Prevention and treatment of malaria in UK travellers

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With around 2500 new cases of malaria being reported each year and more than a million UK residents visiting malaria endemic countries, there has never been a greater need for effective prevention and treatment. The latest information on malaria management is outlined below.

Of the 44 million UK residents making journeys abroad each year, around 1.3 million visit malaria endemic regions. This has implications for tourists and tourism. On an individual level there are around 2500 malaria cases and 12 deaths a year from malaria among UK residents. On a global level, protecting the health of travellers helps sustain tourism on which the economy of host countries are heavily dependent for foreign earnings. The four main aspects to consider when advising on malaria prevention are:

- Awareness — know the risk
- Bites by mosquitoes — prevent or avoid
- Compliance with appropriate chemoprophylaxis
- Diagnose malaria swiftly and treat promptly.

No chemoprophylaxis is 100% effective. Measures to reduce mosquito bites are an essential part of antimalarial advice and should include treating bed nets with permethrin and use of diethyltoluamide (DEET)-containing insect repellents. In addition, travellers require strict instructions to seek a blood film should a new symptom, especially fever, develop following their return from a malarious area. This applies for up to a year after return, but particularly the first 3 months.

THE RISK OF EXPOSURE TO MALARIA

Many factors increase the risk of bite from an infected Anopheline mosquito:

- Region visited
- Type of travel — backpacking *vs* air conditioned, well screened urban hotel
- Duration of stay — the cumulative risk of contracting malaria is proportional to the length of stay in an endemic area
- Pattern of traveller activity — exposure between dusk and dawn
- Season of travel — rainy season
- Altitude of destination — malaria is not transmitted above 2000m.

GEOGRAPHICAL RISKS FOR BRITISH TRAVELLERS

The travel destination is an important factor; *Figure 1* shows a comparison of malaria attack rates in the 10 countries that are the commonest source of malaria imported into the UK. Sierra Leone has the highest rate among UK residents for *Plasmodium falciparum*, reflecting the frequency of visits to friends and relatives (VFRs) in their country of origin. Natural acquired immunity decays rapidly over a period of years and around half of all malaria in UK residents occurs in travellers who have grown up in a malaria-endemic area. Tourists and expatriates constitute only one quarter of all imported cases of falciparum malaria.

MOSQUITO BITE PREVENTION

The importance of bite prevention cannot be over emphasized. Both personal and physical protec-

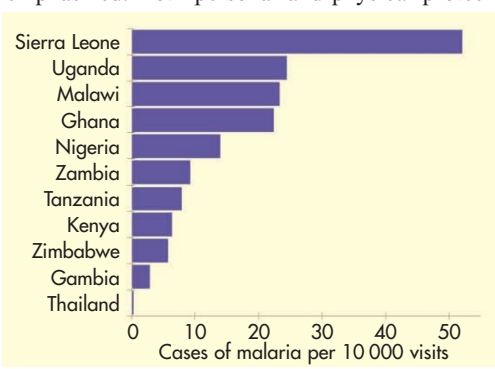

Figure 1. The top 10 countries from which falciparum malaria is reported in travellers from the UK and the incidence of malaria by visit to those countries.

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tion should be recommended. The mainstay of personal protection is appropriate clothing and the use of insect repellent based on the organic solvent DEET (Fradin, 1998) (ideally >20% weight per volume concentration). Physical protection requires a combination of bed nets (always impregnated with an insecticide), window screens or sleeping in an air-conditioned room.

CHEMOPROPHYLAXIS

The following drugs or combinations of drugs are available for use by travellers: chloroquine and proguanil, mefloquine or Malarone®. (Malarone® is currently unlicensed for prophylaxis in the UK.) Doxycycline may be used but is currently not licensed in the UK for this indication. Because of the widespread geographical variation in drug-resistant *P. falciparum*, national guidelines (Bradley and Warhurst, 1997) incorporated in the British National Formulary (Royal Pharmaceutical Society of Great Britain, 1999a) should be referred to for advice on prescribing the optimal chemoprophylactic regimen by country.

In selecting a regimen to use, the following are all major considerations:

- Compliance
- Efficacy
- Toxicity
- The attack rate in the area to be visited
- Factors influencing the outcome of an infection, such as the medical facilities and drugs available for treatment.

Figure 2 provides examples of how various factors may influence risk–benefit profile when selecting a prophylactic regimen. The travelling public's perception of the likelihood of adverse events and willingness to take specific medication are a major factor in compliance with chemoprophylaxis. For example, public concern about the toxicity of mefloquine has significantly reduced its uptake and compliance (Reid et al, 1998), despite the clear benefits it provides through greater effectiveness. Failing to continue prophylaxis for 4 weeks after return is common.

