

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 underreporting, the real figure may be as high as 30 000. International travellers from non-endemic areas are at high risk of malaria and its consequences because they lack immunity. Immigrants from endemic areas who now live in non-endemic areas and return to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity. Fever occurring in a traveller within three months of leaving a malaria-endemic area is a medical emergency and should be investigated urgently.

Travellers who fall ill during travel may find it difficult to access reliable medical care. Travellers who develop malaria upon return to a non-endemic country present particular problems: doctors may be unfamiliar with malaria, the diagnosis may be delayed, and effective antimalarial medicines may not be registered and/or available, resulting in progression to severe and complicated malaria and, consequently, high case-fatality rates.

Cause

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

Transmission

The malaria parasite is transmitted by female *Anopheles* mosquitoes, which bite mainly between dusk and dawn.

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; mortality in non-immune travellers with 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 7 days after the first possible exposure to malaria and 3 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. Falciparum malaria may be fatal if treatment is delayed beyond 24 hours after the onset of clinical symptoms.

Young children, pregnant women, people living with HIV/AIDS, people who are immunosuppressed and elderly travellers are particularly at risk. Malaria, particularly *P. falciparum*, in non-immune pregnant travellers increases the risk of maternal death, miscarriage, stillbirth and neonatal death.

The forms of malaria caused by other Plasmodium species cause significant morbidity but are rarely life-threatening. *P. vivax* and *P. ovale* can remain dormant in the liver. Relapses caused by these persistent liver forms (“hypnozoites”) may appear months, and rarely several years, after exposure. They are not prevented by current chemoprophylactic regimens, with the exception of primaquine. Latent blood infection with *P. malariae* may be present for many years, but it is very rarely life-threatening.

Geographical distribution

The current distribution of malaria in the world is shown in the map (see Chapter 5). Affected countries and territories are listed at the end of this chapter, as well as in the Country list. The risk for travellers of contracting malaria is highly variable from country to country and even between areas in a country and this must be considered in any discussion of 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 the main urban areas of Africa and, to a lesser extent, India. There is usually less risk at altitudes above 1500 metres but, in favourable climatic conditions, the disease 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 or partially lost 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.

Most cases of falciparum malaria in travellers occur because of poor adherence to, or complete failure to use, prophylactic drug regimens, or use of inappropriate medicines, combined with failure to take adequate precautions against mosquito bites. Studies on travellers' behaviour have shown that adherence to treatment can be improved if travellers are informed of the risk of infection and believe in the benefit of prevention strategies. Late-onset vivax and ovale malaria may occur despite effective prophylaxis, as they cannot be prevented with currently recommended prophylactic regimens.

Travellers to countries where the degree of malaria transmission varies in different areas should seek advice on the risk in the specific zones that they will be visiting. If specific information is not available before travelling, then it is recommended that precautions appropriate for the highest reported risk for the area or country should be taken; these precautions can be adjusted when more information becomes available on arrival. 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. Culturally sensitive approaches are needed to advise different groups at risk.

Precautions

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

- Be **A**ware of the risk, the incubation period, the possibility of delayed onset, and the main symptoms.
- Avoid being **B**itten by mosquitoes, especially between dusk and dawn.
- Take antimalarial drugs (Chemoprophylaxis) 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 (or, rarely, later) after departure from a risk area.

Protection against mosquito bites

All travellers should be advised 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, in the section “Protection against vectors”.

Chemoprophylaxis

The most appropriate chemoprophylactic antimalarial drug(s) (if any) for the destination(s) should be prescribed in the correct dosages (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 preferably be started 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.

- 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 because of its effect on early liver-stage parasites (“liver schizonts”). Premature interruption of the daily atovaquone–proguanil prophylaxis regimen may lead to loss of this causal prophylactic effect, in which case atovaquone–proguanil prophylaxis should also be continued for 4 weeks upon return.
- Depending on the type of malaria at the destination, travellers should be advised about possible late-onset *P. ovale* and *P. vivax*.

