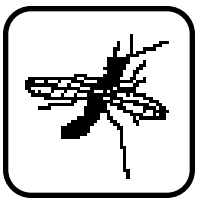
5 Malaria



In 2000, more than 100 countries were considered malarious and this disease threatens nearly 40% of the world's population. Over 300 million acute episodes of illness occur every year, and it is estimated that over 270 million people are chronically infected with malaria parasites.

The World Health Organization (WHO) estimates that as many as 2.7 million people die each year of malaria. The vast majority of malaria deaths occur among young children in sub-Saharan Africa, especially in rural areas with inadequate or nonexistent health care services.

Each year over 7 million Americans travel to countries where malaria occurs and 1,000–1,500 cases are reported (though many more go unreported). While sub-Saharan Africa (except South Africa) is visited by only 2% of American travelers who visit countries where malaria exists, this region (especially East Africa) accounts for 83% of the cases.

Malaria is the most important parasitic disease that you will face in most tropical and subtropical countries. A delay in diagnosis and treatment can have fatal consequences. If you travel to a malarious region, there are five things you must do:

1. Become informed about your risk of acquiring malaria in that particular region.
2. Take measures to prevent mosquito bites. This very important malaria-prevention measure is often underutilized.
3. Take a prophylactic drug such as chloroquine (Aralen), mefloquine (Lariam), atovaquone/proguanil (Malarone), or doxycycline, if necessary. Don't skip prescribed doses.
4. Know the symptoms of malaria.
5. Seek immediate medical treatment if symptoms of malaria occur, especially if you are in, or have returned from, a country where falciparum malaria is endemic. Always consider malaria if you develop a fever after returning from a malarious area. Be aware that the symptoms of malaria can be delayed for weeks or months, sometimes years, after exposure and that you can sometimes get malaria even if you took an effective prophylactic drug. Ninety percent of U.S. and Canadian travelers who acquire malaria don't develop symptoms until after they return home.

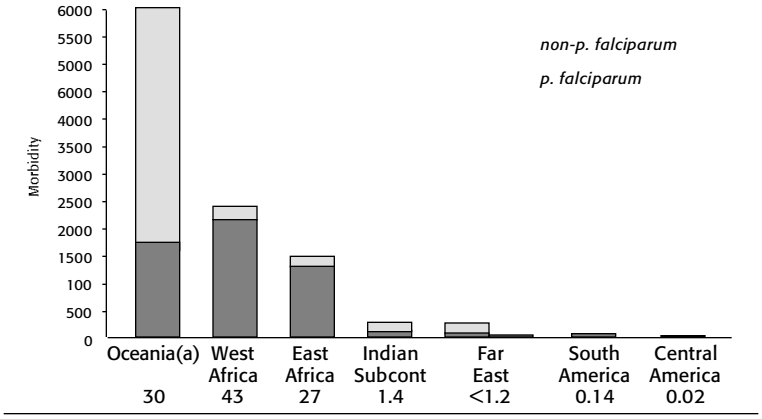
Your Risk of Getting Malaria

It depends upon where you travel and can vary markedly from country to country. The risk of malaria can also vary within any particular destination because the disease may be transmitted only in certain locations within a country, during certain seasons, or below certain altitudes.

Various categories of travelers are also at different risk. Tourists staying in urban air-conditioned, mosquito-free hotels, for example, will usually be at less risk than travelers venturing into low-lying rural areas during the rainy season.

Table 5.1 shows disease rates worldwide. Travel to Oceania (Papua New Guinea, Solomon Islands, and Vanuatu) and sub-Saharan Africa entails the greatest risk, especially from the potentially-fatal *P. falciparum* malaria.

The risk also varies within these regions. The coast of East Africa carries more risk than the interior. In West Africa, the incidence of malaria is less than 2 cases per 1,000 travelers in Senegal and Gabon, 2 to 4 per 1,000 in Burkina Fasso, Ivory Coast, and Cameroon, and 4 to 7+ per 1,000 in Togo, Mali, Guinea, Benin, Congo, and the Central African Republic.



(a) Solomon Islands, Vanuatu, Papua New Guinea

Table 5.1* Morbidity and Mortality in 100,000 nonimmune travelers exposed for 1 month without chemoprophylaxis.

* Steffen R, DuPont H. *Manual of Travel Medicine and Health*. Hamilton: B.C. Decker Inc. 1999:220.

There is intermediate risk on the Indian subcontinent and low risk in frequently visited tourist sites in Latin America and Southeast Asia. NOTE: some areas of Brazil, India, and Thailand carry increased risk.

Tropical Africa is a much higher-risk destination compared to Latin America and Asia for the following reasons:

- Tourists in Africa spend considerable time in rural areas such as game parks, where mosquito activity is high.

- Tourists in Latin America and Asia, however, spend more time in urban or resort areas, where there is little, if any, risk of exposure, and they usually travel to rural areas only during daytime hours when there is little malaria-transmitting mosquito activity.
- In Latin America and Asia, malaria transmission is more seasonal, or focally distributed in rural areas away from the usual tourist routes. For example, 52% of the 1.1 million malaria cases reported from the Americas in 1989 were from Brazil, but 97% of these cases were reported from three gold-mining areas rarely visited by tourists. In Asia (e.g., Thailand), most malaria occurs in remote forested areas—places where few tourists go.
- Malaria is transmitted in most large cities in sub-Saharan Africa, whereas almost all large cities in Latin America (with the exception of Guayaquil, Ecuador) and Southeast Asia are malaria-free. There is no malaria in Hong Kong, Bangkok, Kuala Lumpur, Jakarta, Singapore, Rangoon, Phnom-Penh, Manila, and most other major urban areas. There are some exceptions, such as urban areas of Papua New Guinea and some urban areas in India and Pakistan.
- Mosquitoes in Africa are more apt to be carrying malaria parasites. For example, the mean rate of infected anopheles mosquitoes in western Kenya may exceed 20%, whereas in Latin America and Asia less than 1% of anopheles mosquitoes are infected.

Malaria Fact

In countries where malaria occurs, the highest rates of transmission occur in low-lying rural areas during, and just after, the rainy season. In parts of Africa and Oceania, however, malaria transmission may be high year-round, even in urban areas.

