CHAPTER 7

Malaria

7.1 Background

Malaria is a common and life-threatening disease in many tropical and subtropical areas. There are currently over 100 countries and territories where there is a risk of malaria transmission, and these are visited by more than 125 million international travellers every year.

Each year many international travellers fall ill with malaria while visiting countries/territories where malaria is endemic, and well over 10 000 are reported to become ill with malaria after returning home; however, underreporting means that the real figure may be considerably higher. International travellers to countries/territories with ongoing local malaria transmission arriving from countries with no transmission are at high risk of malaria infection and its consequences because they lack immunity. Migrants from countries/territories with malaria transmission living in malaria-free countries and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity.

Travellers who fall ill during travel may find it difficult to access reliable medical care. Travellers who develop malaria upon returning to a country that is malaria-free face particular problems: medical personnel 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.

Fever occurring in a traveller within 3 months of leaving a country in which there is risk of malaria is a potential medical emergency and should be investigated urgently to exclude malaria. In the absence of rapid access to reliable diagnostic facilities, stand-by emergency treatment (SBET) is indicated (see section 7.3.2, below).

7.1.1 Cause

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

Humans occasionally become infected with *Plasmodium* species that normally infect animals, such as *P. knowlesi*. As yet, there are no reports of human–mosquito–human transmission of such "zoonotic" forms of malaria.

7.1.2 Transmission

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

7.1.3 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 1 week after the first possible exposure is not malaria.

The most severe form is caused by *P. falciparum*; 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, pulmonary oedema, generalized convulsions, circulatory collapse, followed by coma and death. 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 who are immunosuppressed and elderly travellers are particularly at risk of severe disease. Malaria, particularly *P. falciparum*, in non-immune pregnant travellers increases the risk of maternal death, miscarriage, stillbirth and neonatal death.

Human malaria caused by other *Plasmodium* species results in significant morbidity but is rarely life-threatening. Cases of severe *P. vivax* malaria have been reported among populations living in (sub)tropical countries with malaria risk. *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. Relapses 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.

P. knowlesi malaria is primarily a public health problem among populations living or working in forested areas in south-east Asia. In recent years, sporadic cases of travellers' malaria due to *P. knowlesi* have been reported. Humans can be infected with this "monkey malaria" parasite while staying in rainforests and/or their fringe areas, within the range of the natural monkey hosts and mosquito vector of this infection. These areas include parts of Brunei Darussalam, Cambodia, China, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Viet Nam. 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 of malaria. Severe *P. knowlesi* malaria with organ failure may occur, and sporadic fatal outcomes have been described. *P. knowlesi* has no persistent liver forms and relapses do not occur. Travellers to forested areas of south-east Asia where human *P. knowlesi* infections have been reported should protect themselves against mosquito bites between dusk and dawn to prevent infection and take chemoprophylaxis where indicated (see Country list).

7.1.4 Geographical distribution

The current distribution of malaria in the world is shown on the map in this chapter; affected countries and territories are listed both at the end of this chapter and in the Country list. The risk for travellers of contracting malaria is highly variable from country to country and even between areas within a country, and this must be considered in any discussion of appropriate preventive measures.

In most countries/territories with malaria risk, the centres of large urban areas – but not necessarily the peri-urban areas – are free of malaria transmission. However, malaria can be transmitted throughout urban areas of Africa and, to a lesser extent, India. There is usually less risk at altitudes above 1500 m, although in favourable climatic conditions the disease can be contracted at altitudes up to almost 3000 m. The risk of infection may also vary according to the season, being highest at the end of, or soon after, the rainy season.

There is no risk of malaria in many tourist destinations in south-east Asia, the Caribbean and Latin America, and information on malaria risk in each country/territory is given in the Country list.

7.1.5 Risk for travellers

During the transmission season in countries/territories with malaria risk, all non-immune travellers who are 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 countries or areas of no risk. Children who have migrated to countries and areas of no risk are particularly at risk when they travel to malarious areas to visit friends and relatives.

