus (*Rickettsia africae* and *Rickettsia conorii*), Rocky Mountain spotted fever (*Rickettsia rickettsii*), Queensland tick typhus (*Rickettsia australis*), north Asian tick typhus (*Rickettsia sibirica*), and rickettsialpox (*Rickettsia akari*). Tick typhus, also known as Boutonneuse fever, Mediterranean spotted fever, or African tick typhus is typically acquired in southern Africa, the Mediterranean littoral, or south Asia and is the most common rickettsial infection in travellers.[46–48] The typhus group includes louse-borne epidemic typhus (*Rickettsia prowazeki*), murine typhus (*Rickettsia typhi*) and scrub typhus (*Rickettsia tsutsugamushi*). Q fever (*Coxiella burnetii*) is not typically spread by vector bites; transmission is usually through inhalation or ingestion of unpasteurised dairy products. Rickettsial infections are an under-reported infection in travellers and are more common than expected.[46]

Rickettsial illnesses typically have an incubation period of 1–2 weeks (shorter end of the range with tick typhus and the longer end of the range with scrub typhus) and share many clinical features. Most rickettsial infections have an acute presentation and are self-limiting but can be quite severe or even fatal, especially those in the spotted-fever group, scrub typhus, and epidemic typhus. These infections often begin with continuous fever lasting several days concurrent with myalgias, arthralgias, headache, and malaise. Up to a third of patients can present with diarrhoea.[47] An eschar might develop at the site of the bite, which can persist for 1–2 weeks, but its absence does not exclude rickettsial infection and most travellers do not recall being bitten.[47,48] 5–6 days after fever onset a rash develops which is typically macular or maculopapular. Lymphadenopathy is common and the disease can persist for 2 weeks. A few patients develop hepatosplenomegaly. With scrub typhus, dizziness and pleural or pericardial effusions can develop, but this infection is not common in travellers.[47,49] Q fever does not typically cause a rash, but has many presentations and should be considered if pneumonia or hepatitis is present. Screening spotted fever or Weil-Felix tests, which are non-specific, should indicate these infections, and diagnosis may be made with confirmed serological testing.

Diarrhoea

Diarrhea is the most common illness to affect travellers.[3,50,51] By contrast with the generally low risk (less than 10%) in travellers to northern and central Europe, North America, Japan, and Australasia, the risk to travellers elsewhere ranges from medium (15–20%), for example in Russia, South Africa, and China to high (>20%) in Latin America, the rest of Africa, south Asia, and the Middle East.[52–56] The main causes are bacteria, viruses, parasites, and toxins and the risk of at least one attack of diarrhoea in a 2-week trip is 50%.[51,57] However, the cause will be unknown in 20–50% of cases.[58] Diarrhoea can be due to direct effects on the gut or damage left despite the cause no longer being present. Damage can lead to malabsorption or can indicate an underlying gastrointestinal disorder such as inflammatory bowel disease, irritable bowel syndrome, colon cancer, tropical sprue, or small bowel overgrowth.[59–61] Inflammatory bowel disease such as ulcerative colitis may be indistinguishable from amoebic or postdysenteric colitis. Traveller's diarrhoea can have other consequences: for example, shigella infection can cause Reiter's syndrome and campylobacter infections can induce Guillain-Barré syndrome.[51,62] Travellers who have had diarrhoea during their journeys might be vulnerable to complications or diseases for which they were taking drugs such as antimalarials, antiepileptics, antidiabetic drugs, anticoagulants, and contraceptives—all of which will be poorly absorbed during diarrhoea.

