

INFECTIOUS DISEASES

— *tropical diseases seen in UK hospitals*

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As greater numbers of people travel to more exotic locations on holiday or for work, the incidence and range of tropical diseases seen in the UK increases. This article covers some of the more commonly seen diseases

TONY CRADDOCK/SPL

Beach at sunset: increased travel to exotic locations means that more tropical diseases are seen in UK hospitals

Tropical diseases seen in UK hospitals are on the rise as a result of increased travel to more exotic locations. Malaria, typhoid, leishmaniasis, leprosy, amoebiasis and schistosomiasis will be covered in this article. There are many other parasitic infections that may be seen in returning travellers which have not been discussed in this article such as tapeworm, giardia, microfilarial infection, trypanosomiasis, cutaneous larva migrans, cysticercosis, hydatid disease, viral haemorrhagic fevers and strongyloides, most of which are rarely imported into the UK and patients will mostly present to specialist centres.

■ MALARIA

Malaria is a serious and sometimes fatal parasitic disease. There are four types of malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.

The World Health Organization estimates that 300–500 million cases of malaria occur and more than one million people die from the disease each year. Most cases in the UK are in immigrants and travellers returning from malaria-risk areas, mostly sub-Saharan

Africa and the Indian subcontinent. There have been no reported cases of UK infection occurring. In 2003 there were a total of 1,722 cases of malaria in the UK — 1,339 of which were the most lethal form, known as *Plasmodium falciparum*. Deaths as a result of malaria in the UK rose to 16 in 2003 from nine in 2002.¹

Malaria infection is spread by the infected female Anopheles mosquito when the parasites are transferred from the salivary glands of the mosquito to the human who has been bitten. Incubation and replication occur in the liver cells of the human host which in turn release the merozoite phase of the malaria lifecycle into the blood stream where the red blood cells become infected. Mature gametocytes are found in the blood stream and are then transferred back to the mosquito host when an infected human is bitten to complete the lifecycle. It is the blood phases of the lifecycle which cause symptoms of disease.

Locally at the Hospital for Tropical Diseases it is recommended that all patients with *Plasmodium falciparum* malaria are admitted for treatment. This is because many complications can occur even if the patient seems relatively well and has a low parasitaemia. The complications which can result from malaria infection are thrombocytopenia leading to bleeding and disseminated intravascular coagulation, anaemia, jaundice, acute renal failure, hypoglycaemia, cerebral involvement with confusion, convulsions

and coma, and pulmonary oedema. Anaemia, thrombocytopenia and raised liver function tests are frequently seen in many patients due to haemolysis of the malaria infected red blood cells.

Plasmodium vivax and *Plasmodium ovale* have dormant liver phases of their lifecycle which can cause relapse of disease. This is why primaquine is given following chloroquine to eradicate the liver phases and prevent relapse.

There is an incubation period of seven to 30 days from exposure to the first appearance of symptoms. A shorter period of incubation is more likely with *Plasmodium falciparum* and longer with *Plasmodium malariae*. If someone has taken prophylactic antimalarial drugs the onset of symptoms may be delayed further by weeks or months, especially with the dormant liver phases of *Plasmodium ovale* and *Plasmodium vivax*. It is important that malaria is not dismissed as a potential diagnosis for up to one year after someone has returned from an endemic area.

Signs and symptoms Symptoms in the early stages of malaria can be similar to those of many other illnesses caused by bacterial, viral or parasitic infections. Common symptoms are listed in Panel 1 (p 273).

Symptoms may appear in cycles and may come and go at different intensities and for varying periods. However, especially at the beginning of the illness, the symptoms may

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Panel 1: Common signs and symptoms of malaria

- Fever
- Chills
- Headache
- Sweats
- Fatigue
- Nausea and vomiting

These may occur in cycles due to the malaria parasite life cycle

not follow this typical cyclical pattern. The cyclical pattern of symptoms is due to the life cycle of the malaria parasites as they develop, reproduce and are released from the red blood cells and liver cells in the human body. Cyclical symptoms are also one of the common indicators that someone has malaria. Other symptoms may include a dry (non-productive) cough, muscle and back pain, an enlarged spleen and, rarely, reduced consciousness or seizures.

Diagnosis of malaria infection is by examination of a blood film for the presence of malaria parasites inside red blood cells. Quantification is possible in *Plasmodium falciparum* infection by counting the number of red blood cells containing malaria parasites. This is expressed as a percentage to indicate the proportion of cells infected.