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

See Table 7.1 for details on individual drugs.

	Malaria risk	Type of prevention
Type I	Very limited risk of malaria transmission	Mosquito bite prevention only
Type II	Risk of <i>P. vivax</i> malaria only; or fully chloroquine-sensitive <i>P. falciparum</i>	Mosquito bite prevention plus chloroquine chemoprophylaxis
Type III	Risk of <i>P. vivax</i> and <i>P. falciparum</i> malaria transmission, combined with emerging chloroquine resistance	Mosquito bite prevention plus chloroquine+proguanil chemoprophylaxis
Type IV	(1) High risk of <i>P. falciparum</i> malaria, in combination with reported antimalarial drug resistance; or (2) Moderate/low risk of <i>P. falciparum</i> malaria, in combination with reported high levels of drug resistance ¹	Mosquito bite prevention plus mefloquine, doxycycline or atovaquone–proguanil chemoprophylaxis (select according to reported resistance pattern)

¹ Alternatively, when travelling to rural areas with multidrug-resistant malaria and only a very low risk of *P. falciparum* infection, mosquito bite prevention can be combined with stand-by emergency treatment.

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 persistent or significant disability or incapacity – are rare and normally identified in post-marketing surveillance once a drug has been in use for some time. Severe neuropsychiatric disturbances (seizures, psychosis, encephalopathy) occur in approximately 1 in 10 000 travellers receiving mefloquine prophylaxis, and have also been reported for chloroquine at a similar rate. 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 observed (see Table 7.1) to reduce the risk of serious adverse reactions. Pregnant women, people travelling with young children, and people with chronic illnesses should seek individual medical advice. Any traveller who develops severe side-effects to an antimalarial should stop taking the drug and seek immediate medical attention. This applies particularly to neurological or psychological disturbances experienced with mefloquine prophylaxis. Mild nausea, occasional vomiting or loose stools should not prompt discontinuation of prophylaxis, but medical advice should be sought if symptoms persist.

Long-term use of chemoprophylaxis

Adherence and tolerability are important aspects of chemoprophylaxis use in long-term travellers. There are few studies on chemoprophylaxis use in travel lasting more than 6 months. The risk of serious side-effects associated with long-term prophylactic use of chloroquine and proguanil is low, but retinal toxicity is of concern when a cumulative dose of 100 g of chloroquine is reached. Anyone who has taken 300 mg of chloroquine weekly for more than 5 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 3 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. Pharmacokinetic data indicate that mefloquine does not accumulate during long-term intake. Available data on long-term chemoprophylaxis with doxycycline (i.e. more than 12 months) is limited but reassuring. There are few data on long-term use of doxycycline in women, but use of this drug is associated with an increased frequency of

Candida vaginitis. Atovaquone–proguanil is registered in European countries with a restriction on duration of use (varying from 5 weeks to 1 year); such restrictions do not apply in the United States.

Treatment

Early diagnosis and appropriate treatment can be life-saving. A blood sample should be taken from all travellers with suspected malaria and examined without delay for malaria parasites in an experienced, reliable laboratory. If no parasites are found in the first blood film, a series of blood samples should be taken at 6–12-hour intervals and examined very carefully. Malaria rapid diagnostic tests can be useful in centres where malaria microscopy is unavailable. When laboratory analysis is delayed, physicians should begin treatment if the clinical indicators and travel history suggest malaria.

For travellers who are treated for malaria in non-endemic areas, the following principles apply:

- Patients are at high risk of malaria and its consequences because they are non-immune.
- If the patient has taken prophylaxis, the same medicine should not be used for treatment.
- Be alert on the possibility of mixed *P. falciparum*–*P. vivax* infections.

The following antimalarials are suitable for treatment of **uncomplicated falciparum malaria** in travellers returning to non-endemic countries:

- artemether–lumefantrine
- atovaquone–proguanil
- quinine plus doxycycline or clindamycin.