In assessment of the traveller with diarrhoea, it is helpful to divide the condition into acute or chronic types, with chronic defined as persisting for more than 14 days.[63] Acute diarrhoea is typically due to bacteria and viruses, but can also be caused by parasites. It is defined as three or more loose or water stools in 24 h.[64] Most cases of traveller's diarrhoea are self-limiting, last only a few days, and typically occur at the beginning of a trip.[51,65] Most cases of acute traveller's diarrhoea are due to bacteria, mainly *Escherichia coli*, salmonella, shigella, *Campylobacter jejuni*, *Vibrio parahaemolyticus*, *Bacillus cereus* (especially associated with rice), *Staphylococcus aureus*, and clostridia.[50,66] *Legionella pneumophila* infections are also noted for presenting with diarrhoea and *Yersinia enterocolitica* infection can mimic acute appendicitis.[67] *Vibrio cholerae* infection is not commonly seen in travellers, although in 1992, 75 passengers on an airliner from South America to Los Angeles contracted cholera from contaminated seafood served during the flight.[68] Many travellers self-treat for acute diarrhoea during their journeys, and if the diarrhoea persists or recurs, the organism could have been resistant to antibiotics or was a parasite.[57,69] *C jejuni* resistance to fluoroquinolones has become a concern, in particular for travellers visiting southeast Asia; resistance rates in Thailand are nearly 80%.[69] In cases where there is blood, fever, or mucus in the diarrhoea the illness is defined as dysentery, in which the mucosal lining of the intestines is invaded. Organisms likely to cause dysentery are shigella, salmonella, campylobacter, *Entamoeba histolytica*, or *Balantidium coli*. Associated findings can include lower abdominal pain, fever, nausea, vomiting, tenesmus, and dehydration that can be significant. Intestinal malabsorption can present after acute traveller's diarrhoea or dysentery, and although generally self-limiting, can persist for several months after the initial infection.[70] It should be remembered that malaria can occasionally present with diarrhoea. The viral agents that most commonly cause acute traveller's diarrhoea are hepatitis A, Norwalk, rotavirus, adenovirus, enterovirus (which includes poliomyelitis), caliciviruses, and astro-

Panel 9: Skin lesions—descriptions and differential diagnosis

Maculopapular	● Drug reaction, dengue, acute HIV, rickettsia, syphilis, leptospirosis, brucellosis, typhus, bartonellosis, typhoid, rubeola, rubella, scarlet fever, insect bites, cercarial dermatitis, seabather's eruption, eczema, tungiasis, myiasis, scabies, arthropod bites, miliaria rubra
Papulosquamous	● Superficial mycoses or exacerbations of eczema or psoriasis
Petechial/ecchymoses	● Rickettsia, meningococcaemia, yellow fever, viral haemorrhagic fevers, dengue, leptospirosis
Vesicular	● Varicella, herpes simplex, drug reactions, sunburn, photodermatitis
Erythaema migrans	● Lyme
Eschar	● Typhus, anthrax, African trypanosomiasis, Congo-Crimean haemorrhagic fever, tularaemia, spider bites
Nodules	● Onchocerciasis, bartonellosis, myiasis, paracoccidioidomycosis
Ulcers	● Leishmaniasis, tropical ulcers, anthrax, tularaemia, cutaneous diphtheria, ecthyma, syphilis, yaws, tuberculosis, granulomas inguinale, lymphogranuloma venereum, plague, arthropod bite (eg, brown recluse spider)
Urticaria	● Drug reactions, filariasis, onchocerciasis, cutaneous larva migrans, larva currens (strongyloidiasis), acute schistosomiasis, fascioliasis, hymenoptera stings, insect bites, enterobiasis, gnathostomiasis, scabies, cercarial dermatitis, seabather's eruption, nematocyst stings
Swelling/oedema	● Loa loa calabar swellings, trichinosis (especially facial/periorbital)
Migrating	● Cutaneous larva migrans, larva currens, gnathostomiasis, loiasis, myiasis, paragonimiasis sparganosis
Hypopigmentation	● Tinea (pityriasis) versicolour, tinea corporis, leprosy, vitiligo
Vegetation/verrucae	● Bartonellosis, histoplasmosis, leishmaniasis, maduromycosis, paracoccidioidomycosis, pinta, syphilis, tuberculosis, yaws
Linear	● Photodermatitis, cutaneous larva migrans, gnathostomiasis, larva currens, flea bites, *M marinarum*, sporotrichosis, nematocyst stings, lymphangitis

viruses.[50,65] Worms are not a common cause of illness; most cases of intestinal helminthiasis acquired during travel are asymptomatic.[71]