The Cause of Malaria

Malaria is caused by a single-cell protozoan parasite of the genus Plasmodium. There are four different species of Plasmodium parasites that infect humans:

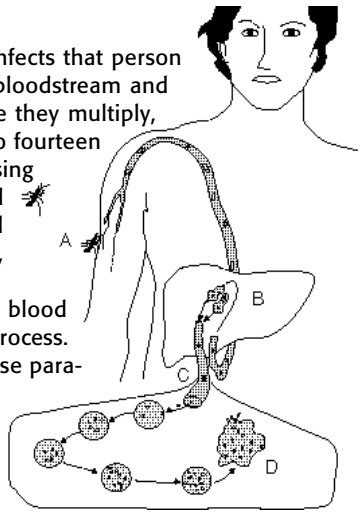
1. *Plasmodium falciparum*, which accounts for 40%–60% of malaria cases worldwide and >95% of all malaria deaths.
2. *Plasmodium vivax*, which causes 30%–40% of malaria cases worldwide, but is rarely fatal.
3. *Plasmodium ovale*, an uncommon parasite found mostly in West Africa.
4. *Plasmodium malariae*, also uncommon, but distributed worldwide.

Worldwide Distribution of Malaria Species

The occurrence of each plasmodium species varies from region to region.

P. falciparum causes 80%–95% of malaria in sub-Saharan Africa. It is also the most common species in Haiti and the Dominican Republic, the Amazon Basin, and parts of Oceania. In South America, outside the Amazon Basin, *P. falciparum*

Figure 5.1. The Cycle of Malaria Transmission



When the anopheles mosquito bites a victim (A) it infects that person with parasites, called sporozoites, which enter the bloodstream and travel rapidly (within 30 minutes) to the liver, where they multiply, producing daughter cells, called merozoites (B). Six to fourteen days later (approximately), the liver cells burst, releasing huge numbers of merozoites which invade red blood cells (C), where they multiply again, rupturing the red cells and releasing even more merozoites (D), triggering an attack of malaria.

The merozoite parasites released from the red blood cells then invade new red blood cells, continuing the process.

Infections with *P. vivax* and *P. ovale*: Some of these parasites (called hypnozoites) remain behind in the liver cells and can cause delayed attacks of malaria, months or years later.

NOTE: The common prophylactic drugs (chloroquine, mefloquine, doxycycline) eliminate malaria parasites only in the blood, at stages C and D. They don't prevent parasites from invading the liver and don't prevent multiplication of parasites within liver cells. They are called *suppressive* prophylactics. Proguanil, atavoquone, and primaquine DO prevent parasite development within the liver. For this reason, these drugs are called *causal* prophylactics.

accounts for 10%–50% of cases. *P. falciparum* is also common on the Indian subcontinent and in SE Asia.

P. vivax causes about 95% of malaria in Mexico and Central America and is also found in South America, North Africa, the Middle East, the Indian subcontinent, China, Asia, and Oceania. Except for Somalia and Ethiopia, vivax malaria is very rarely encountered in sub-Saharan Africa.

P. malariae causes up to 10%–15% of malaria in sub-Saharan Africa and 1%-5% of cases elsewhere, worldwide.

P. ovale is rare. It exists primarily in West Africa where it causes up to 5% of malaria, but it also occurs sporadically in Oceania and SE Asia.

Malaria is uncommon at high altitudes because reproduction of the parasites within the mosquito is temperature sensitive. For this reason, falciparum malaria rarely occurs over 1,000 meters (3250 feet) elevation. Vivax parasites, which are hardier, can reproduce at altitudes as high as 2,000 meters (6,500 feet).

How Malaria Is Transmitted

Malaria is only transmitted by female anopheles mosquitoes. They require a blood meal every 3–4 days to promote the fertilization and growth of their eggs. Worldwide, there are over 400 species of anopheles mosquitoes, of which 60 are known to transmit malaria.

Anopheles mosquitoes feed from dusk to dawn, so when evening comes you need to take extra measures to prevent bites. Not every mosquito transmits

malaria, but it takes just one bite from an infective insect to give you the disease; therefore, even a brief trip to a malarious area can put you at risk.

How Malaria Causes Illness

After they are injected into the body by a feeding mosquito, malaria parasites first invade the liver, then the red blood cells (Figure 5.1), where they again multiply. When the parasite-filled red cells rupture, an attack of malaria occurs.

Falciparum malaria is the most serious and sometimes fatal form of malaria. The severity of *P. falciparum* infections is due to the high percentage of red blood cells (RBCs) that are infected by this particular plasmodium. In extreme infections, up to 80% of RBCs can be parasitized and destroyed. This massive red cell destruction has two primary effects: (1) severe anemia, and (2) clogging of the circulation to vital organs, particularly the brain and kidneys. This circulatory clogging occurs because the infected RBCs produce sticky projections that bind the cells to the walls of the small blood vessels (capillaries) and to other RBCs, forming obstructing clumps of cells (called rosettes). Also, chemicals (called cytokines) are released, causing fever, malaise, and other signs of inflammation.

In contrast, the three other forms of malaria are usually nonlethal. In malaria caused by *P. vivax*, *P. ovale*, and *P. malariae*, only about 1%–2% of RBCs become parasitized, and fatalities are rare.

Severe malaria occurs when more than 5% of RBCs are parasitized. Other criteria defining severe malaria include decreased consciousness (indicates cerebral malaria), severe anemia, hypoglycemia (low blood sugar), kidney/liver failure, pulmonary edema (fluid in the lungs), hyperthermia (high fever), and persistent vomiting and diarrhea.

If you are treated appropriately for malaria, you should improve within 48–72 hours. Indications of successful treatment include (1) reduction of fever and (2) at least a 75% reduction in the number of red blood cells that are parasitized.

Malaria Fact

Travelers do not become immune to malaria after having had the disease. There are no vaccines available at present.

Delayed Attacks of Malaria

If you have been bitten by mosquitoes transmitting *P. vivax* or *P. ovale*, you can have a delayed attack of malaria because some of these parasites (called hypnozoites) can remain dormant in your liver for many months, even years.

Prophylactic drugs such as chloroquine, mefloquine, and doxycycline only work in the blood to suppress the multiplication of parasites in RBCs. You're safe from an attack of malaria only as long as you take the suppressive (prophylactic) drug. To get rid of dormant liver parasites (*P. vivax, P. ovale*), you'll need to take another drug, primaquine, discussed later.