The treatment for **vivax malaria** in travellers is as follows:

- Chloroquine combined with primaquine is the treatment of choice to achieve radical cure (i.e. to cure both the blood stage and liver stage infections, and thereby prevent both recrudescence and relapse).
- Amodiaquine combined with primaquine should be given for chloroquine-resistant vivax malaria. Where amodiaquine is not available, quinine or artemether–lumefantrine can be used instead.
- Travellers must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before receiving primaquine antirelapse treatment. In moderate G6PD deficiency, primaquine should be given in an adjusted regimen of 0.75 mg base/

kg body weight once a week for 8 weeks. In severe G6PD deficiency, primaquine should not be given.

- In mixed *P. falciparum*–*P. vivax* infections, the treatment for *P. falciparum* will usually also cure the attack of *P. vivax*, but primaquine should be added to achieve radical cure and prevent relapses.

Chemoprophylaxis and treatment of falciparum malaria are becoming more complex because *P. falciparum* is increasingly resistant to various antimalarial drugs. Chloroquine resistance of *P. vivax* is rare but increasing. It was first reported in the late 1980s in Indonesia and Papua New Guinea. Focal chloroquine resistance or prophylactic and/or treatment failure have since also been observed in Brazil, Colombia, Ethiopia, Guyana, India, Myanmar, Peru, the Republic of Korea, Solomon Islands, Thailand and Turkey. Chloroquine-resistant *P. malariae* has been reported from Indonesia.

Relapsing malaria caused by *P. ovale* should be treated with chloroquine and primaquine. **Malaria caused by *P. malariae*** should be treated with the standard regimen of chloroquine as for vivax malaria, but it does not require radical cure with primaquine because no hypnozoites are formed in infection with this species.

Returning travellers with **severe falciparum malaria** should be managed in an intensive care unit. Parenteral antimalarial treatment should be with artesunate (first choice), artemether or quinine. If these medicines are not available, use parenteral quinidine with careful clinical and electrocardiographic monitoring.

In recent years, sporadic cases of malaria due to *Plasmodium knowlesi* have been reported in travellers returning from forested areas of South-East Asia. This type of “monkey malaria”, which normally occurs in long-tailed crab-eating and pig-tailed macaques and banded leaf monkeys, is transmitted by mosquitoes of the *Anopheles leucosphyrus* group. Human infections have been described in people staying in rainforests and/or their fringe areas in South-East Asia that are within the range of the natural monkey hosts and mosquito vector of this infection. These areas include parts of Indochina, Indonesia, Malaysia, Myanmar, the Philippines, Singapore and Thailand. On microscopy examination, the mature forms of *P. knowlesi* may be mistaken for *P. malariae*, while its ring forms may resemble *P. falciparum*. The parasite has a life-cycle of 24 hours, and can give rise to daily fever spikes occurring 9–12 days after infection. Symptoms may be atypical. Treatment is with a standard regimen of chloroquine. The clinical condition of patients infected with *P. knowlesi* may deteriorate quickly. Severe *P. knowlesi* malaria with organ failure may occur; it should be treated as for severe falciparum malaria.

Sporadic fatal outcomes have been described. *P. knowlesi* infection should always be considered in patients with a microscopy diagnosis of *P. malariae* and a travel history to forested areas of South-East Asia, including travel to such areas in parts of South-East Asia where malaria is not normally endemic. Travellers to these areas should protect themselves against mosquito bites between dusk and dawn to prevent infection, and take the usual chemoprophylaxis where indicated (see Country list). *P. knowlesi* has no persistent liver forms and relapses do not occur.

The dosage regimens for the treatment of uncomplicated malaria are provided in Table 7.2. The details of the clinical management of severe malaria are addressed in other WHO publications (see list of references).

