

# Malaria

## General considerations

Malaria is a common and life-threatening disease in many tropical and subtropical areas. It is currently endemic in over 100 countries, which are visited by more than 125 million international travellers every year.

Each year many international travellers fall ill with malaria while visiting countries where the disease is endemic, and well over 10 000 are reported to fall ill after returning home. Due to under-reporting, the real figure may be up to 30 000. International travellers are at high malaria risk because they are non-immune and often exposed to late or wrong malaria diagnosis when returning to their home country. Fever occurring in a traveller within three months of leaving a malaria-endemic area is a medical emergency and should be investigated urgently.

## Cause

Human malaria is caused by four different species of the protozoan parasite *Plasmodium*: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.

## Transmission

The malaria parasite is transmitted by various species of Anopheles mosquitoes, which bite mainly between sunset and sunrise.

## Nature of the disease

Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, a febrile illness developing less than one week after the first possible exposure is not malaria.

The most severe form is caused by *P. falciparum*, in which variable clinical features include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain; other symptoms related to organ failure may supervene, such as: acute renal failure, generalized convulsions, circulatory collapse, followed by coma and death. In endemic areas it is estimated that about

1% of patients with *P. falciparum* infection die of the disease; the mortality in non-immune travellers with untreated falciparum infection is significantly higher. The initial symptoms, which may be mild, may not be easy to recognize as being due to malaria. It is important that the possibility of falciparum malaria is considered in all cases of unexplained fever starting at any time between the seventh day of first possible exposure to malaria and three months (or, rarely, later) after the last possible exposure. Any individual who experiences a fever in this interval should immediately seek diagnosis and effective treatment, and inform medical personnel of the possible exposure to malaria infection.

Early diagnosis and appropriate treatment can be life-saving. Falciparum malaria may be fatal if treatment is delayed beyond 24 hours. A blood sample should be examined for malaria parasites. If no parasites are found in the first blood film while there is clinical suspicion of malaria, a series of blood samples should be taken at 6–12-hour intervals and examined very carefully.

Pregnant women, young children and elderly travellers are particularly at risk. Malaria in pregnant travellers increases the risk of maternal death, miscarriage, stillbirth and neonatal death.

The forms of malaria caused by other *Plasmodium* species are less severe and rarely life-threatening.

Chemoprophylaxis and treatment of falciparum malaria are becoming more difficult because *P. falciparum* is increasingly resistant to various antimalarial drugs. Chloroquine resistance of *P. vivax* is rare and was first reported in the late 1980s in Papua New Guinea and Indonesia. Focal “true” chloroquine resistance (i.e. in patients with adequate blood levels at day of failure) or prophylactic and/or treatment failure have later also been observed in Brazil, Columbia, Ethiopia, Guatemala, Guyana, India, Myanmar, Peru, the Republic of Korea, Solomon Islands, Thailand and Turkey. *P. malariae* resistant to chloroquine has been reported from Indonesia.

## Geographical distribution

The current distribution of malaria in the world is shown in a map. Details for affected countries and territories are listed under countries and territories with malarious area. The risk for travellers of contracting malaria is highly variable from country to country and even between areas in a country. This has to be considered when discussing appropriate preventive measures.

In many endemic countries, the main urban areas—but not necessarily the outskirts of towns—are free of malaria transmission. However, malaria can occur

in main urban areas in Africa and India. There is usually less risk of the disease at altitudes above 1500 metres, but in favourable climatic conditions it can occur at altitudes up to almost 3000 metres. The risk of infection may also vary according to the season, being highest at the end of the rainy season or soon after.

There is no risk of malaria in many tourist destinations in South-East Asia, Latin America and the Caribbean.

### **Risk for travellers**

During the transmission season in malaria-endemic areas, all non-immune travellers exposed to mosquito bites, especially between dusk and dawn, are at risk of malaria. This includes previously semi-immune travellers who have lost (part of) their immunity during stays of 6 months or more in non-endemic areas. Children of people who have migrated to non-endemic areas are particularly at risk when they return to malarious areas to visit friends and relatives. Culturally sensitive approaches are needed to advice different groups at risk. Most cases of malaria in travellers occur because of poor compliance with prophylactic drug regimens, or use of inappropriate medicines or no chemoprophylaxis at all, combined with poor prevention of mosquito bites.

Travellers to countries where the degree of malaria transmission varies in different areas should seek advice on the risk of malaria in the specific zones that they will be visiting. If specific information is not available before travelling, it is recommended to prepare as if the highest reported risk for the area or country applies throughout. This applies particularly to individuals backpacking to remote places and visiting areas where diagnostic facilities and medical care are not readily available. Travellers staying overnight in rural areas may be at highest risk.