Treatment It is important that two drugs are used to treat most types of malaria in order to ensure that all phases of the life cycle are removed, thus reducing the risk of relapse. When assessing the efficacy of malaria treatment it is not possible to detect any of the liver forms of the life cycle, only those which are present in the bloodstream.

First-line treatment for *Plasmodium falciparum* malaria remains quinine, unless this is contraindicated or the patient has returned from an area where quinine resistance is likely such as South East Asia. In such cases one of the alternative agents such as proguanil/atovaquone (Malarone) or artemether (sometimes in combination with lumefantrine) would be more appropriate. Artemether is unlicensed in the UK, but is available by importation. Quinine is continued until a negative blood film is obtained, which is frequently between three and five days.

Plasmodium vivax, *Plasmodium ovale* and *Plasmodium malariae* remain more sensitive to chloroquine than *Plasmodium falciparum* and can still be treated with this drug first-line. The liver phases of the life cycle may stay dormant for many months and the relapse rate is high if the chloroquine is not followed by a second drug such as primaquine. Panel 2 summarises the drug treatment of malaria in adults.

Panel 2: The treatment of malaria in adults

Plasmodium falciparum:

Quinine	po	600mg three times a day for a minimum of 3 days (or 10mg/kg [maximum 600mg] three times a day)
	iv	Loading dose (if parasitaemia >5%) 20mg/kg (max 1,400mg) then 10mg/kg every 8–12 hours (max 700mg). Switch to oral therapy as soon as possible (if parasitaemia <2%)

Followed by one of the following when blood film is negative:

Fansidar 3 tablets (one-off dose) or doxycycline 100mg daily for 7 days

Alternatives (especially where quinine resistance is suspected):

Proguanil/atovaquone	po	4 tablets daily for 3 days
Artemether/lumefantrine	po	4 tablets at 0, 8, 24, 36, 48, 60 hours
Artemether	po	200mg daily for 3 days
	im	3.2mg/kg loading dose, followed by 1.6mg/kg daily until parasitaemia is negative, usually 3–5 days followed by mefloquine 500mg for 2 doses (6–8 hours apart)

Plasmodium vivax, *Plasmodium ovale*, *Plasmodium malariae*:

Chloroquine	po	600mg (one-off dose), followed by 300mg after 6 hours and repeated at 24 and 48 hours
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Followed by:

<i>Plasmodium vivax</i>	po	primaquine 15mg twice a day for 2 weeks
<i>Plasmodium ovale</i>	po	primaquine 15mg daily for 2 weeks
<i>Plasmodium malariae</i>		no second drug required

Prevention Prophylactic agents such as chloroquine and proguanil, mefloquine, doxycycline and proguanil/atovaquone are recommended for people travelling to malarious areas. Recommendations are regularly altered therefore it is important that the most up-to-date information is given when requested. Malaria prophylaxis should be commenced at least one week before departure and continued for four weeks after return, except for proguanil/atovaquone, for which a shorter duration is necessary.

— TYPHOID

Typoid infection is caused by the *Salmonella typhi* and *Salmonella paratyphi* bacteria. It is not truly a tropical disease since some patients are infected outside the tropics, but is frequently seen in travellers returning from tropical areas of the world. Most areas of the developed world do not have a significant incidence of typhoid infection, but travellers in Asia and Africa have a significantly greater risk of infection.

It is a waterborne infection which can be spread in areas where there is poor hygiene and water purity. Some people can be carriers of the infection and may pass it to others via food preparation due to poor hand washing. It can also be excreted in the stool and then passed into the water system. *Salmonella enteritidis* and *Salmonella typhimurium* are other subtypes of salmonella infection which are commonly seen in the UK frequently causing food poisoning and diarrhoea.

Salmonella typhi and *Salmonella paratyphi* are ingested in drinking water or that used

to prepare food. Infection occurs if the bacteria penetrate through the intestinal mucosa into the bloodstream. The incubation period is usually 10–20 days. Diagnosis of typhoid fever is from stool or blood samples.

Incidence It is estimated that there are over 16 million cases of typhoid infection per year, with the majority being acquired in the Indian subcontinent. Approximately 3 per cent of those infected who do not receive treatment may pass bacteria in their stool for up to one year while remaining asymptomatic. Almost 300 cases of imported infection with *Salmonella typhi* and *Salmonella paratyphi* were reported to the UK Health Protection Agency in 2003.²

Signs and symptoms Persons with typhoid fever usually have a sustained fever as high as 39 to 40C. Signs and symptoms are summarised in Panel 3 (p 274)

Treatment The following antibiotics may be used to treat typhoid infection:³

- Ciprofloxacin
- Amoxicillin
- Chloramphenicol
- Co-trimoxazole
- Ceftriaxone and other third generation cephalosporins

The incidence of resistance to fluoroquinolones is increasing, especially in the Indian subcontinent. In some situations higher doses may be sufficient to treat the

Panel 3: Signs and symptoms of typhoid fever

- High fevers
- Abdominal pains
- Diarrhoea
- Muscular aches and pains
- Headache

infection, but much of the time a second-line antibiotic such as chloramphenicol, amoxicillin or co-trimoxazole is required. In these cases it is recommended that the duration of therapy should be increased from between five and seven days to at least 14 days.