Most cases of falciparum malaria in travellers occur because of poor adherence to, or use of inappropriate, prophylactic malaria drug regimens, combined with failure to take adequate precautions against mosquito bites. Studies on travellers' behaviour have shown that adherence to chemoprophylaxis 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 these parasites causes relapses that cannot be prevented with medicines currently recommended for chemoprophylaxis.

Malaria risk is not evenly distributed where the disease is prevalent. Travellers to any country/territory in which malaria transmission varies by area should seek advice on the risk of infection in the particular zones that they will be visiting. If specific information is not available before travelling, it is recommended that precautions appropriate for the highest reported risk for the country/territory 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 health facilities are not readily available. Travellers staying overnight in rural areas may be at highest risk.

7.2 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 (**C**hemoprophylaxis) when appropriate, at regular intervals to prevent acute malaria attacks.
- Immediately seek **D**iagnosis and treatment if a fever develops 1 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.

7.2.1 Protection against mosquito bites

All travellers should be advised that personal 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 3.7.4 "Protection against vectors".

7.2.2 Chemoprophylaxis

The most appropriate chemoprophylactic antimalarial drug for the destination should be prescribed in the correct dosage (see Country list and Table 7.2).

Travellers and their doctors should be aware that **no antimalarial prophylactic regimen gives complete protection**, but good chemoprophylaxis (adherence to the recommended drug regimen) significantly reduces the risk of fatal disease. The following should also be taken into account:

- Dosing schedules for children should be based on body weight.
- Weekly chloroquine should be started 1 week before arrival.
- Weekly mefloquine should preferably be started 2–3 weeks before departure, to achieve adequate drug blood levels and to detect possible side-effects before travel so that possible alternatives can be considered.
- Daily prophylaxis with doxycycline or atovaquone–proguanil should be started 1–2 days before arrival (or earlier if drug tolerability needs to be checked before departure).
- 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 it is effective against early liver-stage parasites (liver schizonts). However, in case daily doses have been skipped while the traveller is exposed to malaria risk, atovaquone–proguanil prophylaxis should also be taken for 4 weeks after return.
- Depending on the type of malaria at the destination, travellers should be advised about possible late-onset malaria caused by *P. vivax* and *P. ovale*, due to persistent hepatic forms of these parasites.

Depending on the type of malaria risk in the specific area of the country/territory visited (see Country list), the recommended prevention method may be mosquito bite prevention only, or mosquito bite prevention in combination with chemoprophylaxis and/or stand-by emergency treatment, as shown in Table 7.1 (see also Table 7.2 for details of individual drugs).

There are specific contraindications and possible side-effects for all antimalarial drugs. 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. 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 7.2) 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 adverse effects while using 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 chemoprophylaxis

Adherence and tolerability are important aspects of chemoprophylaxis for people with long-term exposure to risk of malaria infection. There are few studies on chemoprophylaxis use for more than 6 months.

- The risk of serious side-effects associated with long-term prophylactic use of chloroquine 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) are 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 vaginitis due to *Candida*.
- 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.

7.3 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 intervals of 6–12 hours and examined very carefully. Malaria rapid diagnostic tests can be useful in centres where malaria microscopy is unavailable or unreliable. 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 countries or areas of no risk, the following principles apply:

- Patients who are non-immune are at high risk of malaria and its consequences.
- All patients with suspected clinical malaria should be tested for malaria in a reliable diagnostic centre with microscopy or rapid diagnostic test. When laboratory diagnostic results are delayed, treatment should be started on the basis of clinical indicators and travel history.
- If the patient has taken malaria chemoprophylaxis, the same medicine should not be used for treatment.
- Be alert to the possibility of mixed *P. falciparum–P. vivax* infections.