### **Precautions**

Travellers and their advisers should note the four principles of malaria protection:

- Be **A**ware of the risk, the incubation period, and the main symptoms.
- Avoid being **B**itten by mosquitoes, especially between dusk and dawn.
- Take antimalarial drugs (**C**hemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- Immediately seek **D**iagnosis and treatment if a fever develops one week or more after entering an area where there is a malaria risk, and up to 3 months after departure from a risk area.

## Protection against mosquito bites

All travellers should be explained that individual protection from mosquito bites between dusk and dawn is their first line of defence against malaria. Practical measures for protection are described in Chapter 3 section *Protection against vectors*.

## Chemoprophylaxis

The correct dosage of the most appropriate antimalarial drug(s) (if any) for the destination(s) should be prescribed (see Country list and Table 7.1).

Travellers and their doctors should be aware that

### **NO ANTIMALARIAL PROPHYLACTIC REGIMEN GIVES COMPLETE PROTECTION,**

but good chemoprophylaxis (adherence to the recommended drug regimen) does reduce the risk of fatal disease. The following should also be taken into account:

- Dosing schedules for children should be based on body weight.
- Antimalarials that have to be taken daily should be started the day before arrival in the risk area.
- Weekly chloroquine should be started 1 week before arrival.
- Weekly mefloquine should be started at least 1 week, but preferably 2–3 weeks before departure, to achieve higher pre-travel blood levels and to allow side-effects to be detected before travel so that possible alternatives can be considered.
- Antimalarial drugs must be taken with food and swallowed with plenty of water.
- All prophylactic drugs should be taken with unfailing regularity for the duration of the stay in the malaria risk area, and should be continued for 4 weeks after the last possible exposure to infection, since parasites may still emerge from the liver during this period. The single exception is atovaquone/proguanil, which can be stopped 1 week after return.
- Depending on the predominant type of malaria at the destination, travellers should be advised about possible late onset *P. vivax* and *P. ovale*.

Depending on the malaria risk in the area visited (see Country list), the recommended malaria prevention method may be mosquito bite prevention only, or mosquito bite prevention in combination with chemoprophylaxis, as follows:

	<b>Malaria risk</b>	<b>Type of prevention</b>
<b>Type I</b>	Very limited risk of malaria transmission	Mosquito bite prevention only
<b>Type II</b>	Risk of <i>P. vivax</i> malaria or fully chloroquine-sensitive <i>P. falciparum</i> only	Mosquito bite prevention plus chloroquine chemoprophylaxis
<b>Type III</b>	Risk of malaria transmission and emerging chloroquine resistance	Mosquito bite prevention plus chloroquine+proguanil chemoprophylaxis
<b>Type IV</b>	High risk of falciparum malaria plus drug resistance, or moderate/low risk falciparum malaria but high drug resistance	Mosquito bite prevention plus either mefloquine, doxycycline or atovaquone/proguanil (take one that no resistance is reported for in the specific areas to be visited)

See Table 7.2 for details on individual drugs.

All antimalarial drugs have specific contraindications and possible side-effects. Adverse reactions attributed to malaria chemoprophylaxis are common, but most are minor and do not affect the activities of the traveller. Serious adverse events—defined as constituting an apparent threat to life, requiring or prolonging hospitalization, or resulting in permanent disability or incapacity—are rare and normally only identified once a drug has been in use for some time. With mefloquine the incidence range of serious adverse events has been estimated at 1 per 6000 to 1 per 10 600 travellers, compared to 1 per 13 600 with chloroquine. For malaria prophylaxis with atovaquone/proguanil or doxycycline the risks of rare serious adverse events have not yet been established. The risk of drug-associated adverse events should be weighed against the risk of malaria, especially *P. falciparum* malaria, and local drug-resistance patterns.

**Each of the antimalarial drugs is contraindicated in certain groups and individuals, and the contraindications should be carefully considered (see Table 7.2) to reduce the risk of serious adverse reactions.** People with chronic illnesses should seek individual medical advice. Any traveller who develops serious side-effects to an antimalarial should stop taking the drug and seek immediate medical attention. This applies particularly to neurological or psychological disturbances on mefloquine prophylaxis. Mild nausea, occasional vomiting or loose stools should not prompt discontinuation of prophylaxis, but medical advice should be sought if symptoms persist.

Because of the risk of adverse side-effects, chemoprophylaxis should not be prescribed in the absence of malaria risk. It is important to note that malaria is not present in all tropical countries (see map and Country list).