Although acute diarrhoea is more common, chronic diarrhoea is the more likely reason for a traveller to seek medical care. Up to 28% of cases of traveller's diarrhoea last longer than 2 weeks and 3% more than 30 days.[4,52,65] Some cases of chronic diarrhoea are simply due to slow resolution of an acute infection, such as from *Campylobacter* spp, *Yersinia* spp, or enteroadherent *E coli*, although others can be due to emerging infections or are truly idiopathic.[63,72] Additionally, diarrhoea can result from antibiotic use, such as with prolonged doxycycline treatment for the prevention of malaria with the development of *Clostridium difficile* pseudomembranous enterocolitis. Practitioners should inquire whether the traveller had a case of acute traveller's diarrhoea during the journey, and if it was treated, with which antibiotic and for how long. Parasites such as *Giardia* spp, *E histolytica*, *Cryptosporidium* spp, *Cyclospora* spp, and *Isospora* spp commonly cause persistent diarrhoea and occur in up to 22% of travellers with diarrhoea.[50] Giardiasis is the most common protozoal infection in returning travellers and typically presents after a 1–2-week incubation period with a wide range of illness, from asymptomatic or vague intestinal discomfort to a severe illness with intermittent soft foul-smelling stools, foul-smelling flatus or eructation, weight loss, malabsorption, lactose intolerance, abdominal distension, and fatigue.[65] Cyclosporiasis is an increasingly common infection presenting with a very similar pattern to giardiasis and has been contracted in less-developed and developed nations, including those in North America. Another parasite that presents with a similar pattern, *Cryptosporidium* spp, can cause chronic and even fatal diarrhoea in immuno-compromised people. Chronic malabsorption can also be due to helminthic species such as *Strongyloides* spp, *Ascaris* spp, and *Capillaria* spp. Practitioners should be cautious if attributing diarrhoea to amoebae found in stool samples, since *E histolytica* is morphologically indistinguishable from *Entamoeba dispar* and other causes are more likely. Complications of chronic amoebiasis include fulminant colitis, toxic megacolon, strictures, intestinal perforation, and amoebic granuloma. Amoebic liver abscesses can also develop and should be considered if there is right-upper quadrant pain, fever, and possible referred pain to the right shoulder. Interestingly, fewer than 20% of patients with amoebic liver abscess have parasites detectable in the stool, yet 90% of patients with invasive disease will have anti-amoebic antibody production.[73]

Diarrhoea can also be caused by toxins in food, especially fish and shellfish. Ciguatera poisoning occurs after the ingestion of reef fish (grouper, snapper, coral trout, barracuda, etc) contaminated with dinoflagellate *Gambierdiscus* spp, but there is no clinical diagnostic test for ciguatoxin. Scombroid poisoning, which occurs with the ingestion of pelagic fish (tuna, albacore, mackerel, bonito, mahi-mahi, sardine, etc), is due to histidine in the fish flesh as a result of poor preservation, and leads to a histamine-like reaction with urticaria, pruritus, and diarrhoea.

Interviews with returned travellers with diarrhoea should include several topics: types of meals eaten and where they were consumed; the frequency, appearance, consistency, and odour of stools; whether the traveller noted blood or mucus; tenesmus, fevers, chills, nausea, or vomiting; abdominal pain as opposed to cramps; bloating or distension; flatulence or eructation, especially if malodorous; fatigue; weight loss; appetite; and heartburn. The season of travel is also important and often directly related to the degree of risk of contracting pathogens.[65]

In general, returning travellers with diarrhoea should have blood tests for liver function, a complete blood count, and analysis of serum chemistry. Stool samples, fresh and stained specimens, should be examined by microscope for ova, parasites (with at least three samples, ideally obtained on 3 separate days), and white blood cells and cultured for pathogenic organisms. If the traveller has been on antibiotics, stool samples should also be cultured for *C difficile* and tested for its antigens. Further testing will vary with the severity and duration of diarrhoea.