Treatment abroad and 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 a correct diagnosis and safe and effective treatment. In principle, travellers can be treated with artemisinin-based combination therapy (ACT) according to the national policy in the country they will be visiting. National antimalarial drug policies for all endemic countries are listed at <http://www.who.int/malaria/treatmentpolicies.html>.

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

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 in remote locations. In such cases, travellers are advised to carry antimalarial drugs for self-administration (“stand-by emergency treatment”).

Stand-by emergency treatment (SBET) 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 choose to reserve chemoprophylaxis for high-risk areas and seasons only. However, they should continue to take measures to protect against mosquito bites and be prepared for an attack of malaria: they should always carry a course of antimalarial drugs for SBET, seek immediate medical care in case of fever, and take SBET if prompt medical help is not available.

Furthermore, SBET – combined with protection against mosquito bites – may be indicated for those who travel for 1 week or more to remote rural areas where

there is multidrug-resistant malaria but a very low risk of infection, and the risk of side-effects of prophylaxis may outweigh that of contracting malaria. This may be the case in certain border areas of Thailand and neighbouring countries in South-East Asia, as well as parts of the Amazon basin.

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.

Successful SBET depends crucially on travellers’ behaviour, and health advisers need to spend time explaining the strategy. Travellers provided with SBET should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, possible side-effects, and the possibility of drug failure. If several people travel together, the individual dosages for SBET should be specified. Weight-based dosages for children need to be clearly indicated. **Travellers should realize that self-treatment is a first-aid measure, and that they should still seek medical advice as soon as possible.**

In general, travellers carrying SBET 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.
- Do not treat suspected malaria with the same drugs used for prophylaxis.
- 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.
- Complete the stand-by treatment course and resume antimalarial prophylaxis 1 week after the *first* treatment dose. To reduce the risk of drug interactions, at least 12 hours should elapse between the *last* treatment dose of quinine and resumption of mefloquine prophylaxis.

The drug options for SBET are in principle the same as for treatment of uncomplicated malaria (see above). The choice will depend on the type of malaria in the

area visited and the chemoprophylaxis regimen taken. Artemether–lumefantrine has been registered (in Switzerland and the United Kingdom) for use as SBET for travellers. Table 7.2 provides details on individual drugs.

Multidrug-resistant malaria

Multidrug-resistant malaria has been reported from South-East Asia (Cambodia, Myanmar, Thailand, Viet Nam) and the Amazon basin of South America, where it occurs in parts of Brazil, French Guiana and Suriname.

In border areas between Cambodia, Myanmar and Thailand, *P. falciparum* infections do not respond to treatment with chloroquine or sulfadoxine–pyrimethamine, sensitivity to quinine is reduced, and treatment failures in excess of 50% with mefloquine are being reported. In these situations, malaria prevention consists of personal protection measures in combination with atovaquone–proguanil or doxycycline as chemoprophylaxis. SBET with atovaquone–proguanil or artemether–lumefantrine can be used in situations where the risk of infection is very low. However, these drugs cannot be given to pregnant women and young children. Since there is no prophylactic or SBET 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.

Special groups

Some groups of travellers, especially young children, pregnant women and immunosuppressed travelers, are at particular risk of serious consequences if they become infected with malaria. Recommendations for these groups are difficult to formulate because safety data are limited. The special concerns for immigrants from endemic areas who live in non-endemic areas and return to their home countries to visit friends and relatives are addressed in Chapter 9.

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 only of vivax malaria. Pregnant women should seek medical help immediately if malaria is suspected; if this is not possible, they should take stand-

by emergency treatment. Medical help must be sought as soon as possible after starting stand-by treatment. There is very limited information on the safety and efficacy of most antimalarials in pregnancy, particularly during the first trimester. However, inadvertent exposure to antimalarials is not an indication for termination of the pregnancy.

Mosquito bite prevention

Pregnant women are particularly susceptible to mosquito bites and should therefore be vigilant in using protective measures, including insect repellents and insecticide-treated mosquito nets. They should take care not to exceed the recommended dosage of insect repellents.