Prevention Vaccination is recommended when travelling to an area where the incidence of typhoid is relatively high, but does not remove the need for good personal hygiene and avoiding using local tap water for drinking and food preparation. An alternative to bottled water is to boil the water before using.

LEISHMANIASIS

Leishmaniasis is a protozoal infection passed on in a similar manner to malaria. Its invertebrate host is the sandfly and it is transmitted to humans via a bite. Another name for leishmaniasis is "kala azar" or "black sickness".

Leishmaniasis is endemic in many countries of the world, but is most common in Mexico, South American countries, Bangladesh, India, Nepal and Sudan. There are over 350 million people worldwide in 88 different countries affected by this protozoal disease and its effects, with between one and two million cases reported annually.⁴ This may not be an accurate figure though as reporting is not obligatory in many countries. Epidemics of the disease occur occasionally, commonly affecting underdeveloped and impoverished countries and people.

There are two main forms of the disease: cutaneous and visceral. Almost all cases of cutaneous disease are from South American countries and most cases of visceral disease from the Indian subcontinent. People who live in or travel to these areas are at risk of contracting leishmaniasis, and the risk increases for those who are regularly outside at night time. Children are at a greater risk of infection, especially with visceral disease.

Visceral disease (*Leishmania donovani*, *Leishmania infantum*) The incubation period for visceral disease is between one and three months. This is the more severe form of the disease and affects the spleen, liver and lymph nodes. If left untreated mortality is between 75 and 95 per cent.

Panel 4: Drug treatment of leishmaniasis

Cutaneous disease:

Sodium stibogluconate	iv	20mg/kg/day x 21 days
Amphotericin B	iv	0.5-1mg/kg on alternate days for up to 8 weeks to a total dosage of 1.5-2g

Mucocutaneous disease is treated in the same way as cutaneous disease but a longer duration is usually needed

Visceral disease:

Liposomal amphotericin B	iv	3-4mg/kg daily on days 1-5, 10, 17, 24, 31, 38 (unlicensed dose). Duration may depend on immune status of patient
Pentamidine	iv	2-4mg/kg alternate days for 7 doses
Miltefosine	po	100mg daily for 28 days (Not available in UK)

Symptoms include periodic high fevers, weight loss, enlarged liver and spleen and anaemia with or without pancytopenia. It is more difficult to treat the visceral form of the disease, and relapse is common, particularly in immunocompromised patients.

The incidence of visceral disease is increasing in the HIV-infected population, especially in southern Europe where 25-70 per cent of cases are in co-infected patients.

Cutaneous disease (*Leishmania braziliensis*, *Leishmania tropicana*, *Leishmania mexicana*) The incubation period for cutaneous disease is normally 2-8 weeks after initial infection, but it can be longer. The bite will initially appear as a small raised red area which may become secondarily infected. This bite later begins to break down and form a crusted ulcer which is characteristic of the lesions.

Usually a single lesion occurs on the skin which may frequently be self-limiting, but can leave permanent scarring. After resolution of the lesions or completion of treatment, immunity is provided against reinfection. Multiple lesions are suggestive of diffuse cutaneous disease.

Mucocutaneous infection (*Leishmania braziliensis*) The mucocutaneous form of the disease can be disfiguring, especially if left untreated. Destructive lesions occur on the face, particularly around the mouth and nose area and can present in a similar distribution to facial nodular leprosy lesions. It is sometimes necessary for the patient to undergo reconstructive surgery as a result of partial facial destruction.

Treatment Sodium stibogluconate, Amphotericin B, pentamidine and miltefosine are all used in the treatment of leishmaniasis (see Panel 4).

Prevention Mosquito nets and insect repellent such as N,N-diethyl-meta-toluamide (DEET) are the only potential preventive measures currently available, although future developments may include a vaccine.

LEPROSY (HANSEN'S DISEASE)

Leprosy is a chronic granulomatous disease of the skin and peripheral nerves caused by the *Mycobacterium leprae* bacteria. It is a disease which has previously been associated with stigmatisation due to the physical deformities which can result from destruction of cartilage and nerve damage in affected patients. Only about 5 per cent of people infected with the bacteria go on to develop the disease and it may take four to eight years after infection before any symptoms are visible.