### Long-term use of chemoprophylaxis

The risk of serious side-effects associated with long-term prophylactic use of chloroquine and proguanil is low. However, anyone who has taken 300 mg of chloroquine weekly for over five years and requires further prophylaxis should be screened twice-yearly for early retinal changes. If daily doses of 100 mg chloroquine have been taken, screening should start after three years. Data indicate no increased risk of serious side-effects with long-term use of mefloquine if the drug is tolerated in the short-term. Experience with doxycycline for long-term chemoprophylaxis (i.e. more than 4–6 months) is limited, but available data are reassuring. Mefloquine and doxycycline should be reserved for those at greatest risk of chloroquine-resistant infections. Atovaquone/proguanil is registered in European countries with a restriction on duration of use (varying from 5 weeks to 3 months); in the USA no such restrictions apply.

### Stand-by emergency treatment

An individual who experiences a fever 1 week or more after entering an area of malaria risk should consult a physician or qualified malaria laboratory immediately to obtain correct diagnosis and a safe and effective treatment. Many travellers will be able to obtain proper medical attention within 24 hours of the onset of fever. For others, however, this may be impossible, particularly if they will be staying (1 week or more after entering an endemic area) in a remote location. In such cases, travellers are advised to carry antimalarial drugs for self-administration (“stand-by emergency treatment”). The choice of drugs for stand-by emergency treatments in relation to the drugs used for prophylaxis is given in Table 7.1.

The circumstances of stand-by emergency treatment (SBET) are different from treatment administered by competent medical personnel. SBET is taken by a traveller who (1) is sick in a remote location and cannot easily reach a hospital or qualified health professional, (2) may already be taking antimalarials for prophylaxis, and (3) may have to self-diagnose malaria based on non specific clinical symptoms such as fever. In these circumstances the safety and efficacy of drugs given for SBET are even more critical, and not all antimalarials that are normally used for treatment can be confidently prescribed.

Stand-by emergency treatment may also be indicated for travellers in some occupational groups, such as aircraft crews, who make frequent short stops in endemic areas over a prolonged period of time. Such travellers may eventually choose to reserve chemoprophylaxis for high-risk areas only. However, they should continue to take rigorous measures for protection against mosquito bites and be prepared for an attack of malaria: they should always carry a course of antimalarial drugs for stand-by emergency treatment, seek immediate medical care in case of fever, and take stand-by emergency treatment if prompt medical help is not available.

Stand-by emergency treatment—combined with rigorous protection against mosquito bites—may occasionally be indicated for those who travel for 1 week or more to remote rural areas where there is a very low likelihood of multidrug-resistant malaria and the risk of side-effects of prophylaxis outweighs the risk of contracting malaria. This may be the case in certain border areas of Thailand and neighbouring countries in South-East Asia where the risk of side-effects may outweigh the risk of becoming infected. However, most travellers to these areas will be able to access competent medical care within 24 hours of the onset of fever.

Studies on the use of rapid diagnostic tests (“dipsticks”) have shown that untrained travellers experience major problems in the performance and interpretation of these tests, with an unacceptably high number of false-negative results. In addition, dipsticks can be degraded by extremes of heat and humidity, becoming less sensitive. Major technical modifications are required before dipsticks can be recommended for use by travellers.

Travellers’ behaviour is key for successful SBET, and the health advisor needs to spend time explaining the strategy. Travellers provided with stand-by emergency treatment should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, the treatment regimen, possible side-effects, and the possibility of drug failure. If several people travel together, the individual dosages for SBET should be specified. Travellers should be made aware that self-treatment is a first-aid measure, and that they should seek medical advice as soon as possible.

In general, travellers carrying stand-by emergency treatment should observe the following guidelines:

- Consult a physician immediately if fever occurs 1 week or more after entering an area with malaria risk.
- If it is impossible to consult a physician and/or establish a diagnosis within 24 hours of the onset of fever, start the stand-by emergency treatment and

seek medical care as soon as possible for complete evaluation and to exclude other serious causes of fever.

- Complete the stand-by treatment course and resume antimalarial prophylaxis 1 week after the *first* treatment dose. Mefloquine prophylaxis, however, should be resumed 1 week after the *last* treatment dose of quinine.
- Vomiting of antimalarial drugs is less likely if fever is first lowered with antipyretics. A second full dose should be taken if vomiting occurs within 30 minutes of taking the drug. If vomiting occurs 30–60 minutes after a dose, an additional half-dose should be taken. Vomiting with diarrhoea may lead to treatment failure because of poor drug absorption.
- Do not treat suspected malaria with the same drugs used for prophylaxis, because of the increased risk of toxicity and resistance.