Chemoprophylaxis

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, including during the first 3 months of pregnancy. In type IV areas, mefloquine prophylaxis may be given during the second and third trimesters, but there is limited information on the safety of mefloquine during the first trimester. In light of the danger of malaria to mother and fetus, experts increasingly agree that travel to a chloroquine-resistant *P. falciparum* area during the first trimester of pregnancy should be avoided or delayed at all costs; if this is truly impossible, good preventive measures should be taken, including prophylaxis with mefloquine where this is indicated. Doxycycline is contraindicated during pregnancy. Atovaquone–proguanil has not been sufficiently investigated to be prescribed in pregnancy.

Treatment

Clindamycin and quinine are considered safe, including during the first trimester of pregnancy; artemisinin derivatives can be used to treat uncomplicated malaria in the second and third trimesters, and in the first trimester only if no other adequate medicines are available. Amodiaquine and chloroquine can be safely used for treatment of vivax malaria in pregnancy, but primaquine anti-relapse treatment should be postponed until after delivery. Atovaquone–proguanil and artemether–lumefantrine have not been sufficiently investigated to be prescribed in pregnancy.

The recommended treatment for **uncomplicated falciparum malaria in the first trimester** is quinine +/- clindamycin. For the **second and third trimesters**, the options are: artemisine-based combination therapy (ACT) in accordance with national policy; artesunate plus clindamycin; or quinine plus clindamycin.

Pregnant women with falciparum malaria, particularly in the second and third trimesters of pregnancy, are more likely than other adults to develop severe malaria, often complicated by hypoglycaemia and pulmonary oedema. Maternal mortality in severe malaria is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common. **Pregnant women with severe malaria** must be treated without delay with full doses of parenteral antimalarial treatment. In the **first trimester**, either quinine or artesunate can be used. **In the second and third trimesters**, artesunate is the first option and artemether the second option. Treatment must not be delayed, so if only one of the drugs artesunate, artemether, or quinine is available it should be started immediately.

Information on the safety of antimalarial drugs during breastfeeding is provided in Tables 7.1 and 7.2.

Women who may become pregnant during or after travel

Malaria prophylaxis may be taken, but pregnancy should preferably be avoided during the period of drug intake and for 1 week after doxycycline, 3 weeks after atovaquone-proguanil, and 3 months after mefloquine prophylaxis is stopped. If pregnancy occurs during antimalarial prophylaxis, this is not considered to be an indication for pregnancy termination.

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 risk of falciparum malaria. If travel cannot be avoided, children must be very carefully protected against mosquito bites and be given appropriate chemoprophylactic

drugs. Long-term travellers and expatriates should adjust the chemoprophylaxis dosage according to the increasing weight of the growing child.

Mosquito bite prevention

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.

Chemoprophylaxis

Chloroquine, proguanil and mefloquine are considered compatible with breastfeeding. 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, and tablets should be crushed and ground as necessary. The bitter taste of the tablets can be disguised with jam or other foods. Chloroquine and proguanil are safe for babies and young children but their use is now very limited, because of spreading chloroquine resistance. Mefloquine may be given to infants of more than 5 kg body weight. Atovaquone–proguanil is generally not recommended for prophylaxis in children who weigh less than 11 kg, because of limited data; in Belgium, Canada and the United States it is given for prophylaxis in infants of more than 5 kg body weight. Doxycycline is contraindicated in children below 8 years of age. 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.

Treatment

Acutely ill children with falciparum malaria require careful clinical monitoring as their condition may deteriorate rapidly. Every effort should be made to give oral treatment and ensure that it is retained. ACT as per national policy may be used as first-line treatment while abroad. Oral treatment options for SBET and returning travellers are: artemether-lumefantrine (not recommended under 5 kg because of lack of data), atovaquone–proguanil (apparently safe in children weighing 5 kg or more, but limited data), and quinine plus clindamycin (safe, but limited data on clindamycin). Quinine plus doxycycline is an option for children of 8 years and older. Parenteral treatment and admission to hospital are indicated for young children who cannot swallow antimalarials reliably.

