Malaria

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By Melissa K Slate, RN, BA, MA

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

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

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

Nature of the disease
Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, a febrile illness developing less than one week after the first possible exposure is not malaria. The most severe form is caused by *P. falciparum,* in which variable clinical features include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhea and abdominal pain; other symptoms related to organ failure may supervene, such as: acute renal failure, generalized convulsions, circulatory collapse, followed by coma and death. In endemic areas it is estimated that about 1% of patients with *P. falciparum* infection die of the disease; the mortality in non-immune travelers with untreated falciparum infection is significantly higher. The initial symptoms, which may be mild, may not be easy to recognize as being due to malaria. It is important that the possibility of falciparum malaria is considered in all cases of unexplained fever starting at any time between the seventh day of first possible exposure to malaria and three

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months (or, rarely later) after the last possible exposure. Any individual who experiences a fever in this interval should immediately seek diagnosis and effective treatment, and inform medical personnel of the possible exposure to malaria infection. Early diagnosis and appropriate treatment can be life-saving. Falciparum malaria may be fatal if treatment is delayed beyond 24 hours. A blood sample should be examined for malaria parasites. If no parasites are found in the first blood film while there is clinical suspicion of malaria, a series of blood samples should be taken at 6–12-hour intervals and examined very carefully. Pregnant women, young children and elderly travelers are particularly at risk. Malaria in pregnant travelers increases the risk of maternal death, miscarriage, stillbirth and neonatal death. The forms of malaria caused by other Plasmodium species are less severe and rarely life-threatening. Chemoprophylaxis and treatment of falciparum malaria are becoming more difficult because *P. falciparum* is increasingly resistant to various antimalarial drugs. Chloroquine resistance of *P. vivax* is rare and was first reported in the late 1980s in Papua New Guinea and Indonesia. Focal “true” chloroquine resistance (i.e. in patients with adequate blood levels at day of failure) or prophylactic and/or treatment failure have later also been observed in Brazil, Colombia, Ethiopia, Guatemala, Guyana, India, Myanmar, Peru, the Republic of Korea, Solomon Islands, Thailand and Turkey. *P. malariae* resistant to chloroquine has been reported from Indonesia.

Geographical distribution

The current distribution of malaria in the world on shown in a map. Details for affected countries and territories are listed under countries and territories with malarious area. The risk for travelers of contracting malaria is highly variable from country to country and even between areas in a country. This has to be considered when discussing appropriate preventive measures. In many endemic countries, the main urban areas—but not necessarily the outskirts of towns—are free of malaria transmission. However, malaria can occur in main urban areas in Africa and India. There is usually less risk of the disease at altitudes above 1500 meters, but in favorable climatic conditions it can occur at altitudes up to almost 3000 meters. 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 travelers

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

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

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

Protection against mosquito bites
All travelers should be explained that individual protection from mosquito bites between dusk and dawn is their first line of defense against malaria.

Chemoprophylaxis
The correct dosage of the most appropriate antimalarial drug(s) (if any) for the destination(s) should be prescribed. Travelers and their doctors should be aware that **NO ANTIMALARIAL PROPHYLACTIC REGIMEN GIVES COMPLETE PROTECTION,** but good chemoprophylaxis (adherence to the recommended drug regimen) does reduce the risk of fatal disease. The following should also be taken into account:
● Dosing schedules for children should be based on body weight.
● Antimalarials that have to be taken daily should be started the day before arrival in the risk area.
● Weekly chloroquine should be started 1 week before arrival.
● Weekly mefloquine should be started at least 1 week, but preferably 2–3 weeks before departure, to achieve higher pre-travel blood levels and to allow side effects to be detected before travel so that possible alternatives can be considered.
● Antimalarial drugs must be taken with food and swallowed with plenty of water.
● All prophylactic drugs should be taken with unfailing regularity for the duration of the stay in the malaria risk area, and should be continued for 4 weeks after the last possible exposure to infection, since parasites may still emerge from the liver during this period. The single exception is atovaquone/proguanil, which can be stopped 1 week after return.
● Depending on the predominant type of malaria at the destination, travelers

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should be advised about possible late onset *P. vivax* and *P. ovale.*
Depending on the malaria risk in the area visited, the recommended malaria prevention method may be mosquito bite prevention only, or mosquito bite prevention in combination with chemoprophylaxis, as follows:
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 traveler. Serious adverse events — defined as constituting an apparent threat to life, requiring or prolonging hospitalization, or resulting in permanent disability or incapacity—are rare and normally only identified once a drug has been in use for some time. With mefloquine the incidence range of serious adverse events has been estimated at 1 per 6000 to 1 per 10,600 travelers, compared to 1 per 13,600 with chloroquine. For malaria prophylaxis with atovaquone/proguanil or doxycycline the risks of rare serious adverse events have not yet been established. The risk of drug associated adverse events should be weighed against the risk of malaria, especially *P. falciparum* malaria, and local drug-resistance patterns.