The following combination therapies are suitable for treatment of **uncomplicated falciparum malaria** in travellers on return to countries or areas of no risk:

– artemether–lumefantrine
– atovaquone–proguanil
– dihydroartemisinin–piperaquine
– 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).
- Dihydroartemisinin–piperaquine or artemether–lumefantrine should be given for chloroquine-resistant vivax malaria. Where these are not available, quinine can be used instead. All these treatments should be combined with primaquine.
- Travellers must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before receiving primaquine anti-relapse treatment. Primaquine is contraindicated in travellers with G6PD deficiency.
- In mixed *P. falciparum–P. vivax* infections, the treatment for *P. falciparum* will usually also cure the attack of *P. vivax.* After G6PD testing, primaquine should be given 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 can no longer be used for prevention and treatment of falciparum malaria in travellers. Chloroquine resistance of *P. vivax* is still rare but increasing. Focal chloroquine resistance or prophylactic and/or treatment failure of *P. vivax* has now been observed in 23 countries: Afghanistan, Bolivia, Brazil, Cambodia, China, Colombia, Ethiopia, Guyana, India, Indonesia, Madagascar, Malaysia (Borneo), Myanmar, Pakistan, Papua New Guinea, Peru, the Republic of Korea, Solomon Islands, Sri Lanka, Thailand, Turkey, Vanuatu and Viet Nam. Chloroquine-resistant *P. malariae* has been reported from Indonesia.

Relapsing malaria caused by *P. ovale* can be treated with chloroquine and primaquine. **Malaria caused by *P. malariae*** can be treated with the standard regimen of chloroquine, but it does not require radical cure with primaquine because no hypnozoites are generated by 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, parenteral quinidine should be used, with careful clinical and electrocardiographic monitoring.

On microscopy examination, the mature forms of ***P. knowlesi*** may be mistaken for *P. malariae*, while its ring forms may resemble *P. falciparum*. Knowlesi malaria can be treated with a standard regimen of chloroquine or with the antimalarials recommended for uncomplicated falciparum malaria. 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.

P. knowlesi infection should always be considered in patients with a microscopy diagnosis of *P. malariae* and a history of travel to forested areas of south-east Asia, including areas where malaria is not normally present.

The dosage regimens for the treatment of uncomplicated malaria are given in Table 7.3. Details of the clinical management of severe malaria are addressed in other WHO publications (see “Further reading” at the end of this chapter).

7.3.1 Treatment during travel

An individual who experiences a fever 1 week or more after entering an area with 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 are visiting. National antimalarial drug policies for all countries/territories with risk are listed at http://www.who.int/malaria/areas/treatment/drug_policies/en/index.html.

In light of the spread of counterfeit drugs in some malaria-endemic settings, travellers are advised to buy antimalarial medicines from reliable sources.

7.3.2 Stand-by emergency treatment (SBET)

Many travellers will be able to obtain proper medical attention within 24 hours of the onset of fever. For travellers staying in remote locations where prompt access to medical care may be problematic, it is advisable to carry antimalarial drugs for self-administration ("stand–by emergency treatment" - SBET).

SBET may also be indicated for travellers in some occupational groups who make frequent short stops in countries or areas with malaria risk 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 short-term travellers going for 1 week or more to certain remote rural areas where there is very low risk of infection (see Country list).

Studies on the use of rapid diagnostic tests (RDTs) 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. When performed by well-trained staff, good-quality RDTs are reliable and several tests have good diagnostic performance (see http://apps.who.int/iris/bitstream/10665/77748/1/9789241504720_eng.pdf).

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 inadequate response to treatment. 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 SBET 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 as were 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 antimalarial medicine. 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 SBET course and resume antimalarial prophylaxis 1 week after the *first* treatment dose.
- The drug options for SBET are in principle the same as for treatment of uncomplicated malaria (section 7.3). 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. Quinine is less feasible for SBET because of the long and complex treatment regimen and the dose-dependent side-effects. If quinine is taken for SBET, at least 12 hours should elapse between the *last* treatment dose of quinine and resumption of mefloquine prophylaxis to reduce the risk of drug interactions. Table 7.3 provides details on individual drugs.