Fortunately, *P. falciparum* and *P. malariae* parasites don't have a dormant liver phase, so prophylaxis continued for 1 to 4 weeks after exposure usually gives your body enough time to eliminate them. However, inadequately suppressed *P. falciparum* or *P. malariae* can sometimes result in low-grade blood stream infections, leading to recurrence of symptoms. *P. malariae*, in fact, can cause infections lasting 25 years or more.

Symptoms of Malaria

Getting malaria makes you feel like you have the flu—only worse. Before an attack of malaria begins, you may have one or two days of headache, fatigue, loss of appetite, and a low-grade fever. The acute attack starts abruptly with chills, soon followed by a high fever, lasting 2–6 hours. During this time you may also notice pains in your chest, back, stomach, joints, and muscles. The attack ends with 2–3 hours of heavy sweating. If you are not treated promptly, symptoms will recur and complications may develop, especially if the attack is caused by *P. falciparum*. In some cases, malaria fevers recur periodically, every 48 to 72 hours.

NOTE: Malaria can occur as soon as seven days after an infective bite, and almost all cases of falciparum malaria occur within 60 days after the bite in people not taking a prophylactic drug or people using inadequate prophylaxis.

Other important causes of fever in the returned traveler include typhoid fever, dengue, brucellosis, hepatitis, urinary tract infections, tick typhus, and, rarely, amebic liver abscess.

Although a blood smear is required to make the final diagnosis, the most important aspect of diagnosis is always *to think of malaria as a possible cause of your illness.* This is especially important because not every case of malaria presents with the typical periodic fever pattern. If you are in a malarious area and you develop fever, and medical care is not available within 24–48 hours, it may be advisable for you to start self-treatment before a diagnosis is established. Self-treatment is discussed later, starting on page 97.

The self-test kit employs a 10-minute enzymatic assay to measure plasmodium LDH isoforms in a patient's blood. More details can be found at *www.malariatest.com*

Diagnosis

Malaria is diagnosed by observing under the microscope plasmodium parasites within red blood cells. This technique can also distinguish the more dangerous *P. falciparum* from the other species. The problem with the blood smear test is its sensitivity. Parasites may not be observed unless prolonged, repeated searches are done, or they may not be appropriately recognized by the technician, especially in facilities where malaria is rarely seen. Malaria should not be excluded as a diagnosis until three blood films, obtained 12–24 hours apart, have been examined.

Advances in technology have now made the rapid diagnosis of malaria poten-

tially much easier and faster. One example, the OptiMAL® assay, is a sensitive, simple to use dipstick assay that permits the detection of all major species of human malaria and can distinguish between *P. falciparum* and *P. vivax*. The test has a reported sensitivity of 88% and a specificity of 99% for *P. falciparum*.

NOTE: Although these rapid diagnostic tests for malaria appear promising, recent studies have shown that travelers, especially when ill, may be unable to perform these test satisfactorily, and thus may fail to diagnose the disease. In addition, the kits must be stored at temperatures not exceeding 20°C—25°C. Storing the kits under adverse environmental conditions could invalidate the test results.

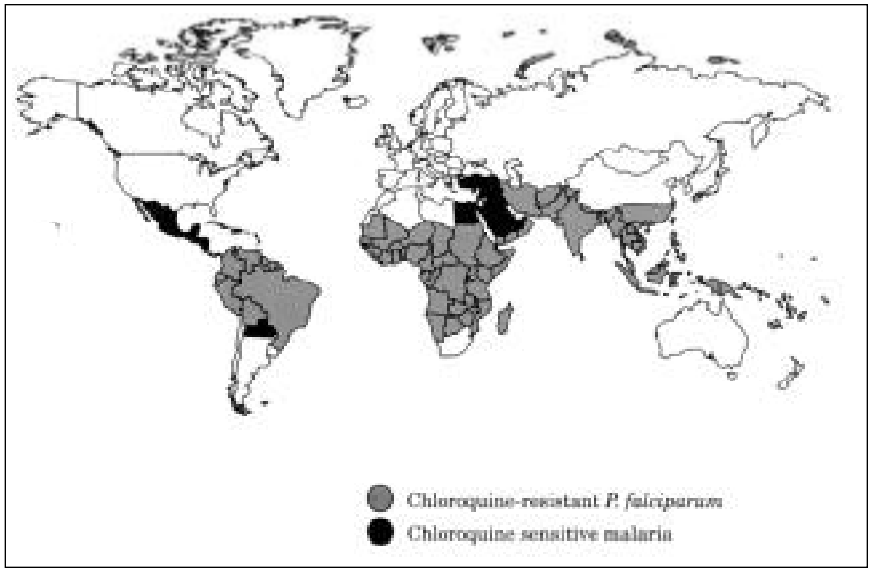
MALARIA PREVENTION

Virtually all cases of malaria can be prevented. Most studies show that a high proportion of travelers who acquire malaria simply did not receive appropriate information on, or did not comply with, malaria prevention measures.

Avoiding malaria requires that you (1) know where it exists, (2) prevent mosquito bites, and (3) take a prophylactic drug (see Table 5.2)

Chapter 6 summarizes the best methods of insect-bite prevention.

Figure 5.2. Distribution of Malaria and Chloroquine-Resistant Falciparum Malaria—1997



The map shows those areas where malaria caused by chloroquine-resistant *P. falciparum* is reported. NOTE: Chloroquine-resistant *P. vivax* is now reported in Papua New Guinea, Irian Jaya, Colombia, Guyana, Brazil, Myanmar, and Malaysia. Both mefloquine- and chloroquine-resistant falciparum malaria are found along the Thai/Myanmar & Cambodian borders.

Chemoprophylaxis

Before departing for a malarious area, you and your doctor should decide if prophylaxis is indicated and which drug, if any, you should take. Current malaria prophylaxis recommendations are summarized in Table 5.2. In general, if your risk of exposure will be moderate to high, prophylaxis is necessary and the drug you will use, depending on your itinerary and other factors, will be chloroquine (Aralen), mefloquine (Lariam), doxycycline (Vibramycin), or atovaquone/proguanil (Malarone).

If the risk of malaria is low, the benefits of prophylaxis have to be more carefully assessed. In low-risk situations where prompt medical care is available, it may be acceptable not to take a prophylactic drug, but to rely instead on immediate treatment. However, the malaria branch of the CDC recommends prophylaxis in any situation, no matter how low the risk.