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

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

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

Long-term use of chemoprophylaxis
The risk of serious side-effects associated with long-term prophylactic use of chloroquine and proguanil is low. However, anyone who has taken 300 mg of chloroquine weekly for over five years and requires further prophylaxis should

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

Stand-by emergency treatment

An individual who experiences a fever 1 week or more after entering an area of malaria risk should consult a physician or qualified malaria laboratory immediately to obtain correct diagnosis and a safe and effective treatment. Many travelers will be able to obtain proper medical attention within 24 hours of the onset of fever. For others, however, this may be impossible, particularly if they will be staying (1 week or more after entering an endemic area) in a remote location. In such cases, travelers are advised to carry antimalarial drugs for self administration (“stand-by emergency treatment”). The circumstances of stand-by emergency treatment (SBET) are different from treatment administered by competent medical personnel. SBET is taken by a traveler who (1) is sick in a remote location and cannot easily reach a hospital or qualified health professional, (2) may already be taking antimalarials for prophylaxis, and (3) may have to self-diagnose malaria based on non specific clinical symptoms such as fever. In these circumstances the safety and efficacy of drugs given for SBET are even more critical, and not all antimalarials that are normally used for treatment can be confidently prescribed. Stand-by emergency treatment may also be indicated for travelers in some occupational groups, such as aircraft crews, who make frequent short stops in endemic areas over a prolonged period of time. Such travelers may eventually choose to reserve chemoprophylaxis for high-risk areas only. However, they should continue to take rigorous measures for protection against mosquito bites and be prepared for an attack of malaria: they should always carry a course of antimalarial drugs for stand-by emergency treatment, seek immediate medical care in case of fever, and take stand-by emergency treatment if prompt medical help is not available. Stand-by emergency treatment—combined with rigorous protection against mosquito bites—may occasionally be indicated for those who travel for 1 week or more to remote rural areas where there is a very low likelihood of multi drug resistant malaria and the risk of side-effects of prophylaxis outweighs the risk of contracting malaria. This may be the case in certain border areas of Thailand and neighboring countries in South-East Asia where the risk of side-effects may outweigh the risk of becoming infected. However, most travelers to these areas will be able to access competent medical care within 24 hours of the onset of fever. Studies on the use of rapid diagnostic tests (“dipsticks”) have shown that untrained travelers experience major problems in the performance and interpretation of these tests, with an unacceptably high number of false-negative

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results. In addition, dipsticks can be degraded by extremes of heat and humidity, becoming less sensitive. Major technical modifications are required before dipsticks can be recommended for use by travelers. Travelers' behavior is key for successful SBET, and the health advisor needs to spend time explaining the strategy. Travelers provided with stand-by emergency treatment should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, the treatment regimen, possible side-effects, and the possibility of drug failure. If several people travel together, the individual dosages for SBET should be specified. Travelers should be made aware that self-treatment is a first-aid measure, and that they should seek medical advice as soon as possible. In general, travelers carrying stand-by emergency treatment should observe the following guidelines:

● Consult a physician immediately if fever occurs 1 week or more after entering an area with malaria risk.
● If it is impossible to consult a physician and/or establish a diagnosis within 24 hours of the onset of fever, start the stand-by emergency treatment and seek medical care as soon as possible for complete evaluation and to exclude other serious causes of fever.
● Complete the stand-by treatment course and resume antimalarial prophylaxis 1 week after the *first* treatment dose. Mefloquine prophylaxis, however, should be resumed 1 week after the *last* treatment dose of quinine.
● Vomiting of antimalarial drugs is less likely if fever is first lowered with antipyretics. A second full dose should be taken if vomiting occurs within 30 minutes of taking the drug. If vomiting occurs 30–60 minutes after a dose, an additional half-dose should be taken. Vomiting with diarrhea may lead to treatment failure because of poor drug absorption.
● Do not treat suspected malaria with the same drugs used for prophylaxis, because of the increased risk of toxicity and resistance.

Depending on the area visited and the chemoprophylaxis regimen taken, one of the following stand-by treatment regimens can be recommended: chloroquine, (*P. vivax* areas only), mefloquine, quinine, or quinine plus doxycycline.

Artemether/lumefantrine has been registered in Switzerland for use as stand-by emergency treatment for travelers. Some national health authorities recommend atovaquone/proguanil as SBET for areas of multidrug resistance. See Table 7.3 for details on individual drugs. Halofantrine is **contra-indicated** for stand-by treatment following reports that it can result in ventricular dysrhythmias, prolongation of Q–T intervals and sudden death in susceptible individuals. These risks may be accentuated if halofantrine is taken with other antimalarial drugs that may reduce myocardial conduction. In light of the spread of counterfeit drugs in some resource-poor settings, travelers who may become sick while abroad may opt to buy a reserve antimalarial treatment before departure, so that they can be confident of drug efficacy and safety should they fall ill.