Other considerations when prescribing antimalarials, which may warrant referral for expert advice, include:

- Previous and current medical conditions, including psychiatric disorders and epilepsy
- Other medication
- Pregnancy or intended conception
- Extremes of age.

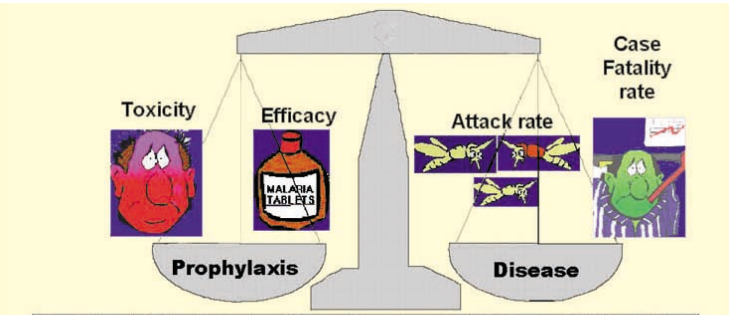
Chloroquine and proguanil

This combination has been used extensively. In areas with limited or moderate chloroquine resistance, such as occur in sub-Saharan Africa, this combination provides substantially inferior protection than mefloquine.

Side-effects occur with the same frequency as the other main regimens, but its effectiveness in one study was of the order of 70% (Steffen et al, 1993). Serious toxicity, such as acute psychosis, can occur with chloroquine. More frequent problems include apthous mouth ulcers, dyspepsia, diarrhoea, itching (especially in black races), and problems with fluid in the anterior chamber of the eye leading to problems of visual accommodation. There is no evidence of chloroquine retinal toxicity when used long term at prophylactic doses. Chloroquine (combined with proguanil) is safe to take for at least 5 years as prophylaxis, but poor compliance is a major problem in long-term expatriates.

Mefloquine

The efficacy of mefloquine is approximately 90% in Africa and the Pacific, but on the Thai border of Burma and Cambodia resistance is widespread. Despite much media criticism, severe adverse events, defined as: 'a threat to life or resulting in a prolonged admission to hospital or severe disability', are rare. A review of six randomized and seven prospective comparative trials (Lobel and Kozarsky, 1997) failed to demonstrate significant differences in overall adverse effects or discontinuation rates between mefloquine and other chemoprophylactic regimens. Between 25 and 45% of users develop some side-effects, most of which are mild and self-limiting. The most frequently reported are nausea, strange dreams, dizziness, mood swings, insomnia, headaches or diarrhoea. An independent review (Drugs and Therapeutics Bulletin, 1998) concluded there was no evidence of increased incidence of serious CNS side-effects



Drug Regimen	Toxicity	No. with adverse event	Efficacy	Susceptible travellers	Malaria attack rate 2% Malaria Cases	Case fatality rate (worst) 4% Malaria Cases
Effective Drug - High Toxicity	1:1,000	10	90%	1000	20	0
Less Effective Drug - Low Toxicity	1:10,000	1	50%	5000	100	4

Based on 10,000 visits and assuming 100% compliance

Figure 2. Major factors influencing the risk–benefit analysis in selecting the optimal chemoprophylaxis.

compared to other regimens. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses (1/10 000 to 1/13 000) and occur more frequently in women than men.

In travellers to areas where mefloquine is the recommended drug of choice, explanation of the risk and severity of malaria can be used to counterbalance the concerns over drug toxicity. Most adverse reactions to antimalarials occur within the first few doses; over 78% of adverse reactions to mefloquine (Winstanley and Behrens, 1999) are apparent by the third dose. It is therefore optimal to take mefloquine 3 weeks before departure to allow time to change prophylaxis should problems arise.

Neither mefloquine or chloroquine should be given to people with a history of epilepsy. In addition, because mefloquine can induce severe neuropsychiatric symptoms, it should not be prescribed where there is a history of psychiatric disease.

Malarone

Malarone® (Glaxo Wellcome, Middlesex) is a combination of atovaquone and proguanil, which are synergistic and highly effective in the prevention of falciparum, and possibly vivax, malaria. A review of three placebo-controlled trials of Malarone® prophylaxis suggests its efficacy is as high as 98% (Shanks et al, 1999). Malarone® appears to be well-tolerated. The most common side-effects include headaches, abdominal pain, dyspepsia, gastritis and diarrhoea.

Doxycycline

Doxycycline is an alternative to mefloquine, particularly for travellers to multidrug resistant regions of South East Asia. In two small studies, doxycycline was found to have similar efficacy to mefloquine (>90%) (Andersen et al, 1998). Its main side-effects are diarrhoea, photosensitive dermatitis, vaginal thrush, oesophageal ulceration and dyspepsia. It is not licensed for use as a chemoprophylactic in the UK. Doxycycline is contraindicated in children and pregnancy.