Mefloquine and chloroquine should be started 1–2 weeks before departure, continued regularly during travel and taken for 4 weeks after leaving the malarious area. Atovaquone/proguanil and primaquine can be started one day before exposure, continued daily during travel, and discontinued one week after leaving the risk area. Doxycycline can be started one day before entering the malaria risk area, taken daily, and discontinued 4 weeks after leaving the risk area.

Factors determining your need for, and choice of, prophylaxis include (1) your itinerary, (2) the intensity and duration of your exposure to mosquito bites, especially those transmitting *P. falciparum*, (3) your ability to obtain rapid, qualified medical care should symptoms occur, (4) your own knowledge of malaria and its symptoms, (5) your medical history and personal health status, (6) your history of known drug allergies or known ability (or inability) to tolerate certain prophylactic drugs, (7) your use of other medications that may be incompatible with prophylactic drugs, (8) your age, and (9) your pregnancy status, if applicable.

The complexity of the situation is one reason why seeing a travel medicine specialist is advisable when exposure to malaria is likely. Remember, though, that the best prophylaxis is still mosquito-bite prevention. If you don't get bitten, you can't get malaria.

Important Malaria Information

Since no current antimalarial prophylactic drug regimen is 100% protective, travelers must also take measures to prevent mosquito bites (see Chapter 6). Travelers who develop a fever during travel or during the first year of return from a malarious area should seek medical attention promptly, inform their health-care provider of their possible exposure, and request blood films for diagnosis. Serial blood films, repeated daily for 3 days, may be necessary to rule out the infection. Results of these tests should be expected within 24 hours.

Table 5.2

Malaria Prophylaxis According to Geographic Area[1]

Chloroquine-Sensitive Areas	First-Line Drug(s)	Alternative Drug(s)
Central America	chloroquine	mefloquine
Caribbean	"	doxycycline[1]
Middle East, N. Africa	"	atovaquone/proguanil
Chloroquine-Resistant Areas		
South America	mefloquine atovaquone/proguanil doxycycline	primaquine[3]
Africa[2] (sub-Saharan)	mefloquine doxycycline atovaquone/proguanil	primaquine[3]
Indian subcontinent	mefloquine atovaquone/proguanil doxycyline	primaquine[3]
Southeast Asia	mefloquine	primaquine[3]
Oceania Papua New Guinea Vanuatu Solomon Islands	atovaquone/proguanil doxycycline	
Thailand (border areas only)	doxycycline	atovaquone/proguanil or, proguanil plus sulfonamide[4]

1. In Central and South America and Southeast Asia, travelers are generally at risk only in rural areas during evening and nighttime hours. In sub-Saharan Africa and Oceania, malaria is often transmitted in both urban and rural areas.
2. Fansidar (page 91) can be carried for use as emergency treatment in remote areas if malaria is suspected in travelers taking chloroquine and/or proguanil.
3. Requires G-6-PD screening test.
4. Combination of proguanil and a sulfa is an alternative for travelers in Thailand unable to take doxycycline or atovaquone/proguanil. Dosage: proguanil, 200 mg daily, plus either sulfisoxazole, 75 mg/kg daily, or sulfamethoxazole, 1,500 mg daily. Mefloquine resistance is common along the Thai/Myanmar and Thai/Cambodian borders.

Chloroquine

Chloroquine phosphate is a synthetic 4-aminoquinolone that is the drug of choice to prevent susceptible strains of *P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*. The drug is used when prophylaxis is needed in malarious areas of the Caribbean (parts of the Dominican Republic and Haiti), Mexico and Central America, temperate South America, North Africa, and parts of the Middle East.

Adult dosage—500 mg salt (300 mg base) once weekly, beginning one week before and continuing four weeks after leaving the malarious area. Starting chloroquine before you leave gives you a protective blood level and also lets you know if any unusual side effects will occur.

Child dosage—8.3 mg/kg salt (5 mg/kg base) once weekly, up to maximum adult dose of 500 mg salt/week.

Generic chloroquine tablets are sold in the United States in strengths of 250 mg and 500 mg. Brand name chloroquine (Aralen™) is available only in the 500 mg tablet strength. Only the tablet form of chloroquine is available in the United States, but liquid chloroquine for pediatric use is readily available overseas. The Aralen tablet is difficult to crush for children. The generic tablets are easier to split and crush, but are bitter. Parents can crush tablets into powder, divide it, and then mask flavor with syrup, jam, etc. Another strategy is to have a pharmacist pulverize the tablets and prepare gelatin capsules with the proper weekly dose. Mixing the powder from the capsule with food (e.g., chocolate sauce or ice cream) or drink will make the bitter taste more palatable.

Side effects—Chloroquine is generally well-tolerated and serious side effects rarely occur. Nausea, however, is not uncommon. Gastrointestinal side effects can usually be controlled by taking chloroquine with meals. Dizziness, headache, blurred vision, and itching may also occur, but these symptoms will rarely require you to stop taking the drug. Itching is a frequent occurrence among people of African descent and is not an allergic reaction. Fears about long-term prophylaxis causing degenerative eye (retinal) changes are unfounded. Chloroquine can safely be taken by pregnant women and children, including infants.

CAUTION: An overdose of chloroquine (even *one* tablet in a small child) can be fatal. The drug should be kept in a child-safe container at all times.

NOTE: Chloroquine interferes with the antibody response to rabies vaccine when the vaccine is administered intradermally. If you are taking chloroquine prophylaxis and need rabies vaccination, the vaccine must be given intramuscularly.

Hydroxychloroquine

An alternative to chloroquine phosphate is hydroxychloroquine (Plaquenil). It has the same action as chloroquine, but causes fewer gastrointestinal side effects. (Hydroxychloroquine can also be used to treat chloroquine-sensitive malaria.)

Adult prophylactic dosage—400 mg salt (310 mg base) weekly.

Child dosage—6.5 mg/kg salt (5.0 mg base/kg) weekly, up to the adult dosage.

Chloroquine-Resistant *P. vivax*

Resistance of *P. vivax* to chloroquine has been confirmed in Myanmar (Burma), Papua New Guinea, the island of Nias (Indonesia), Irian Jaya (Indonesian New Guinea) Sabah, Borneo (Malaysia), Colombia, and Guyana. Mefloquine and doxycycline are effective prophylactic agents for these strains of malaria.