7.3.3 Multidrug-resistant malaria

Multidrug-resistant malaria is defined as malaria that is resistant to drugs of more than two different chemical families. The term is most often used when in addition to chloroquine and sulfadoxine-pyrimethamine resistance, also *P. falciparum* resistance to mefloquine and/or artemisinins have been reported.

Mefloquine resistance affects travellers' choices of prophylaxis and SBET, and is currently reported in Cambodia, south-eastern Myanmar, and Thailand. In these areas, the choice of chemoprophylaxis is limited to doxycycline and atovaquone–proguanil. Artemisinin resistance has no implication for prophylaxis choices but has an impact on treatment; it is reported in Cambodia, Myanmar, Thailand and Viet Nam, and most recently in the Lao People's Democratic Republic. In these countries, SBET options are limited to atovaquone–proguanil only. Local treatment should be with the ACTs recommended at national level. To reduce the danger of spreading artemisinin-resistant parasites to other endemic parts of the world, all malaria patients who have travelled in these areas should be promptly diagnosed and treated effectively. The addition of a single oral dose of primaquine (0.25 mg base/kg body weight) to treatment will accelerate the removal of *P. falciparum* gametocytes and thereby reduce the risk of onward

transmission in other endemic areas. The medical staff should follow national reporting requirements, especially for imported falciparum malaria cases that originated from travel to the above-described border areas of multidrug-resistance.

7.4 Special groups

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

7.4.1 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 follow the recommendations given below.

Mosquito bite prevention during pregnancy

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 usage of insect repellents.

Chemoprophylaxis during pregnancy

In areas with exclusively *P. vivax* transmission, chloroquine prophylaxis may be used. In *P. falciparum* transmission areas, mefloquine prophylaxis may be given during the second and third trimesters, but chemoprophylaxis with this drug is not recommended in the first trimester because of the limited information on safety of mefloquine during this period of pregnancy. In light of the danger of malaria to mother and fetus, experts increasingly agree that **travel to a *P. falciparum* transmission area during the first trimester of pregnancy should be avoided or delayed; if this is truly impossible, good preventive measures should be taken, including prophylaxis with mefloquine where this is indicated**. Doxycycline is contraindicated during pregnancy. The data on safety of exposure to atovaquone–proguanil during pregnancy are limited and, for this reason, this combination is not recommended for use in pregnancy.

Treatment during pregnancy

Clindamycin and quinine are considered safe, including during the first trimester of pregnancy; ACTs 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. Chloroquine can be safely used for treatment of vivax malaria during pregnancy, but primaquine anti-relapse treatment should be postponed until after delivery. Pregnant women treated for vivax malaria should continue weekly chloroquine prophylaxis post-treatment until delivery to avoid relapse during the pregnancy.

The recommended treatment for **uncomplicated falciparum malaria in the first trimester** is quinine +/– clindamycin. For the **second and third trimesters**, the options are: ACT in accordance with national policy; artesunate + clindamycin; or quinine + 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: artesunate is the treatment of choice, and artemether or quinine should be used if artesunate is not available. Treatment must not be delayed and should be started immediately. Information on the safety of antimalarial drugs during breastfeeding is provided in Tables 7.2 and 7.3.

7.4.2 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 the last dose of mefloquine prophylaxis. If pregnancy occurs during antimalarial prophylaxis, this is not considered to be an indication for pregnancy termination.

7.4.3 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 a malaria-endemic country/territory. 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 infants or young children to areas where there is risk of falciparum malaria. If travel cannot be avoided, children must be very carefully protected against mosquito bites and 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 for young children

Infants 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 doses must not be exceeded.

Chemoprophylaxis in young children

Chloroquine and mefloquine are considered compatible with breastfeeding. Breastfed, as well as bottle-fed, infants 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 is safe for infants and young children but its use is now very limited because of 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, France 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 of young children

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 data are limited), dihydroartemisinin–piperaquine (considered safe in infants weighing 5 kg or more) and quinine plus clindamycin (safe, but data on clindamycin are limited). Quinine plus doxycycline is an option for children aged 8 years and older. Parenteral treatment and admission to hospital are indicated for young children who cannot swallow antimalarials reliably.