Skin

Skin disorders are fairly common, useful in assessment of returned ill travellers, and can result from infections, environmental factors, and envenoming.[74] The most common skin disorders are infected insect bites, myiasis, tungiasis, urticaria, fever with rash, tinea, cutaneous larva migrans, and leishmaniasis.[75,76]

Lesions can be maculopapular, pustular, ulcerative, pruritic, vesicular, nodular, or petechial (panel 9). Papulosquamous lesions are most commonly due to superficial mycoses or exacerbations of eczema or psoriasis.[75] Petechial lesions suggest rickettsia, meningococcaemia, or viral haemorrhagic fevers and tend to indicate more serious illness than papulosquamous types. Vesicular lesions can indicate viral infections such as varicella, herpes simplex, or drug reactions, which are common causes of skin lesions in travellers. Eschars are typically associated with anthrax, African trypanosomiasis, tularaemia, spider bites, and rickettsial infections such as typhus. Skin ulcers occur in leishmaniasis, tropical ulcers, anthrax, and certain spider bites. With spider bites the lesion is often painful, whereas with anthrax the ulcer is typically painless. Leishmaniasis, contracted from the bite of sandflies, is an increasing risk worldwide, and in travellers one is most likely to see cutaneous leishmaniasis rather than mucocutaneous or visceral leishmaniasis (kala-azar).[77] Impetigo, cellulitis, and abscesses due to bacterial infection are more common in tropical than in temperate climates.[76]

Cutaneous larva migrans, better known as creeping eruption, is typically caused by dog and cat hookworm larvae (also *Strongyloides* spp and *Gnathostoma* spp) in soil, which penetrate skin and migrate in confusion, since the organism does not recognise human beings as a host species. The incubation period ranges from a few days to several months.[78] Serpiginous tracks that are intensely pruritic are typically found where larvae usually enter on the feet, buttocks, and thighs.[78] Symptoms can last from weeks to months.[79] Cutaneous myiasis, an infestation in skin by fly larvae, is an increasing problem in travellers:[74,80] in tropical parts of the Americas it is due to *Dermatobia hominis* (bot fly) eggs deposited by mosquitoes; in tropical Africa to *Cordylobia anthropophaga* (tumbu fly) laying eggs on clothing, then hatched larvae placed against the skin burrow inwards. As the larvae mature in the skin, they cause furuncle-like lesions that are pruritic and can be painful. Tungiasis is a painful infestation of the epidermis by the sand flea, *Tunga penetrans*, and is typically located on the toes and feet.

Respiratory illnesses

Possible causes of respiratory problems in travellers include viral upper respiratory infections, bronchitis, viral and bacterial pneumonia, followed by uncommon causes such as tuberculosis, Loeffler's syndrome (acute ascariasis or strongyloidiasis), paragonimiasis, Q fever, tropical pulmonary eosinophilia, coccidioidomycosis, legionella, and melioidosis. Melioidosis, which is most common in southeast Asia, can readily be mistaken for tuberculosis. Most of these pulmonary conditions will present with fever at some point. There is a high association between travel and Legionnaires' disease, and many travel-acquired cases have occurred within Europe.[81] The patterns for influenza transmission are opposite in the northern and southern hemispheres, so a returning traveller who has been on the other side of the planet can return ill with this virus, despite it not being the local influenza season.

The incidence of tuberculosis infection in travellers is unknown, but might be as high as for residents of endemic regions for travel of greater than 1 month duration, especially in high-risk destinations.[82] Cases of tuberculosis have also been acquired from long flights.[83] In general, however, tuberculosis is not a common cause of illness in returning travellers.