Chloroquine and amodiaquine can be safely given to treat *P. malariae*, *P. ovale* or *P. vivax* infections in young children. The lower age limit for anti-relapse treatment with primaquine has not been established; it is generally contraindicated in young infants.

Information on the safety of drugs for prophylaxis and treatment of young children is provided in Tables 7.1 and 7.2.

Immunosuppressed travellers

Immunosuppressed travellers are at increased risk of malaria, and prevention of malaria through avoidance of mosquito bites and use of chemoprophylaxis is particularly important. Individual pre-travel advice should be carefully sought. There may be an increased risk of antimalarial treatment failure in people living with HIV/AIDS. However, at present, there is insufficient information to permit modifications to treatment regimens to be recommended. Pharmacokinetic interactions between certain antimalarials (including artemether–lumefantrine), and antiretrovirals (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) are theoretically possible and should be avoided as they could lead to toxicity. Cutaneous drug reactions following treatment with sulfadoxine–pyrimethamine are more common in people infected with HIV. Treatment with ACT containing sulfadoxine–pyrimethamine should be avoided in HIV-infected patients receiving co-trimoxazole prophylaxis.

Table 7.1 Use of antimalarial drugs for prophylaxis in travellers

Generic name	Dosage regimen	Use in special groups			Main contraindications ^a	Comments ^a
		Duration of prophylaxis	Pregnancy	Breast-feeding		
Atovaquone–proguanil combination tablet	One dose daily. 1.1–20 kg: 62.5 mg atovaquone plus 25 mg proguanil (1 paediatric tablet) daily 2.1–30 kg: 2 paediatric tablets daily 3.1–40 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	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance < 30 ml/min).	Registered in European countries for chemoprophylactic use with a restriction on duration of use (varying from 5 weeks to 1 year). 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 <i>Adult dose:</i> 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	Hypersensitivity to chloroquine; history of epilepsy, psoriasis.	Concurrent use of chloroquine may 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	Hypersensitivity to chloroquine and/or proguanil; liver or kidney insufficiency; history of epilepsy; psoriasis.	Concurrent use of chloroquine may reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.

^a Please see package insert for full information on contraindications and precautions.

Table 7.1 Use of antimalarial drugs for prophylaxis in travellers (*continued*)

Generic name	Dosage regimen	Use in special groups				Main contraindications ^a	Comments ^a
		Duration of prophylaxis	Pregnancy	Breast-feeding	Children		
Doxycycline	1.5 mg salt/kg daily <i>Adult dose:</i> 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	Hypersensitivity to tetracyclines; liver dysfunction.	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 hydrate.
Mefloquine	5 mg/kg weekly <i>Adult dose:</i> 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 (also see page 160)	Safe	Not recommended under 5 kg because of lack of data	Hypersensitivity to mefloquine; psychiatric (including depression) or convulsive disorders; history of severe neuropsychiatric disease; concomitant halofantrine treatment; treatment with mefloquine in previous 4 weeks; not recommended in view of limited data for people performing activities requiring fine coordination and spatial discrimination, e.g. pilots, machine operators.	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 may increase mefloquine blood levels.
Proguanil	3 mg/kg daily <i>Adult dose:</i> 2 tablets of 100 mg daily	Start 1 day before departure and continue for 4 weeks after return	Safe	Safe	Safe	Liver or kidney dysfunction.	Use only in combination with chloroquine. Proguanil may interfere with live typhoid vaccine.

^a Please see package insert for full information on contraindications and precautions.