Chloroquine 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 is 1 year. Information on the safety of drugs for prophylaxis and treatment of young children is provided in Tables 7.2 and 7.3.

7.4.4 Immunosuppressed travellers

Immunosuppressed travellers are at increased risk of malaria disease, and prevention of malaria through avoidance of mosquito bites and use of chemoprophylaxis is particularly important. Individual pre-travel advice should be diligently sought. There may be an increased risk of antimalarial treatment failure in people living with HIV/AIDS. At present, however, there is insufficient information to permit modifications to currently recommended treatment regimens for this specific population group (Chapter 9).

Table 7.1 **Malaria risk and type of prevention**

	Malaria risk	Type of prevention
Type A	Very limited risk of malaria transmission	Mosquito bite prevention only
Type B	Risk of *P. vivax* malaria only	Mosquito bite prevention plus chloroquine chemoprophylaxis[a]
Type C	Risk of *P. falciparum* malaria, with reported chloroquine and sulfadoxine–pyrimethamine resistance	Mosquito bite prevention plus atovaquone–proguanil or doxycycline or mefloquine chemoprophylaxis (select according to reported side-effects and contraindications)[a]
Type D	Risk of *P. falciparum* malaria in combination with reported multidrug	Mosquito bite prevention plus atovaquone–proguanil or doxycycline or mefloquine chemoprophylaxis (select according to

resistance	reported drug resistance pattern, side-effects and contraindications)[a,b]

[a] Alternatively, for travel to rural areas with low risk of malaria infection, mosquito bite prevention can be combined with stand-by emergency treatment (SBET).

[b] In certain areas with multidrug-resistant malaria, mefloquine chemoprophylaxis is no longer recommended. At present this includes Cambodia, south-eastern Myanmar, and Thailand.

Table 7.2 **Use of antimalarial drugs for prophylaxis in travellers**

Generic name	Dosage regimen	Duration of prophylaxis	Use in special groups			Main contraindications[a]	Comments[a]
			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 <11 kg because of limited data	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance <30 ml/min)	Take with food or milky drink to increase absorption. 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. May interfere with live typhoid vaccine.
Choroquine	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 may reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.

[a] See package insert for full information on contraindications and precautions.

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

Generic name	Dosage regimen	Duration of prophylaxis	Use in special groups			Main contraindications[a]	Comments[a]
			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	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 *Candida* 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 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	Do not give mefloquine within 12 h 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. Do not give concomitantly with oral typhoid vaccine. In the United States, mefloquine is recommended as a chemoprophylaxis option for all trimesters of pregnancy

[a] See package insert for full information on contraindications and precautions.

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

eneric name	Dosage regimen	Use in special groups			Main contraindications[a]	Comments[a]
		Pregnancy	Breast-feeding	Children		
Artemether–lumefantrine combination tablet	3-day course of 6 doses total, taken at 0, 8, 24, 36, 48 and 60 h *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:* 4 tablets per dose	Limited data in first trimester	Safe	Safe in children 5 kg	Hypersensitivity to artemether and/or lumefantrine	Must be taken with fatty foods to improve absorption. A flavoured dispersible paediatric formulation is now available, enhancing its use in young children.
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 recommen-ded	No data, not recommen-ded	Apparently safe in children >5 kg, but limited data	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance <30 ml/min)	Take with food or milk drink to increase absorption. Plasma concentrations of atovaquone are reduced when the drug is co-administered with rifampicin, rifabutin, metoclopramide or tetracycline. May interfere with live typhoid vaccine.
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 *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi*. Concurrent use of chloroquine may Reduce the antibody response to intradermally administered human diploid-cell rabies vaccine.