There are several subclassifications of leprosy: tuberculoid (paucibacillary), borderline tuberculoid (paucibacillary), borderline lepromatous (multibacillary) and lepromatous (multibacillary). Paucibacillary leprosy is the less severe form of the disease and patients have a lower bacterial load, fewer skin lesions but a more vigorous immune response to the *Mycobacterium leprae* bacteria. These patients would be smear negative. Multibacillary disease is associated with a higher bacterial burden requiring a longer duration of treatment, but a lower immune response to the disease. These patients are smear positive. Infection is thought to be spread by respiratory droplet inhalation or close skin contact.

Incidence In 2002, the number of new cases detected worldwide was 763,917. The World Health Organization listed Brazil, Madagascar, Mozambique, Tanzania, and Nepal as having 90 per cent of these cases. Leprosy now remains a major public health problem in only 10 countries of the world. There are approximately one to two million people worldwide who are permanently disabled as a result of leprosy.⁵

Symptoms Skin lesions may be single or multiple, and are usually less pigmented than the surrounding normal skin. Sometimes the lesion is reddish or copper-coloured. A variety of skin lesions may be seen but macules (flat), papules (raised), or nodules are common. Sensory loss is a typical feature of leprosy. The skin lesion may show loss of

sensation to pin prick or light touch. Thickened nerves constitute another feature of leprosy. A thickened nerve is often accompanied by other signs as a result of damage to the nerve. These may be loss of sensation in the skin and weakness of muscles supplied by the affected nerve.

Diagnosis Diagnosis is by slit skin smears (a small slit made in pinched skin, allowing the edges to be scraped) to assess the bacterial load. These are taken from skin in areas such as ear lobes, eyebrows, the edge of a lesion and the fingers. They should be taken from six different sites at one time and should be repeated annually to assess the effects of drug therapy. Patients are non-infectious when live bacteria are no longer detected.

Treatment Dapsone, rifampicin and clofazimine are used in the treatment of leprosy (see Panel 5, p 278).

Complications Irreversible peripheral neuritis leading to loss of feeling and sensation, or anaesthetic areas, over the affected nerves are complications of leprosy. This means that patients are at a significant risk of developing ulceration of or damage to the affected area as they are unable to distinguish if they have injured that area. To minimise the risk of significant damage patients are encouraged to examine their hands and feet daily and ensure that the skin is effectively moisturised to prevent dry cracked skin developing. If ulcers develop on the soles of the feet then bed rest has been shown to aid healing.

Nerve damage may also occur around the eye area causing the loss of the blinking reflex (which protects the eye from injury and moistens the surface). The eyes can become dry and infected, and blindness may result. Because of numbness of the eye, the person cannot feel dirt or scratches in the eye. Damage to the internal lining of the nose may also occur causing scarring and eventual collapse of the nose.

Reversal or type I immunological reactions occur in up to one third of patients with borderline tuberculoid or borderline lepromatous forms of leprosy as a result of the body's response to the *Mycobacterium leprae* bacteria resulting in oedema and painful inflammation of the lesions and nerves. This occurs when patients with borderline disease change between tuberculoid and lepromatous forms or vice versa. These symptoms usually respond well to oral prednisolone in doses up to 40mg daily, which may be required for several months.

Erythema nodosum leprosum (ENL) or type II reactions may occur in lepromatous or borderline lepromatous leprosy. Crops of red painful papules appear most often on the thighs and upper arms but they can be widespread. The reaction can be severe with fever and ulceration and may be confused with other causes of fever. There may also be swelling of the hands and feet or joints. It may be necessary to admit the patient to hospital so they can rest and be given treatment with systemic steroids if necessary. Thalidomide at a dose of 400mg daily is also frequently useful in this situation.⁶

— AMOEBIASIS

About 10 per cent of the worldwide population is infected with *Entamoeba histolytica*, the protozoan responsible for amoebic infections, with about 90 per cent of those people being asymptomatic. The remaining 10 per cent of people have symptoms of infection ranging from amoebic dysentery to liver abscesses. The highest incidence is in countries such as India and in central and South America. Approximately 35 to 50 million cases are reported worldwide each year.⁷ The closely related *Entamoeba dispar* is non-pathogenic.

Amoebiasis is commonly spread by water contaminated by faeces or from food served by contaminated hands. When the cyst of *Entamoeba histolytica* enters the small intestine, active amoebic parasites (trophozoites) are released, which can invade the epithelial cells of the large intestines, causing flask-shaped ulcers. It can also spread to other organs such as the liver, lungs, and brain. Asymptomatic carriers pass cysts in the faeces.