TREATMENT OF MALARIA

Untreated falciparum malaria is a fatal disease. Delay in the diagnosis and effective treatment may result in a rapid decline in the patient's condition as a result of multiorgan failure. The severity of disease and prognosis varies according to the degree of parasitaemia and the immunity of the affected individual. Malarial immunity is highly complex, never totally protective, and broadly determined by the degree of malaria transmission in the place where childhood was spent. This partial immunity is poorly sustained without continuing exposure to infection. Children aged 6 months to 3 years and non-immune visitors to a malarious area are particularly vulnerable to severe disease.

DIAGNOSIS

A diagnosis of malaria is made on the basis of a history of a febrile illness and finding the asexual forms of the parasite on a blood film (or detected by a rapid antigen test). A travel history is essential for the diagnosis of malaria to be suspected; missed diagnoses are nearly always because a travel history was not sought. Once the diagnosis of malaria is considered, a blood film should be requested and the result seen on the day of request (*Figure 3*). Malaria can progress to coma within 24–48 hours of first symptoms.

FALCIPARUM MALARIA

Patients with falciparum malaria may deteriorate even after commencing therapy and admission to hospital is advisable even when symptoms are mild. Quinine orally or parenterally remains the treatment of first choice (*Table 1*) irrespective of antimalarial prophylaxis used. *Table 2* lists the criteria for patients with severe disease in whom the aim should be to achieve rapid therapeutic levels by 12-hourly intravenous therapy, beginning with a loading dose. Cardiac monitoring is not required, but plasma quinine level should be measured before the fourth dose in view of its potential cardiotoxicity. Oral quinine is given 8-hourly for mild disease, but this may be modified to a 12-hourly regimen if side-effects such as nausea, tinnitus and deafness (cinchonism) occur.

Quinine is usually discontinued when the patient is better, afebrile and has no falciparum trophozoites on a thick film. The sexual form, the gametocytes, may persist for a number of

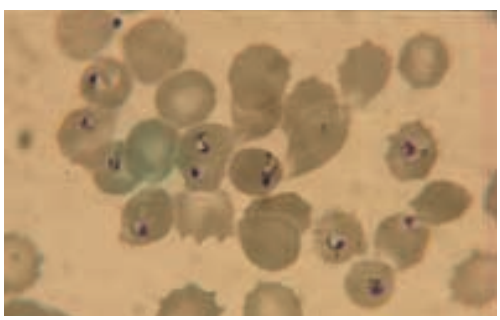


Figure 3. A giemsa-stained thin blood film of a patient with a heavy parasitaemia of* Plasmodium falciparum *trophozoites.

TABLE 1.
Treatment of *Plasmodium falciparum* malaria

Severe	Intravenous quinine dihydrochloride 20 mg/kg loading dose, followed by 10 mg/kg 12-hourly		
Mild	Oral quinine 10 mg salt/kg 8-hourly		
	Reduce to 12-hourly if develops cinchonism		
	Discontinue and give second drug when patient better and parasitaemia cleared (3–4 days)	Second drug one of the following	If pregnant consider weekly chloroquine until delivery
			Fansidar 3 tablets stat
			Doxycycline 100 mg daily for 14 days
			Tetracycline 250 mg 6 hourly for 7 days

From Warrell (1990)

weeks, but does not require specific treatment. Those with mild malaria are usually found to have a negative film after 3 days of quinine, making the 7-day course advocated by the British National Formulary (Royal Pharmaceutical Society of Great Britain, 1999b) excessive. Following quinine with a second drug such as Fansidar® (Roche Products Ltd, Welwyn Garden City) is necessary to overcome possible quinine resistance. Outpatient follow-up is not usually required, but patients should be warned of the small possibility of recrudescence. They should be advised to seek immediate medical advice and a blood film in the event of a further febrile illness occurring within 3 months.

COMPLICATIONS

Management of the complications of severe falciparum malaria is best carried out on an intensive care unit at a specialist centre where cardiovascular monitoring and haemofiltration are available. Any impairment of cerebral function, however minor, should be taken seriously, as this may be an early sign of cerebral involvement. In adults with a parasitaemia of greater than 10%, renal failure and pulmonary oedema are likely complications. Renal failure is usually a consequence of acute tubular necrosis and should be managed with carefully monitored fluid replacement. Haemofiltration may be required to correct fluid overload and acidosis. Respiratory failure secondary to excessive fluid administration or adult respiratory distress syndrome, typically occurring after 1 or 2 days' treatment, is a common cause of death.