Depending on the area visited and the chemoprophylaxis regimen taken, one of the following stand-by treatment regimens can be recommended: chloroquine, (*P. vivax* areas only), mefloquine, quinine, or quinine plus doxycycline. Artemether/lumefantrine has been registered in Switzerland for use as stand-by emergency treatment for travellers. Some national health authorities recommend atovaquone/proguanil as SBET for areas of multidrug resistance. See Table 7.3 for details on individual drugs.

Halofantrine is **contra-indicated** for stand-by treatment following reports that it can result in ventricular dysrhythmias, prolongation of Q–T intervals and sudden death in susceptible individuals. These risks may be accentuated if halofantrine is taken with other antimalarial drugs that may reduce myocardial conduction.

In light of the spread of counterfeit drugs in some resource-poor settings, travellers who may become sick while abroad may opt to buy a reserve antimalarial treatment before departure, so that they can be confident of drug efficacy and safety should they fall ill.

### Treatment of *P. vivax*, *P. ovale* and *P. malariae* infections

*P. vivax* and *P. ovale* can remain quiescent in the liver for many months. Relapses caused by the persistent liver forms may appear months, and rarely up to 2 years, after exposure. They are not prevented by current chemoprophylactic regimens. Relapses can be treated with chloroquine (or mefloquine or quinine if resistance is suspected) and further relapses prevented by a course of primaquine, which eliminates any remaining parasites in the liver. In patients with known or



suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency, expert medical advice should be sought since primaquine may cause haemolysis in G6PD-deficient patients. G6PD deficiency must be excluded before travellers receive antirelapse therapy with primaquine. Blood infection with *P. malariae* may be present for many years, but it is not life-threatening. It can be treated with chloroquine (or mefloquine or quinine if resistance is suspected).

## Special groups

Some groups of travellers, especially young children and pregnant women, are at particular risk of serious consequences if they become infected with malaria.

### Pregnant women

Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and low birth weight with associated risk of neonatal death.

Pregnant women should be advised to **avoid** travelling to areas where malaria transmission occurs. When travel cannot be avoided, it is very important to take effective preventive measures against malaria, even when travelling to areas with transmission of vivax malaria only.

Pregnant women should be extra diligent in using measures to protect against mosquito bites, but should take care not to exceed the recommended dosage of insect repellents.

In “type II” areas with exclusively *P. vivax* transmission or where *P. falciparum* can be expected to be fully sensitive to chloroquine, prophylaxis with chloroquine alone may be used. In “type III” areas, prophylaxis with chloroquine plus proguanil can be safely prescribed, also during the first 3 months of pregnancy. In “type IV” areas, mefloquine prophylaxis may be given during the second and third trimester, but there is limited information on its safety during the first trimester. Doxycycline is contraindicated during pregnancy. Atovaquone/proguanil has not been sufficiently investigated to be prescribed for chemoprophylaxis in pregnancy.

Pregnant women should seek medical help immediately if malaria is suspected; if this is not possible, they should take emergency stand-by treatment with quinine. Medical help *must* be sought as soon as possible after stand-by treatment.

Pregnant women with falciparum malaria may rapidly develop any of the clinical symptoms of severe malaria. They are particularly susceptible to hypoglycaemia and pulmonary oedema. They may develop postpartum haemorrhage, and

hyperpyrexia leading to fetal distress. Any pregnant woman with severe falciparum malaria should be transferred to intensive care. Because of the risk of quinine-induced hyperinsulinaemia and hypoglycaemia, artesunate and artemether are the drugs of choice for treatment of severe malaria in the second and third trimester. Data on the use of artemisinin derivatives in the first trimester are still limited. However, neither quinine nor artemisinin derivatives should be withheld in any trimester if they are considered life saving for the mother.

Information on the safety of drugs during breastfeeding is provided in Tables 7.2 and 7.3.

### Women who may become pregnant during or after travel

Both mefloquine and doxycycline prophylaxis may be taken, but pregnancy should preferably be avoided during the period of drug intake and for 3 months after mefloquine and 1 week after doxycycline prophylaxis is stopped. If pregnancy occurs during antimalarial prophylaxis with mefloquine or doxycycline, this is not considered to be an indication for pregnancy termination. Due to its half-life of 2-3 days in adults, more than 99% of atovaquone will usually be eliminated from the body by 3 weeks after the last dose was taken.