Table 7.2 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers

Generic name	Dosage regimen	Use in special groups			Main contraindications ^a	Comments ^a
		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> .
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.	Must be taken with fatty foods to improve absorption.
Artemisinin and derivatives	<i>Artemisinin</i> : 10 mg/kg daily for 7 days <i>Artemisinin derivatives</i> : 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 (as ACT), 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 3 consecutive days 5–8 kg: 2 paediatric tablets daily (at 62.5 mg atovaquone plus 25 mg proguanil per tablet) 9–10 kg: 3 paediatric 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.

^a Please see package insert for full information on contraindications and precautions.

Table 7.2 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (*continued*)

Generic name	Dosage regimen	Use in special groups			Main contraindications ^a	Comments ^a
		Pregnancy	Breast-feeding	Children		
Choroquine	25 mg base/kg divided in daily dose (10, 10, 5 mg base/kg) for 3 days	Safe	Safe	Safe	Hypersensitivity to chloroquine; history of epilepsy, psoriasis.	Use only for malaria caused by <i>P. vivax</i> , <i>P. ovale</i> or <i>P. malariae</i> . Concurrent use of chloroquine may reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.
Clindamycin	<i>Under 60 kg</i> : 5 mg base/kg 4 times daily for 5 days <i>60 kg and over</i> : 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.	Used in combination with quinine in areas of emerging quinine resistance.
Doxycycline	<i>Adults > 50 kg</i> : 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 <i>Children 8 years and older</i> : 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	Hypersensitivity to tetracyclines; liver dysfunction.	Used in combination with quinine in areas of emerging quinine resistance.

^a Please see package insert for full information on contraindications and precautions.

Table 7.2 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (*continued*)

Generic name	Dosage regimen	Use in special groups			Main contraindications ^a	Comments ^a
		Pregnancy	Breast-feeding	Children		
Mefloquine	25 mg base/kg as split dose (1.5 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	Hypersensitivity to mefloquine; psychiatric (including depression) or convulsive disorders; history of severe neuropsychiatric disease; concomitant halofantrine treatment; treatment with mefloquine in previous 4 weeks; use with caution in people whose activities require fine coordination and spatial discrimination, e.g. pilots and machine operators.	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 may increase mefloquine blood levels.
Primaquine	0.25 mg base/kg, taken with food once daily for 14 days in Oceania and South-East Asia. the dose should be 0.5 mg base/kg	Contraindicated	Safe	Lower age limit not established. Generally contraindicated in young infants	G6PD deficiency; active rheumatoid arthritis; lupus erythematosus; conditions that predispose to granulocytopenia; concomitant use of drugs that may induce haematological disorders.	Used as anti-relapse treatment for <i>P. vivax</i> and <i>P. ovale</i> infections.

^a Please see package insert for full information on contraindications and precautions.

Table 7.2 Use of antimalarial drugs for treatment of uncomplicated malaria in travellers (*continued*)

Generic name	Dosage regimen	Use in special groups			Main contraindications ^a	Comments ^a
		Pregnancy	Breast-feeding	Children		
Quinine	8 mg base/kg 3 times daily for 7 days	Safe	Safe	Safe	Hypersensitivity to quinine or quinidine; tinnitus; optic neuritis; haemolysis; myasthenia gravis. 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.	In areas of emerging resistance to quinine, give in combination with doxycycline, tetracycline or clindamycin. Quinine may induce hypoglycaemia, particularly in (malnourished) children, pregnant women and patients with severe disease.

^a Please see package insert for full information on contraindications and precautions.

Countries and territories with malarious areas

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

(* = *P. vivax* risk only)

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

Further reading

Guidelines for the treatment of malaria. Geneva, World Health Organization, 2006 (WHO/HTM/MAL/2006.1108).

Malaria vector control and personal protection: report of a WHO Study Group. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 936).

Management of severe malaria: a practical handbook, 2nd ed. Geneva, World Health Organization, 2000.

These documents are available on the WHO Global Malaria Programme web site:
<http://www.who.int/malaria>.