Mefloquine

Mefloquine (Lariam) is currently one of the recommended drugs for malaria prophylaxis in almost all countries where there is chloroquine-resistant *P. falciparum*. The drug is also effective against *P. vivax*, *P. ovale*, and *P. malariae*. In western Cambodia and along the border areas of Thailand, however, the incidence of mefloquine-resistant *P. falciparum* is as high as 50%, and prophylaxis with doxycycline is recommended. Recent reports also indicate possible, as yet undocumented, mefloquine resistance in West Africa.

Adult dosage—250 mg (one tablet) once weekly during travel in malarious areas and for 4 weeks after leaving such areas. Mefloquine should be started at least one to two weeks prior to departure to see if bothersome side effects will occur and to ensure adequate blood levels build up. Some travel doctors recommend starting the mefloquine dosing even earlier, at 3–4 weeks prior to departure, to ascertain tolerance to the drug.

Child dosage—Children: 5–14 kg, 1/8 tablet weekly; 15–19 kg 1/4 tablet weekly; 20–30 kg, 1/2 tablet weekly; 31–45 kg, 3/4 tablet weekly; and > 45 kg, 1 tablet weekly. Under 5 kg an proportionately lower dose should be given.

Mefloquine Facts

- The rate of dizziness, anxiety, and insomnia is greater for mefloquine as compared with chloroquine.
- Serious neuropsychiatric adverse events with mefloquine are rare. Severe side effects (seizures and psychotic episodes) occur in 1:10,000–13,000 prophylactic users. Several case reports and recent media publicity suggest that side effects may occur much more frequently than suggested, and two recent studies showed that "disabling" side effects, sufficient to impact on daily activities, occur in 1:250 to 1:500 users. However, fewer than 3% of those taking mefloquine discontinue the drug because of side effects. (about 10% in the U.K.)
- Older travelers and children have fewer side effects than younger adults. Women have more side effects than men.
- A liquid form of mefloquine is not available.
- Contraindications to mefloquine use are epilepsy, neuropsychiatric disorders, and cardiac conduction disorders.
- There is still controversy regarding the true incidence and severity of mefloquine-induced adverse events. A case of fatal toxic epidermal necrolysis has been reported. Cardiac conduction disorders may occur if halofantrine is used in conjunction with mefloquine. By itself, mefloquine has no adverse cardiac effects.

Loading dose of mefloquine—Some travel medicine physicians give a loading dose (250 mg daily for 3 days, then once weekly) to achieve therapeutic levels rapidly—and to "screen" for side effects. A loading dose ensures that if there are any significant side effects, they will occur within one week instead of 3–7 weeks when the drug is initiated on a weekly basis. The loading dose should be taken 2 weeks prior to travel. This approach appears to be safe and well-tolerated, but the CDC states that there is no documentation of cases related to not giving a loading dose. NOTE: If you have been taking quinidine or procainamide for cardiac problems, 12 hours should elapse before you take mefloquine.

Side effects—Mefloquine in prophylactic doses is generally well-tolerated, but about 10% of users report mild-to-moderate side effects—strange dreams, insomnia, nausea, dizziness, and weakness. Serious neuropsychological side effects (anxiety, depression, agitation, nightmares) requiring discontinuation of the drug may occur in 0.5% of users, and severe neuropsychiatric side effects (psychosis, seizures) may affect 0.01% of users. Side effects may be reduced by splitting the weekly dose and taking one-half tablet twice weekly. Taking the drug with food lessens stomach upset.

CAUTIONS: The CDC and the manufacturer recommend that mefloquine not be used by travelers with a history of epilepsy, psychiatric disorders, or cardiac conduction disturbances. Cautions are also listed by the manufacturer for use by drivers of vehicles, pilots, operators of machinery and heavy equipment, scuba divers, and mountain climbers. These latter cautions, however, are based on limited data or theoretical concerns only and are not absolute contraindications.

Mefloquine is now considered safe for prophylaxis during the second and third trimesters of pregnancy (and, by extension, safe for infants). The drug has not been associated with congenital malformations or adverse postnatal outcomes when used for prophylaxis. There may be a slight trend toward miscarriage when mefloquine is taken during the first trimester, but the data are not firm. Travel medicine physicians will prescribe mefloquine during the first trimester when exposure to chloroquine-resistant falciparum malaria is high and unavoidable. Inadvertent use of mefloquine during the first trimester is not an indication for therapeutic abortion. However, a recent study showed that high-dose mefloquine treatment (3–5 times the prophylactic dose) was associated with an increased risk of fetal death.

Doxycycline

Doxycycline is a tetracycline-related drug that is more than 90% effective against multidrug-resistant *P. falciparum.* You can use doxycycline as an equally effective alternative to mefloquine. The drug is also effective against *P. vivax*, *P. ovale*, and *P. malariae.* Doxycycline is the prophylactic of choice in forested border areas in Thailand and some parts of Cambodia where there is a high incidence of malaria due to chloroquine- and mefloquine-resistant *P. falciparum.*

An advantage of doxycycline is its price. Generic doxycycline costs 10 to 20 cents a tablet, versus $7–$10/tablet for mefloquine. Another advantage is that it will also protect against other important infections such as typhus, plague, Lyme disease, and leptospirosis.

A disadvantage of doxycycline is that it must be taken every day. One or two missed doses will put the traveler at risk of malaria.

Doxycycline is contraindicated for pregnant women and children under the age of 8 unless required for the treatment of a serious infection such as falciparum malaria or ehrlichiosis.

Adult dosage—100 mg daily. Doxycycline should be started 1 to 2 days prior to travel. It should be continued daily in malarious areas and for 4 weeks after departure from the area.

Child dosage (for children older than 8 years of age)—2 mg per kg of body weight per day up to the adult dose of 100 mg daily.

Side effects—Most travelers tolerate doxycycline well, but nausea, vomiting, and heartburn can occur. Doxycycline should be taken with sufficient liquid or food to ensure complete passage of the drug into the stomach because if the tablet remains in the esophagus it can cause mucosal erosions or even esophageal perforation. In addition, doxycycline can cause phototoxicity (an exaggerated sunburn reaction to strong sunlight). Risk is reduced by avoiding prolonged, direct exposure to the sun, using a broadspectrum sunscreen (these contain both a UVA and UVB blocker), and taking the drug in the evening. Women taking doxycycline may develop a vaginal yeast infection and therefore should carry a self-treatment dose of an antifungal agent such as fluconazole (Diflucan).