### Young children

**Falciparum malaria in a young child is a medical emergency** it may be rapidly fatal. Early symptoms are atypical and difficult to recognize, and life-threatening complications can occur within hours of the initial symptoms. Medical help should be sought immediately if a child develops a febrile illness within 3 months (or, rarely, later) of travelling to an endemic area. Laboratory confirmation of diagnosis should be requested immediately, and treatment with an effective antimalarial drug initiated as soon as possible. In infants, malaria should be suspected even in non-febrile illness.

Parents should be advised **not** to take babies or young children to areas with transmission of chloroquine-resistant *P. falciparum*. If travel cannot be avoided, children must be very carefully protected against mosquito bites and be given appropriate chemoprophylactic drugs. Babies should be kept under insecticide-treated mosquito nets as much as possible between dusk and dawn. The manufacturer's instructions on the use of insect repellents should be followed diligently, and the recommended dosage must not be exceeded.

Breastfed, as well as bottle-fed, babies should be given chemoprophylaxis since they are not protected by the mother's prophylaxis. Dosage schedules for children should be based on body weight. Chloroquine and proguanil are safe for babies and young children but only suitable for areas with low levels of chloroquine resistance. Mefloquine may be given to infants of more than 5 kg body weight. Atovaquone/proguanil can not be recommended for prophylaxis in children who weigh less than 11 kg, because of the lack of data. Doxycycline is contraindicated in children below 8 years of age. Information on the safety of drugs for treatment of young children is provided in Table 7.3. All antimalarial drugs should be kept out of the reach of children and stored in childproof containers. Chloroquine is particularly toxic in case of overdose.

### **Special situations—multidrug-resistant malaria**

In border areas between Cambodia, Myanmar and Thailand, *P. falciparum* infections do not respond to treatment with chloroquine or sulfadoxine-pyrimethamine, and sensitivity to quinine is reduced. Treatment failures in excess of 50% with mefloquine are also being reported. In these situations, doxycycline or atovaquone/proguanil can be used for chemoprophylaxis together with rigorous personal protection measures. However, these drugs cannot be given to pregnant women and young children. Since there is no prophylactic regimen that is both effective and safe for these groups in areas of multidrug-resistant malaria, pregnant women and young children should avoid travelling to these malarious areas.

Multidrug-resistant malaria has also been reported from Viet Nam and in the Amazon basin of South America, where it occurs in parts of Brazil, French Guiana and Suriname.

Table 7.1 **Choice of stand-by emergency treatment according to recommended chemoprophylactic regimen**

**Note.** A drug selected for stand-by emergency treatment should always be different from the drugs used for prophylaxis, and should be one to which no resistance has been reported in the countries to be visited (see Country list).

Recommended prophylactic regimen	Stand-by emergency treatment
None	Chloroquine, for <i>P. vivax</i> areas only Mefloquine Quinine Artemether and lumefantrine <sup>a</sup> Atovaquone/proguanil <sup>a</sup>
Chloroquine alone or with proguanil	Mefloquine Quinine
Mefloquine	Quinine <sup>b</sup> Quinine + doxycycline or tetracycline for 7 days <sup>b</sup>
Doxycycline	Mefloquine Quinine + tetracycline for 7 days
Atovaquone/proguanil	Quinine + doxycycline/tetracycline for 7 days

<sup>a</sup> There is limited experience at present on drug interactions of artemether/lumefantrine and atovaquone/proguanil with other antimalarial drugs. Therefore, if the patient is already taking an antimalarial as prophylaxis, these drugs should only be used if no other antimalarial treatment option is available.

<sup>b</sup> In these situations, mefloquine prophylaxis should only be resumed 7 days after the last self-treatment dose of quinine.