Neurological illnesses

There are many causes for neurological conditions in returning travellers. Meningococcal meningitis, which occurs regularly in sub-Saharan Africa, can present with a similar clinical picture to enteroviral meningitis, cerebral malaria, leptospirosis, typhoid fever, rickettsial infection, Japanese encephalitis, or tick-borne encephalitis. Nearly all cases of meningococcal meningitis are due to five *Neisseria meningitidis* serotypes with an incubation period of 2–10 days: A, B, C, W-135, and Y. Pre-travel immunisation against *N meningitides* does not rule out infection, since the quadrivalent vaccine does not cover the B strain. If this infection is suspected it should be considered an emergency since it has a 5–10% case-fatality rate, even with antibiotic treatment.[84] Poliomyelitis is a threat in south Asia and parts of Africa. Other neurological conditions can result from HIV infection, African trypanosomiasis, rabies, spinal schistosomiasis, Lyme disease, toxoplasmosis, arbovirus infection, *Cryptococcus* spp, neurocysticercosis, bartonellosis, brucellosis, listeriosis, *Naegleria* spp, paragonimiasis, gnathostomiasis, angiostrongyliasis, decompression illness from scuba diving, and ciguatera and other seafood toxins.

Sexually transmitted diseases

Some travellers have unplanned sexual intercourse, and often engage in risky behaviour, notably failing to use condoms.[85–88] Sexually transmitted diseases may or may not have symptoms directly related to genitalia: gonorrhoea, chlamydia, primary syphilis, and herpes simplex are fairly easy to identify; however, hepatitis B, hepatitis C, HIV, and late-stage syphilis infections might be less obvious. Travellers are associated with the spread of HIV infection and other sexually transmitted diseases across borders. Furthermore, antibiotic resistance of venereal organisms is increasing and can complicate treatment.[89]

Less common infections

Rare, but important, potential causes of fever in travellers include schistosomiasis and African trypanosomiasis. Schistosomiasis, also known as bilharzia, is a parasitic infection resulting from contact with freshwater and is increasingly seen in returning travellers.[90,91] It is widespread throughout the tropics, but is most prevalent in Africa.[92,93] There tend to be four stages to infection. The first stage is dermatitis, usually a pruritic papular rash, arising from penetration of cercariae. The second, acute stage occurs 4–6 weeks later, and is known as Katayama fever, with fever, lethargy, myalgias, arthralgias, non-specific pulmonary symptoms, diarrhoea, headaches, and anorexia. The physical signs of a patient at this point are typically not specific, but can include wheezing, cough, and mild hepatosplenomegaly. Acute Katayama fever presents in only a few infected travellers, but can be incapacitating and be mistaken for malaria.[90] Once the infection becomes patent, in the third stage, beginning 4–8 weeks later, fever is not a notable feature of the illness, and many patients are asymptomatic. This period is when eggs become present in stool or urine. Terminal haematuria is a classic sign of infection with *Schistosoma haematobium*, and occurs at this point. The fourth stage is when complications from

Panel 10: **Initial laboratory investigations**

General
- Complete blood count to include platelets and microscopy
- Glucose-6-phosphate dehydrogenase level if primaquine therapy for malaria may be needed
- Blood films for malaria; repeat every 12 h up to three if previous films negative; attempt to obtain blood samples during fever. Tests should include both thick and thin giemsa-stained blood smears
- Liver function tests and electrolytes
- Urine analysis and culture as indicated; urine microscopy for *S haematobium* eggs
- Culture: blood, urine, sputum, stool, cerebrospinal fluid, lesions as indicated
- Serologies: amoebae, schistosomes, arboviruses, hepatitis (be cautious about interpreting serologies not done at the appropriate time. Also, helminthic serologies are not standardised, and there is a cross-reactivity between helminths. Furthermore, one cannot distinguish between a current versus past infection in frequent travellers or expatriates)
- Sputum microscopy as indicated
- Lumbar puncture as indicated
- Tuberculosis skin testing and follow-up radiograph as necessary
- Biopsies of lesions or of bone marrow, especially if suspected typhoid, leishmaniasis, or tuberculosis
- Radiographic tests such as radiograph, ultrasonography, computed radiography, or MRI. Radiographs useful with tuberculosis and other pulmonary infections including paragonimus and trichinosis and cysticercosis whose calcified cysts can be visualised on soft-tissue films; ultrasonography is useful for abscesses, especially amoebic liver abscess and echinococcal cysts