Atovaquone/proguanil (Malarone)

The FDA has just approved the combination of atovaquone (250 mg) and proguanil (100 mg) for the prophylaxis or treatment of malaria caused by *P. falciparum*. This drug is a welcome addition because it not only is very effective, but it provides an alternative for persons intolerant of mefloquine or doxycycline, for children younger than eight, who cannot take doxycycline, and for those going on short trips (it is expensive). Prophylaxis studies conducted in Kenya, Zambia, and Gabon demonstrated that Malarone was 98% to 100% effective in partially-immune subjects. An unpublished trial showed similar efficacy in nonimmune transmigrants in Irian Jaya.

The CDC no longer recommends that Malarone be used only by travelers who cannot take either mefloquine or doxycycline.

Malarone acts against both the blood and liver phases of *P. falciparum*. However, it will not kill the liver parasites (hypnozoites) of *P. vivax* or *P. ovale* so persons at high risk for these infections should receive terminal prophylaxis with primaquine.

Adult prophylactic dose: 1 tablet, started one or two days before travel, taken daily during the stay, and for 7 days after leaving the malarious region.

Child dosage: In the United States a pediatric formulation is available and the dosage is based on weight: 10 kg–20 kg=1 pediatric-strength tablet, 21–30 kg=2 pediatric-strength tablets, 31–40 kg=3 pediatric-strength tablets, and more than 40 kg, 1 adult-strength tablet.

Tablets should be taken with food or a milky drink at the same time each day. If vomiting occurs within one hour after dosing, a repeat dose should be taken. Side effects are minimal; they include stomach upset, cough, and skin rash. Atovaquone/proguanil is contraindicated during pregnancy.

Proguanil

Proguanil (Paludrine) is active against chloroquine-sensitive falciparum malaria as well as *P. vivax*, *P. ovale*, and *P. malariae.* In chloroquine-sensitive areas, proguanil can be used as an alternative to chloroquine. In sub-Saharan Africa, proguanil, combined with weekly chloroquine, is a widely used prophylactic regimen, but is much less efficacious than mefloquine or doxycycline (65% efficacy for proguanil vs. 85–90% for mefloquine or doxycycline).

Adult dosage—200 mg daily, and continue for 4 weeks after leaving the area. Proguanil is not available in the United States but is available over the counter in many countries and by prescription in Canada. It is not available in liquid form.

Child dosage—Less than 2 years, 50 mg daily; 2–6 years, 100 mg daily; 7–10 years, 150 mg daily; over 10 years, 200 mg daily.

Side effects—Toxicity is very low. Nausea, vomiting, and mouth ulcers are common. Serious reactions (such as neuropsychiatric events) are not reported. Proguanil is safe to take during pregnancy.

Chloroquine & Proguanil

Chloroquine, combined with proguanil, is only 65% effective against chloroquine-resistant *P. falciparum* in East Africa and is recommended only when a traveler to sub-Saharan Africa is unable to take either mefloquine or doxycycline. This combination is not recommended for prophylaxis against chloroquine-resistant *P. falciparum* in geographic regions outside of Africa.

Dosage (adults)—chloroquine, 500 mg weekly, plus proguanil, 200 mg daily. Continue prophylaxis for 4 weeks after exposure.

Side effects—Mainly nausea and mouth ulcers. The relatively high incidence (about 30%) of gastrointestinal side effects from the combination is reported to cause a significant number of travelers to discontinue prophylaxis.

Proguanil & sulfonamide—Combining proguanil with a sulfonamide, such as sulfisoxazole or sulfamethoxazole, may dramatically increase prophylactic effectiveness, especially against chloroquine-resistant *P. falciparum.* Studies done in Thailand with this combination in the 1980s have shown over 90% protection. (see Table 5.2)

Other Drugs for Malaria Prevention

Primaquine—When taken by adults in a daily dose of 30 mg (or 0.5 mg/kg), an effectiveness of 85%–95% against *P. falciparum* and *P. vivax* has been demonstrated. This is comparable to the effectiveness of doxycycline and mefloquine. Primaquine, unlike these other two drugs, does not have to be taken for 4—6 weeks after leaving a malarious area. Taking the drug for one week post-exposure is sufficient. This is because primaquine is a "causal prophylactic" and eradicates parasites in the liver. Delayed infections are therefore prevented.

Side effects: Primaquine is better tolerated than chloroquine, but it causes methemoglobinemia and red blood cell destruction (hemolysis) in people with the G-6-PD enzyme deficiency. *A G-6-PD screening test is required before using this drug.* Primaquine is contraindicated in pregnant women. Stomach upsets can be reduced by taking the drug with food.

Note: Primaquine is not routinely recommended at this time, but some physicians are prescribing the drug for the traveler who cannot tolerate mefloquine or doxycycline.

RADICAL CURE

Primaquine

If you have traveled to a region where vivax malaria predominates, and have discontinued prophylaxis after returning, you may be at risk for a delayed malaria attack, caused by dormant *P. vivax* parasites released from your liver. Your risk of malaria is proportional to your degree of exposure to mosquito bites, and primaquine treatment (called "radical cure") may be advised. You have two options:

1. Treat: Take primaquine, as outlined below, to eliminate any possible dormant P. vivax liver parasites. If you were in a malarious area for more than 2 months, then your chance of harboring dormant parasites is probably high enough to justify treatment (except in sub-Saharan Africa where P. vivax malaria is almost nonexistent). Start the 2-week course of primaquine after finishing prophylaxis.

   OR

2. Wait and watch: If your exposure was low to moderate, the chance of infection is less. Defer primaquine and watch for symptoms. Get treated for malaria if it occurs. Another reason for waiting is that primaquine is occasionally toxic and also requires that you get a pretreatment blood test to screen for G-6-PD enzyme deficiency. This enzyme deficiency is most common in blacks, Asians, and people of Mediterranean descent. If primaquine is administered to a person with G-6-PD deficiency, hemolytic anemia will occur.
   Adult dosage—15 mg base (26.3 mg salt) daily for 14 days.
   Child dosage—0.3 mg base per kg (0.5 mg/kg salt) daily for 14 days.