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

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P. vivax and *P. ovale* can remain quiescent in the liver for many months. Relapses caused by the persistent liver forms may appear months, and rarely up to 2 years, after exposure. They are not prevented by current chemo prophylactic regimens. Relapses can be treated with chloroquine (or mefloquine or quinine if resistance is suspected) and further relapses prevented by a course of primaquine, which eliminates any remaining parasites in the liver. In patients with known or suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency, expert medical advice should be sought since primaquine may cause haemolysis in G6PDdeficient patients. G6PD deficiency must be excluded before travelers receive antirelapse therapy with primaquine. Blood infection with *P. malariae* may be present for many years, but it is not life-threatening. It can be treated with chloroquine (or mefloquine or quinine if resistance is suspected).

Special groups

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

Pregnant women

Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and low birth weight with associated risk of neonatal death. Pregnant women should be advised to **avoid** travelling to areas where malaria transmission occurs. When travel cannot be avoided, it is very important to take effective preventive measures against malaria, even when travelling to areas with transmission of vivax malaria only. Pregnant women should be extra diligent in using measures to protect against mosquito bites, but should take care not to exceed the recommended dosage of insect repellents. In “type II” areas with exclusively *P. vivax* transmission or where *P. falciparum* can be expected to be fully sensitive to chloroquine, prophylaxis with chloroquine alone may be used. In “type III” areas, prophylaxis with chloroquine plus proguanil can be safely prescribed, also during the first 3 months of pregnancy. In “type IV” areas, mefloquine prophylaxis may be given during the second and third trimester, but there is limited information on its safety during the first trimester. Doxycycline is contraindicated during pregnancy. Atovaquone/proguanil has not been sufficiently investigated to be prescribed for chemoprophylaxis in pregnancy. Pregnant women should seek medical help immediately if malaria is suspected; if this is not possible, they should take emergency stand-by treatment with quinine. Medical help *must* be sought as soon as possible after stand-by treatment. Pregnant women with falciparum malaria may rapidly develop any of the clinical symptoms of severe malaria. They are particularly susceptible to hypoglycemia and pulmonary edema. They may develop postpartum hemorrhage, and hyperpyrexia leading to fetal distress. Any pregnant woman with severe falciparum malaria should be transferred to intensive care. Because of the risk of quinine-induced hyperinsulinaemia and hypoglycemia, artesunate and artemether are the drugs of choice for treatment of severe malaria in the second and third trimester. Data on the use of artemisinin derivatives in the first trimester are still limited. However, neither quinine nor artemisinin derivatives

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

Young children

Falciparum malaria in a young child is a medical emergency it may be rapidly fatal. Early symptoms are atypical and difficult to recognize, and life-threatening complications can occur within hours of the initial symptoms. Medical help should be sought immediately if a child develops a febrile illness within 3 months (or, rarely, later) of travelling to an endemic area. Laboratory confirmation of diagnosis should be requested immediately, and treatment with an effective antimalarial drug initiated as soon as possible. In infants, malaria should be suspected even in non-febrile illness. Parents should be advised **not** to take babies or young children to areas with transmission of chloroquine-resistant *P. falciparum*. If travel cannot be avoided, children must be very carefully protected against mosquito bites and be given appropriate chemo prophylactic drugs. Babies should be kept under insecticide treated mosquito nets as much as possible between dusk and dawn. The manufacturer's instructions on the use of insect repellents should be followed diligently, and the recommended dosage must not be exceeded. Breastfed, as well as bottle-fed, babies should be given chemoprophylaxis since they are not protected by the mother's prophylaxis. Dosage schedules for children should be based on body weight. Chloroquine and proguanil are safe for babies and young children but only suitable for areas with low levels of chloroquine resistance. Mefloquine may be given to infants of more than 5 kg body weight. Atovaquone/proguanil cannot be recommended for prophylaxis in children who weigh less than 11 kg, because of the lack of data. Doxycycline is contraindicated in children below 8 years of age. All antimalarial drugs should be kept out of the reach of children and stored in childproof containers. Chloroquine is particularly toxic in case of overdose.

Special situations—multidrug-resistant malaria

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

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

Choice of stand-by emergency treatment according to recommended chemo prophylactic regimen

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

Recommended prophylactic regimen	Stand-by emergency treatment
None	Chloroquine, for P. vivax areas only Mefloquine Quinine Artemether and lumefantrinea Atovaquone/proguanila
Chloroquine alone or with proguanil	Mefloquine Quinineb
Mefloquine	Quinineb Quinine + doxycycline or tetracycline for 7 days before travel
Doxycycline	Mefloquine Quinine + tetracycline for 7 days
Atovaquone/proguanil	Quinine + doxycycline/tetracycline for 7 days

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

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

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