For diarrhoea
- Stool microscopy: fresh, with iodine, acid-fast and trichome or iron-haematoxylin stains
- Stool haemoccult
- Stool culture and sensitivity for enteric pathogens
- Stool serology for giardia antigens as well as *C difficile* antigen. Blood tests should also include complete blood count with a differential, amoebic serology and chemistries. Urine can be tested for D-xylose
- In cases of chronic diarrhoea, consider a lactose tolerance test or a Schilling test with intrinsic factor
- Endoscopy with biopsy and duodenal aspirate or colonoscopy with biopsies and cultures should follow if initial testing in non-diagnostic; also consider ultrasonography, computerised or magnetic imaging studies as well

Less common tests
- Day and night blood concentrations for filarial blood smears
- Skin snips for onchocerciasis
- Rectal snips for schistosomiasis
- Urine concentration for schistosomiasis
- Sputum for ova and parasites in suspect paragonimiasis and migrating larvae

the chronic infection arise, such as portal hypertension with *S mansoni* or bladder cancer with *S haematobium*. Complications from ectopic egg deposition can be substantial and unexpected, as with spinal schistosomiasis. There is also an association between schistosomiasis and chronic salmonellosis.[92] Eosinophilia is a reliable sign during acute infections, but diagnosis is best confirmed by finding eggs in urine or stool samples (but low egg count is quite likely during the acute stage),[93] or in biopsy samples of rectum, bladder, or liver. ELISA testing might also be helpful in making the diagnosis, but seroconversion can take as long as 1·6 months.[90]

Sleeping sickness occurs only in Africa. There are two forms of infection with protozoal haemoflagellates causing African trypanosomiasis: the chronic and indolent Gambian version due to *Trypanosoma brucei gambiense* in west and central Africa; and the more acute and aggressive form caused by *Trypanosoma brucei rhodesiense*, found in east and southern Africa. The only country in which both types of disease exist is Uganda. Travellers are most likely to be exposed while on safari in East Africa.[94–96] The incubation period ranges from 1 to 4 weeks, with about 80% of patients noting symptom onset within 14 days of a tsetse fly bite.[95] Initially, there is an eschar at the bite site, followed by fever, headache, malaise, lethargy, and an evanescent rash. As the infection progresses, parasites enter the central nervous system and can result in confusion, altered mental and psychological states, and coma. There does not seem to be any increased susceptibility or worsening clinical illness in AIDS patients.[97] The diagnosis is confirmed with motile trypanosomes in the blood on fresh specimens or giemsa-stained blood or cerebrospinal fluid.

Laboratory investigations

Panel 10 lists useful tests for investigating illness in returned travellers. Many tests, especially those entailing microscopy, are reliant on the expertise of the individual laboratory, and thus reference laboratories should be used whenever possible. Eosinophilia in returning travellers is most likely to be a helminthic infection, followed by allergy or drug reaction.[98] Raised eosinophil counts are commonly associated with migrating larvae through tissue, but the degree of eosinophilia will decrease with prolonged time of infection. Eosinophilia can result from helminthic invasion despite a negative stool sample test until the infection becomes patently established.[99] Although blood eosinophilia has a high correlation with helminthic infection in the returning traveller, helminthic infections often occur without eosinophilia.[98]

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None declared.

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