Primaquine is contraindicated during pregnancy. Pregnant women who are at significant risk of *P. vivax* malaria should continue prophylaxis during gestation and receive primaquine after delivery.

Primaquine-Resistant *P. vivax*

Primaquine-resistant strains of *Plasmodium vivax* are reported in scattered areas throughout SE Asia and Oceania, and recently in Somalia. Some travel medicine experts treat individuals returning from these areas who have had heavy exposure to mosquitoes with a higher dose of primaquine (a total of 6 mg base per kg of body weight) for two weeks. For adults, this higher dose of primaquine is usually given as 30 mg per day for 14 days.

MALARIA TREATMENT

Principles of Malaria Treatment

Malaria is a medical emergency, particularly in expatriates who, unlike nationals living in an endemic area, lack immunity to infection. Treatment should be initiated as soon as possible. Individuals who develop malaria, but who have been compliant with their chemoprophylactic regimen, should take an alternative drug for malaria treatment. When in doubt about the diagnosis or the infecting species, presumptive treatment should always be directed against life-threatening chloroquine-resistant falciparum malaria. In addition, malaria that develops in an individual located in an area known to have drug resistance, or in an individual on chemoprophylaxis, should be treated as a drug-resistant infection. When more than one drug is required for the treatment of malaria, quinine or artemisinin should be administered first because of their rapidity of action.

If you suspect that you have malaria, urgently seek medical care. If medical care is not readily available within 48 hours, don't wait—if you are carrying standby antimalarial drugs, start self-treatment (page 93).

Chloroquine

In areas where chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* is NOT reported, start treatment on the following schedule:

- Day 1. Chloroquine 500 mg (salt) by mouth immediately, then chloroquine, 250 mg (salt), six hours later. (500 mg salt=300 mg base)
- Day 2. Chloroquine 250 mg orally.
- Day 3. Chloroquine 250 mg orally.

Severe chloroquine-sensitive malaria requires an intravenous infusion of chloroquine, 0.83 mg/kg/hr (base), or intramuscular chloroquine, 3.5 mg/kg (base) repeated every 6 hours until parasitemia decreases. Oral chloroquine can then be started: the total dose is 25 mg/kg (base).

Note: Since intravenous chloroquine is not readily available in the U.S. or Canada, intravenous quinidine or quinine may be substituted (see below).

Mefloquine (Lariam)

This drug is highly active against all malaria strains, except in Thailand, where cure rates against *P. falciparum* have fallen to 50%–70%.

Dosage—1,250 mg (15–25 mg/kg) is best given as a divided dose of 750 mg (or 15 mg/kg) followed by 500 mg (or 10 mg/kg) 6 hours later. (25 mg/kg is required to treat falciparum malaria from Thailand and 15 mg/kg elsewhere.)

Side effects—Adverse side effects are much more frequent with treatment dosages of mefloquine than with prophylactic doses (page 82). Reports of severe neuropsychiatric side effects, in fact, have tempered the enthusiasm for using mefloquine in the treatment of malaria. The frequency of severe neuropsychiatric symptoms (hallucinations, seizures, delirium, acute psychosis) with treatment doses of mefloquine is estimated at about 1:250-1:1700 treatment courses.

Other adverse reactions include nausea and vomiting, loss of balance and coordination, dizziness, inability to concentrate, headache, and insomnia. Side effects usually last for only a few days but occasionally persist for several weeks and rarely for many months.

Mefloquine should be administered cautiously when the patient has previously received, or is receiving, chloroquine, quinine, quinidine, or procainamide. If these drugs are being used, mefloquine administration should be delayed at least 12 hours after the last dose. Cardiac side effects may occur when halofantrine is administered following mefloquine treatment. Mefloquine has no adverse cardiac effects when given by itself.

Atovaquone/Proguanil (Malarone)

This combination (atovaquone, 250 mg plus proguanil, 100 mg), is now available in the United States. Malarone has been shown to be effective in regions where high failure rates occur with other antimalarials including chloroquine, halofantrine, and mefloquine. In fact, Malarone now appears to be the most effective treatment for acute uncomplicated falciparum malaria, including multidrug-resistant strains. In Thailand, Malarone cured 100% of cases of *P. falciparum* malaria vs. 86% for mefloquine. Elsewhere, an overall success rate of 98.7% has been reported.

Adult dosage:	4 tablets once daily for 3 days
Child dosage:	11–20 kg: 1 adult tablet daily for 3 days
	21–30 kg: 2 adult tablets once daily for 3 days
	31–40 kg: 3 adult tablets once daily for 3 days
	> 40 kg: 4 adult tablets once daily for 3 days

Side effects—Nausea, vomiting, loss of appetite, abdominal pain, headache, and itching. Dividing the dose and giving it twice daily may reduce the gastrointestinal side effects which occur in 10%–15% of patients.

Treatment of vivax malaria—Malarone has not yet been recommended for the prophylaxis or treatment of *P. vivax* malaria, but efficacy has been high in reported cases. However, even with treatment, primaquine is needed to prevent relapse because Malarone does not eradicate P. vivax liver parasites.

Atovaquone/Doxycycline

If Malarone is not commercially available, the combination of atovaquone with doxycycline (1 gm of atovaquone and 200 mg of doxycycline daily for 3 days) has been shown to be as effective as Malarone.

Pyrimethamine/sulfadoxine (Fansidar)

Fansidar is a combination of pyrimethamine and sulfadoxine, and may be used for self-treatment. Resistance to the drug is widespread in Southeast Asia and South America and is becoming more of a problem in Africa.

Fansidar is slower in action than chloroquine or quinine and should not be used alone for the treatment of a severe infection. Nor should Fansidar be used as sole treatment for chloroquine-resistant falciparum malaria, even though the infection may be uncomplicated. Fansidar can be used to treat vivax malaria, but *P. vivax* infections clear more slowly after treatment with Fansidar than after treatment with other drugs (chloroquine, quinine, or mefloquine).

Adult dosage—3 tablets, taken at once.

Child dosage—Less than 1 year, 1/4 tablet; 1 to 3 years, 1/2 tablet; 4 to 8 years, 1 tablet; 9 to 14 years, 2 tablets.