Table 7.2 Use of antimalarial drugs for prophylaxis in travellers

Generic name	Dosage regimen	Duration of prophylaxis	Use in special groups			Main contraindications <sup>a</sup>	Comments <sup>a</sup>
			Pregnancy	Breast-feeding	Children		
Atovaquone–proguanil combination tablet	One dose daily. 11–20 kg: 62.5 mg atovaquone plus 25 mg proguanil (1 paediatric tablet) daily 21–30 kg: 2 paediatric tablets daily 31–40 kg: 3 paediatric tablets daily > 40 kg: 1 adult tablet (250 mg atovaquone plus 100 mg proguanil) daily	Start 1 day before departure and continue for 7 days after return	No data, not recommended	No data, not recommended	Not recommended under 11 kg because of lack of data	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance <30 ml/min).	Experience with this drug for prophylaxis in non-immune travellers is still limited. It is registered in European countries for chemoprophylactic use with a restriction on duration of use (varying from 5 weeks to 3 months) and in Canada with a restriction on body weight (>40 kg). In the USA the restrictions do not apply. Plasma concentrations of atovaquone are reduced when it is co-administered with rifampicin, rifabutin, metoclopramide or tetracycline.
Chloroquine	5 mg base/kg weekly in one dose, or 10 mg base/kg weekly divided in 6 daily doses Adult dose: 300 mg chloroquine base weekly in one dose or 600 mg chloroquine base weekly divided over 6 daily doses of 100 mg base (with one drug-free day per week)	Start 1 week before departure and continue for 4 weeks after return. If daily doses: start 1 day before departure.	Safe	Safe	Safe	Hypersensitivity to chloroquine; history of epilepsy, psoriasis.	Concurrent use of chloroquine can reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.
Chloroquine–proguanil combination tablet	> 50 kg: 100 mg chloroquine base plus 200 mg proguanil (1 tablet) daily	Start 1 day before departure and continue for 4 weeks after return	Safe	Safe	Tablet size not suitable for persons of < 50 kg body weight	Hypersensitivity to chloroquine and/or proguanil; liver or kidney insufficiency; history of epilepsy; psoriasis.	Concurrent use of chloroquine can reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.

Table 7.2 Use of antimalarial drugs for prophylaxis in travellers (*continued*)

Generic name	Dosage regimen	Duration of prophylaxis	Use in special groups			Comments <sup>a</sup>
			Pregnancy	Breast-feeding	Children	
Doxycycline	1.5 mg salt/kg daily adult dose: 1 tablet of 100 mg daily	Start 1 day before departure and continue for 4 weeks after return.	Contra-indicated	Contra-indicated	Contra-indicated under 8 years of age	Doxycycline makes the skin more susceptible to sunburn. People with sensitive skin should use a highly protective (UVA) sunscreen and avoid prolonged direct sunlight, or switch to another drug. Doxycycline should be taken with plenty of water to prevent oesophageal irritation. Doxycycline may increase the risk of vaginal <i>Candida</i> infections. Studies indicate that the monohydrate form of the drug is better tolerated than the hyclate.
Mefloquine	5 mg/kg weekly adult dose: 1 tablet of 250 mg weekly	Start at least 1 week (preferably 2–3 weeks) before departure and continue for 4 weeks after return	Not recommended in first trimester because of lack of data	Safe	Not recommended under 5 kg because of lack of data	Do not give mefloquine within 12 hours of quinine treatment. Mefloquine and other cardioactive drugs may be given concomitantly only under close medical supervision. Ampicillin, tetracycline and metoclopramide can increase mefloquine blood levels. Vaccination with live bacterial vaccines (e.g. oral live typhoid vaccine, cholera vaccine) should be completed at least 3 days before the first prophylactic dose of mefloquine.
Proguanil	3 mg/kg daily adult dose: 2 tablets of 100 mg daily	Start 1 day before departure and continue for 4 weeks after return	Safe	Safe	Safe	Use only in combination with chloroquine. Proguanil can interfere with live typhoid vaccine.

<sup>a</sup>Please see package insert for full information on contra-indications and precautions.

Table 7.3 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers

Generic name	Dosage regimen	Use in special groups			Main contraindications <sup>a</sup>	Comments <sup>a</sup>
		Pregnancy	Breast-feeding	Children		
Amodiaquine	30 mg base/kg taken as 10 mg base/kg for 3 days	Apparently safe but limited data	Apparently safe but limited data	Safe	Hypersensitivity to amodiaquine; hepatic disorders.	Use only for malaria caused by <i>P. vivax</i> , <i>P. ovale</i> or <i>P. malariae</i> , or for fully chloroquine-sensitive <i>P. falciparum</i> .
Artemether/lumefantrine combination tablet	3-day course of 6 doses total, taken at 0, 8, 24, 36, 48, and 60 hours 5–14 kg: 1 tablet (20 mg artemether plus 120 mg lumefantrine) per dose 15–24 kg: 2 tablets per dose 25–34 kg: 3 tablets per dose 35 kg and over: 4 tablets per dose	No data, not recommended	No data, not recommended	Not recommended under 5 kg because of lack of data	Hypersensitivity to artemether and/or lumefantrine.	Better absorbed if taken with fatty foods
Artemisinin and derivatives	Artemisinin: 10 mg/kg daily for 7 days Artemisinin derivatives: 2 mg/kg daily for 7 days Artemisinin and its derivatives are given with a double divided dose on the first day	Not recommended in first trimester because of lack of data	Safe	Safe	Hypersensitivity to artemisinins.	Normally taken in combination with another effective antimalarial, which reduces the duration of treatment to 3 days. As monotherapy these drugs should be taken for a minimum of 7 days, to prevent recrudescences.
Atovaquone/proguanil combination tablet	One dose daily for three consecutive days 5–8 kg: 2 pediatric tablets daily (at 62.5 mg atovaquone plus 25 mg proguanil per tablet) 9–10 kg: 3 pediatric tablets daily 11–20 kg: 1 adult tablet (250 mg atovaquone plus 100 mg proguanil) daily 21–30 kg: 2 adult tablets daily 31–40 kg: 3 adult tablets daily > 40 kg: 4 adult tablets (1 g atovaquone plus 400 mg proguanil) daily	No data, not recommended	No data, not recommended	Apparently safe in children > 5 kg, but limited data	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance < 30 ml/min).	Plasma concentrations of atovaquone are reduced when the drug is co-administered with rifampicin, rifabutin, metoclopramide or tetracycline.