TABLE 2.
Severe *Plasmodium falciparum* malaria

Any of the following are indications for intravenous quinine and specialist advice:	Temperature ≥ 39°C
	Non-ambulant
	Vomiting
Complications present	Cerebral involvement (drowsiness, confusion, stupor, fits, coma)
	Haemoglobin <8 g/dl
	Platelets < 20 x 10^{12}/l
	Jaundice
	Pulmonary oedema
	Hypovolaemia
	Hypoglycaemia
Parasitaemia >2%	
Schizonts or pre-schizonts present	

CHILDREN AND PREGNANCY

The clinical picture of severe malaria in children differs in some respects from adults; cerebral involvement and marked anaemia are the more common complications in children. Convulsions should be managed in the standard manner. Transfer to a specialist high dependency unit is strongly recommended. Pregnant women with severe malaria are particularly susceptible to anaemia, pulmonary oedema and quinine-induced hypoglycaemia. Non-immune pregnant patients are at risk of developing premature uterine contractions, fetal distress and possible miscarriage.

ANCILLARY TREATMENTS

Various adjunctive treatments for cerebral malaria have been investigated without adequate evidence of benefit and may, in fact, be hazardous. These include corticosteroids and other anti-inflammatory agents, osmotic diuretics, dextran, adrenaline, heparin, prostacyclin and oxpentifylline. Exchange transfusion of red blood cells has been shown to reduce parasitaemia more rapidly than with chemotherapy alone and may be of benefit, although no randomized controlled trials have been undertaken. The Hospital for Tropical Diseases policy is to exchange transfuse six units if the parasitaemia is greater than 20% or if there is organ failure in the presence of a parasitaemia of greater than 10%.

QUININE RESISTANCE

Decreased efficacy of quinine has been documented in some parts of the world, notably Thailand and its neighbouring countries. For severe malaria in these areas, the World Health Organization recommends Qinghaosu derivatives such as artemether and artesunate in combination with mefloquine, but artemesinin derivatives are not currently licensed in the UK. For uncomplicated infections Malarone® is an effective, although expensive, alternative regimen.

Other sources of information

Doctors and practice nurses who need more detailed prophylaxis advice may contact the Public Health Laboratory Service Malaria reference laboratory on 0207 636 3924

Malaria treatment advice (and a treatment protocol) is available through the on-call Specialist Registrar, Hospital for Tropical Diseases 0207 387 4411

TABLE 3.
Treatment of *Plasmodium vivax* and *Plasmodium ovale* malaria

Oral chloroquine course (for 40–80 kg patient)*		
hours	mg	tablets
0	600	4
6	300	2
24	300	2
48	300	2
Prevention of relapse		
Primaquine eradicates liver hypnozoites		
Primaquine 15 mg twice daily (0.25 mg/kg in children) for 14 days		
Avoid if pregnant or glucose-6-phosphate dehydrogenase deficient		
If mild glucose-6-phosphate dehydrogenase deficiency consider 30–45 mg weekly for 8 weeks		
If pregnant consider weekly chloroquine 300 mg until delivery		
Primaquine is an unlicensed drug		

* This is the standard regimen used for treatment of falciparum malaria in endemic areas

KEY POINTS

- There are four main aspects to consider when advising on malaria prevention: awareness, bite prevention, prophylaxis, and swift diagnosis and treatment.
- Risk depends on region visited, type of travel, season of travel and altitude of destination.
- The importance of bite prevention cannot be over-emphasized.
- Major considerations in selecting a chemoprophylaxis regimen include compliance, efficacy, toxicity, attack rate in area to be visited and factors influencing outcome of infection.
- Quinine remains the treatment of choice for falciparum malaria.
- The possibility of multi-species infection should be considered when a treatment regimen is decided.

BENIGN MALARIAS

Malarias caused by *P. vivax*, *P. ovale* or *P. malariae* generally cause milder disease and fatalities are rare. They are treated with a four-dose course of chloroquine (*Table 3*). If doubt exists over the speciation the patient should be admitted and treated as for falciparum malaria with quinine. The possibility of multi-species infection should also be considered, particularly in patients infected in East or West Africa. Chloroquine is generally well tolerated, although Africans frequently report pruritis, a genetic predisposition that does not respond well to antihistamines. Quinine or Fansidar® may be used as an alternative.

P. vivax and *P. ovale* have a dormant liver stage (hynozoite) which require a course of primaquine to eradicate them, otherwise relapses up to 2–3 years after exposure may occur. Primaquine is not licensed in the UK but can be acquired from the manufacturer on a named-patient basis (B&S Durbin, 0208 422 1303). It may precipitate haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Significant haemolysis is rarely provoked by quinine and chloroquine in G6PD-deficient individuals. HM

Conflict of interest: Dr Behrens has received research funding from Zeneca and Glaxo Wellcome and has received financial support to lecture at educational meetings.

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