[a] 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	Dosage regimen	Use in special groups			Main contraindications[a]	Comments[a]
		Pregnancy	Breast-feeding	Children		
Clindamycin	*Under 60 kg:* 5 mg base/kg 4 times daily for 5 days *≥60 kg:* 300 mg base 4 times daily for 5 days	Safe	Safe	Safe	Hypersensitivity to clindamycin or lincomycin; history of gastrointestinal disease, particularly colitis; severe liver or kidney impairment	Use in combination with quinine in areas of emerging quinine resistance.
Dihydroartemisinin–piperaquine	One dose daily for 3 consecutive days. Target dose = 4 mg/kg per day dihydroartemisinin and 18 mg/kg per day piperaquine *Adults >50 kg:* 3 tablets daily for 3 days	Limited data in first trimester	Safe	Safe in children ≥5 kg	Hypersensitivity to dihydroartemisinin and/or piperaquine	
Doxycycline	*Adults >50 kg:* 800 mg salt over 7 days, taken as 2 tablets (100 mg salt each) 12 h 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	Hypersensitivity to tetracyclines; liver dysfunction	Used in combination with quinine in areas of emerging quinine resistance.

[a] 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	Dosage regimen	Use in special groups			Main contraindications[a]	Comments[a]
		Pregnancy	Breast-feeding	Children		
Mefloquine	25 mg base/kg as split dose (15 mg/kg plus 10 mg/kg 6–24 h apart)	Not recommended by producer in first trimester because of lack of data (see Comments)	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	Mefloquine is used with artesunate as Artemisinine-based combination therapy (ACT). Do not give mefloquine within 12 h 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. In the United States, mefloquine is recommended as a treatment option for all trimesters of pregnancy.
Primaquine	0.25mg base/kg with food once daily for 14 days. In Oceania and south-east Asia the dose should be 0.5 mg base/kg	Contra-indicated	Contra-indicated	Contra-indicated <1 year	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 *P. vivax* and *P. ovale* infections.

[a] 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	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] See package insert for full information on contraindications and precautions.

7.5 Countries and territories with malarious areas

The following list shows all countries/territories for which some malaria information is included in the Country list. 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. Some countries have not reported any cases in recent years. 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
Algeria*
Angola
Argentina*
Azerbaijan*
Bangladesh
Belize
Benin
Bhutan
Bolivia, Plurinational State of
Botswana
Brazil
Burkina Faso
Burundi
Cambodia
Cameroon
Cape Verde
Central African Republic
Chad
China
Colombia
Comoros
Congo
Congo, Democratic Republic of the (former Zaire)
Costa Rica
Côte d'Ivoire
Djibouti
Dominican Republic
Ecuador
Egypt
El Salvador
Equatorial Guinea
Eritrea
Ethiopia
French Guiana
Gabon
Gambia
Georgia*
Ghana
Greece*
Guatemala
Guinea
Guinea-Bissau
Guyana
Haiti
Honduras
India
Indonesia
Iran, Islamic Republic of
Iraq*
Kenya
Korea, Democratic People's Republic of*
Korea, Republic of*
Kyrgyzstan*
Lao People's Democratic Republic
Liberia
Madagascar
Malawi
Malaysia
Mali
Mauritania
Mayotte
Mexico
Mozambique
Myanmar
Namibia
Nepal
Nicaragua
Niger
Nigeria
Oman
Pakistan
Panama
Papua New Guinea
Paraguay*
Peru
Philippines
Russian Federation*
Rwanda
Sao Tome and Principe
Saudi Arabia
Senegal
Sierra Leone
Solomon Islands
Somalia
South Africa
Sri Lanka
Sudan
South Sudan
Suriname
Swaziland
Syrian Arab Republic*
Tajikistan
Thailand
Timor-Leste
Togo
Turkey*
Uganda
United Republic of Tanzania
Uzbekistan*
Vanuatu
Venezuela, Bolivarian Republic of
Viet Nam
Yemen
Zambia
Zimbabwe

Further reading

Guidelines for the treatment of malaria, second edition. Geneva, World Health Organization, 2010.

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, third edition. Geneva, World Health Organization, 2012.

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