Panel 5: Drug treatment of leprosy

Paucibacillary disease:

for 6 months

Dapsone	po	100mg daily
Rifampicin	po	600mg once a month

Multibacillary disease:

for a minimum of 2 years

Rifampicin	po	600mg once a month
Clofazimine	po	300mg once a month
Dapsone	po	100mg daily
Clofazimine	po	100mg 3–4 times a week or 50mg daily

Panel 6: Treatment of amoebic infections

Asymptomatic cyst carriers

Diloxanide	po	500mg three times a day for 10 days
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Intestinal disease (dysentery)

Metronidazole	po	800mg three times a day for 5 days
(or tinidazole)	po	2g daily for 5 days

Followed by

Diloxanide	po	500mg three times a day for 10 days
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Extra intestinal disease

Metronidazole	po	400mg three times a day for 5 days
(or tinidazole)	po	2g daily for 3 days

Followed by

Diloxanide	po	500mg three times a day for 10 days
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Signs and symptoms Infection may be intra- or extra-intestinal. It may take between one and four weeks before symptoms develop. The most common type of amoebic infection is asymptomatic cyst passage. Symptomatic patients initially have lower abdominal pain and diarrhoea and later develop dysentery (with blood and mucus in stool). Severe distension of the bowel can occur.

Amoebic liver abscesses may present as pyrexia of unknown origin. Patients may also have right upper abdominal pain. Jaundice is rare. The abscess can sometimes rupture into the pleural, peritoneal or pericardial cavities.

Treatment Diloxanide, metronidazole and tinidazole are used in the treatment of amoebiasis (see Panel 6). There is currently a manufacturing problem with diloxanide tablets. An alternative agent may be oral paromomycin which is unlicensed in the UK, but available from Italy via an importer.

SCHISTOSOMIASIS (BILHARZIA)

Schistosomiasis is a parasitic worm infection which causes chronic ill health. There are five species which cause infection in humans: *Schistosoma japonicum*, *Schistosoma mansoni*, *Schistosoma intercalatum* and *Schistosoma mekongi* which cause intestinal infection and *Schistosoma haematobium* which causes urinary infection.⁸

Transmission The schistosoma parasites use snails as an intermediate host. People suffering from schistosomiasis excrete eggs in their faeces which pass into the water system. In areas of poor sanitation these eggs may also contaminate fresh water. Snails take up the miracidia (larva) which are released from the eggs on contact with water and multiply to form thousands of cercariae (larva which emerge from the snail), which are released into the water again. The cercariae can penetrate the skin of humans and the small worms make their way to the intestine or bladder where they mature into larger schistosoma worms over the next 30–45 days. The female worms produce many eggs, some of which are released into the faeces and some of which remain in the tissues and ultimately cause damage by forming granulomas or becoming calcified. The long-term complications which may occur are due to the eggs and not the worms.

It is likely that in excess of 200 million people worldwide are infected with schistosomiasis, with children and adolescents having a higher prevalence of infection.

Signs and symptoms Many people report a “swimmers itch”, which is an itchy rash that occurs as a result of the cercariae penetrating the skin, after leaving an infected fresh water supply. Acute symptoms such as Katayama fever may occur as soon as two or three weeks after infection. This is a syndrome including fever, lack of appetite, weight loss, abdominal pain, haematuria, weakness, headaches, joint and muscle pain, diarrhoea, nausea and cough. Urinary infection manifests as haematuria and may lead to bladder cancer or renal problems. Intestinal infections lead to more non-specific symptoms such as abdominal pain, lethargy, diarrhoea and blood in the faeces. This may ultimately result in liver and splenic enlargement and portal hypertension due to infiltration of the venous circulation with schistosoma eggs.

Diagnosis Diagnosis is achieved by detecting the presence of eggs in the faeces or by serological studies from blood.

Treatment Two doses of praziquantel 20mg/kg given four to six hours apart will kill most of the adult worms and eggs and reduce the likelihood of serious consequences developing. In areas where the incidence of schistosomiasis is high an eradication programme is usually in operation to try to reduce the spread of the disease and long-term organ damage by reducing the “worm-load”. Praziquantel is an unlicensed drug which is available from Merck for this purpose.

Prevention Avoidance of bathing in fresh water in endemic countries, especially in rural areas, is the best means of prevention. If fresh water is required then filter paper should remove the cercariae as will standing the water for at least three days after which the cercariae will have died.

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