Table 7.3 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (continued)

Generic name	Use in special groups			Main contraindications <sup>a</sup>	Comments <sup>a</sup>
	Dosage regimen	Pregnancy	Breast-feeding	Children	
Chloroquine	25 mg base/kg divided in daily dose (10, 10, 5 mg base/kg) for 3 days.	Safe	Safe	Safe	Concurrent use of chloroquine can reduce the antibody response to intradermally administered human diploid-cell rabies vaccine. Use only for malaria caused by <i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , or fully sensitive <i>P. falciparum</i> .
Clindamycin	Under 60 kg: 5 mg base/kg 4 times daily for 5 days 60 kg and over: 300 mg base 4 times daily for 5 days	Apparently safe but limited data	Apparently safe but limited data	Apparently safe but limited data	Hypersensitivity to clindamycin or lincomycin; history of gastrointestinal disease, particularly colitis; severe liver or kidney impairment.
Doxycycline	Adults > 50 kg: 800 mg salt over 7 days, taken as 2 tablets (100 mg salt each) 12 hours apart on day 1, followed by 1 tablet daily for 6 days Children 8 years and older: 25–35 kg: 0.5 tablet per dose 36–50 kg: 0.75 tablet per dose > 50 kg: 1 tablet per dose	Contra-indicated	Contra-indicated	Contra-indicated under 8 years of age	Used in combination with quinine in areas of emerging quinine resistance.
(Halofantrine)	8 mg base/kg in 3 doses at 6-hour intervals. Repeat full course after 1 week	No data, not recommended	No data, not recommended	Not recommended under 10 kg because of lack of data	Risk of fatal cardiotoxicity. <b>To be used only in well-equipped medical facilities under close medical supervision, if no other treatment options are available.</b>

<sup>a</sup>Please see package insert for full information on contraindications and precautions.



Table 7.3 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (*continued*)

Generic name	Use in special groups				Comments <sup>a</sup>
	Dosage regimen	Pregnancy	Breast-feeding	Children	Main contraindications <sup>a</sup>
Mefloquine	25 mg base/kg as split dose (15 mg/kg plus 10 mg/kg 6–24 hours apart)	Not recommended in first trimester because of lack of data	Safe	Not recommended under 5 kg because of lack of data	Do not give mefloquine within 12 hours of last dose of quinine treatment. Mefloquine and other related compounds (such as quinine, quinidine, chloroquine) may be given concomitantly only under close medical supervision because of possible additive cardiac toxicity and increased risk of convulsions; co-administration of mefloquine with anti-arrhythmic agents, beta-adrenergic blocking agents, calcium channel blockers, antihistamines including H1-blocking agents, and phenothiazines may contribute to prolongation of QTc interval. Ampicillin, tetracycline and metoclopramide can increase mefloquine blood levels.
Primaquine	Infections acquired south of the equator: 0.5 mg base/kg for 14 days; Infections acquired north of the equator: 0.25 mg base/kg for 14 days	Contra-indicated	Safe	Contra-indicated under 4 years of age	G6PD deficiency; active rheumatoid arthritis; lupus erythematosus; conditions that predispose to granulocytopenia; concomitant use of drugs that may induce haematological disorders.

<sup>a</sup>Please see package insert for full information on contra-indications and precautions.

Table 7.3 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (*continued*)

Generic name	Use in special groups				Main contraindications <sup>a</sup>	Comments <sup>a</sup>
	Dosage regimen	Pregnancy	Breast-feeding	Children		
Quinine	8 mg base/kg 3 times daily for 7 days	Safe	Safe	Safe	<p>Hypersensitivity to quinine or quinidine; tinnitus; optic neuritis; haemolysis; myasthenia gravis.</p> <p>Use with caution in persons with G6PD deficiency, and in patients with atrial fibrillation, cardiac conduction defects, or heart block. Quinine may enhance effect of cardiosuppressant drugs. Use with caution in persons using beta blockers, digoxin, calcium channel blockers, etc.</p>	<p>In areas of high-level resistance to quinine: give in combination with doxycycline, tetracycline or clindamycin.</p> <p>Quinine may induce hypoglycaemia, particularly in (malnourished) children, pregnant women and patients with severe disease.</p>
Sulfadoxine–pyrimethamine combination tablet	5–60 kg: single dose calculated as 25 mg/kg of the sulfa component 60 kg and over: single dose of 3 tablets (1500 mg sulfadoxine plus 75 mg pyrimethamine)	Safe	Safe	Safe	<p>Hypersensitivity to sulfa drugs or pyrimethamine; severe liver or kidney dysfunction; megaloblastic anaemia; concomitant use of other sulfa drugs or folate antagonists.</p>	<p>Cutaneous drug reactions more common in people infected with HIV.</p> <p>Widespread resistance occurs.</p>
Tetracycline	25–49 kg: 5 mg salt/kg 4 times daily for 7 days 50 kg and over: 250 mg salt (1 tablet) 4 times daily for 7 days	Contra-indicated	Contra-indicated	Contra-indicated under 8 years of age	<p>Hypersensitivity to tetracyclines; liver or kidney dysfunction; systemic lupus erythematosus.</p>	<p>Used in combination with quinine in areas of emerging quinine resistance.</p>

<sup>a</sup>Please see package insert for full information on contraindications and precautions.

## Countries and territories with malarious areas

The following list shows all countries where malaria occurs. In some of these countries, malaria is present only in certain areas or up to a particular altitude. In many countries, malaria has a seasonal pattern. These details are provided in the Country list, together with information on the predominant malaria species, status of resistance to antimalarial drugs and recommended chemoprophylactic regimen.

(\* = *P. vivax* risk only)

Afghanistan	Gambia	Pakistan
Algeria*	Georgia*	Panama
Angola	Ghana	Papua New Guinea
Argentina*	Guatemala	Paraguay
Armenia*	Guinea	Peru
Azerbaijan*	Guinea-Bissau	Philippines
Bangladesh	Guyana	Rwanda
Belize	Haiti	Sao Tome and Principe
Benin	Honduras	Saudi Arabia
Bhutan	India	Senegal
Bolivia	Indonesia	Sierra Leone
Botswana	Iran, Islamic Republic of	Solomon Islands
Brazil	Iraq*	Somalia
Burkina Faso	Kenya	South Africa
Burundi	Korea, Democratic	Sri Lanka
Cambodia	People's Republic of*	Sudan
Cameroon	Korea, Republic of*	Suriname
Cape Verde	Kyrgyzstan	Swaziland
Central African Republic	Lao People's Democratic	Syrian Arab Republic*
Chad	Republic	Tajikistan
China	Liberia	Tanzania, United
Colombia	Madagascar	Republic of
Comoros	Malawi	Thailand
Congo	Malaysia	Timor-Leste
Congo, Democratic	Mali	Togo
Republic of the	Mauritania	Turkey*
(former Zaire)	Mauritius*	Turkmenistan*
Costa Rica	Mayotte	Uganda
Côte d'Ivoire	Mexico	Uzbekistan
Djibouti	Morocco*	Vanuatu
Dominican Republic	Mozambique	Venezuela
Ecuador	Myanmar	Viet Nam
Egypt	Namibia	Yemen
El Salvador	Nepal	Zambia
Equatorial Guinea	Nicaragua	Zimbabwe
Eritrea	Niger	
Ethiopia	Nigeria	
French Guiana	Oman	
Gabon		

### Further reading

WHO Roll Back malaria Department website at <http://mosquito.who.int/malariacontrol>  
*Management of severe malaria: a practical handbook*, 2nd ed. Geneva, WHO, 2000. ISBN: 92 4 154523 2.

The use of antimalarial drugs, report of an informal consultation, WHO/CDS/RBM/2001.33.

*WHO Expert Committee on Malaria. Twentieth report.* WHO, Geneva, 2000 (WHO Technical Report Series, No. 892).