Side effects—Minor side effects can include headache, nausea, vomiting, and skin rash. The risk of a life-threatening reaction (e.g., exfoliative dermatitis) from a single treatment dose of Fansidar is estimated to be 1: 50,000.

Contraindications include people who are allergic to sulfa drugs and infants less than one month of age. Fansidar has been used to treat malarial infection in large numbers of pregnant women without apparent harmful effects on the fetus.

Halofantrine (Halfan)

Halofantrine is chemically similar to mefloquine, with which it shares cross resistance. It is highly effective against all four plasmodium species, including *P. falciparum*. Outside of Thailand, the cure rate is generally more than 90% with a 1-day course of treatment and 100% effective when two courses of treatment are administered.

In Thailand, there is a high incidence of mefloquine-resistant falciparum malaria, and the standard 1-day treatment course of halofantrine is only about 65% effective. High-dose halofantrine (3-day treatment) is 90% curative but side effects, some of which may be potentially fatal, are also increased.

Halofantrine is currently available in many countries in Africa and Europe but is not approved in the U.S. or Canada.

Standard dose—500 mg (or 8 mg/kg) every 6 hours for 3 doses. A second 3-dose treatment should be administered 7 days later.

Because of its erratic absorption and short half-life, halofantrine is not used for chemoprophylaxis. The drug is available in 250 mg tablets and in a pediatric suspension of 100 mg/5 ml. Halofantrine should be taken on an empty stomach.

Side effects—Minor side effects consist of GI upset (diarrhea, nausea, abdominal pain), pruritus (itching), skin rash, and a slight elevation of liver transaminase enzymes.

Serious cardiac side effects—Halofantrine causes a dose-related prolongation of atrioventricular conduction and QTc interval. This effect is increased by mefloquine. Mobitz type I and II conduction blocks have been observed with high-dose halofantrine. The effects of halofantrine (even in standard doses) on cardiac conduction may increase the risk of ventricular tachyarrhythmias and cardiac arrest in people with a prolonged QTc interval (Romano-Ward syndrome). Contraindications to the use of halofantrine are as follows:

- QTc interval >0.44 msec
- A family history of prolonged QTc interval
- A history of ventricular arrhythmias or syncope
- Recent mefloquine use. Halofantrine not to be used to treat mefloquine failures.

Prior to treatment with halofantrine, an ECG to measure the QTc interval is mandatory, followed by in-hospital cardiac monitoring for 8–12 hours. Even with these precautions, *the CDC does not recommend halofantrine for treatment because of the potential side effects and the availability of safer alternative drugs.*

The drug should not be used for self-treatment unless a pretreatment ECG has been done. This is an unlikely scenario and the drug has basically been eliminated as a choice for self-treatment in the field.

Halofantrine is contraindicated during pregnancy or breast feeding.

Quinine

Quinine is an ancient drug that originated from the cinchona plant. It is active against all four species of plasmodia. Quinine is also one of the most rapidly-acting drugs for treatment of severe falciparum malaria. Oral quinine is available as quinine sulfate in tablet and capsule form. In the United States, intravenous quinine is not available and quinidine (see below) must be used if intravenous treatment is required.

Although quinine rapidly reduces parasite counts, quinine by itself may not be adequate for eliminating all parasites permanently from the blood, and recrudescent infections can occur. Therefore a second drug, such as doxycycline, tetracycline, Fansidar, or clindamycin, must also be used in conjunction with quinine.

Despite its effectiveness, resistance to quinine is increasing. In Thailand, quinine cures only 90% of patients with falciparum malaria, even when the drug is combined with tetracycline. Malarone (see below) appears to be more effective.

Dosage for complicated malaria—Quinine dihydrochloride salt by intravenous infusion, 20 mg/kg loading dose over 4 hours, followed by 10 mg/kg every 8 hours given over 2–4 hours. Oral therapy with quinine sulfate, followed by tetracycline, doxycycline, or clindamycin, should be instituted as soon as possible.

Table 5.3

Summary of Treatment of Malaria (by oral route)

A Chloroquine-sensitive malaria (*P. vivax, P. ovale, P. malariae* and sensitive strains of *P. falciparum)*

	Adult Dose	Pediatric Dose
Chloroquine phosphate (Aralen) (250 mg salt = 150 mg base per tablet)	1 gram of salt (4 tabs) immediately; then 500 mg (2 tabs) in 6 hrs, then 500 mg (2 tabs) once/day for 2 days	10 mg base/kg (max 600 mg) immediately; then 5 mg/kg in 6 hrs, then 5 mg/kg/day for 2 days

B *P. vivax* and *P. ovale* malaria
To prevent relapses after chloroquine therapy, add:

Primaquine (21.5 mg salt = 15 mg base/tablet)	15 mg base (1 tab) daily for 14 days	0.3 mg/kg/day for 14 days

C Chloroquine-resistant malaria

Malarone	4 tablets daily x 3 days	See page 91
Quinine sulphate	600 gm salt q8h* x 5–7 days (7 days required in SE Asia)	10 mg salt/kg q8h x 5–7 days (7 days required in SE Asia)
Plus one of the following:		
1. Fansidar** or	3 tablets (75 mg pyrimethamine and 1,500 mg sulfadoxine) once	1.25 mg/kg of pyrimethamine and 25 mg/kg of sulfadoxine once
2. Tetracycline or doxycycline or	250 mg q6h x 7 days 100 mg q12h x 7 days	Contraindicated under 8 years of age
3. Clindamycin	10 mg/kg q8h x 7 days	Same as adult dose
Alternative treatments:		
Mefloquine	1–1.5 gm (15–25 mg/kg) in a divided dose over 12 hours	Inadequate studies
Halofantrine	500 mg (2 tabs) q6h x 3 doses; repeat in 1 week	8 mg/kg dose q6h x 3 doses; repeat in 1 week

* q8h = every 8 hours ** In SE Asia, use tetracycline or doxycycline.

Dosage for uncomplicated malaria—Quinine sulfate, 650 mg (or 10 mg/kg) orally every 8 hours for 3 to 7 days. Follow quinine with one of the following: (1) doxycycline, 100 mg twice daily, (2) tetracycline, 250 mg four times daily, or (3) clindamycin, 450–900 mg three times daily. For malaria acquired in SE Asia, quinine should be administered for 7 days, and for 5 days if acquired elsewhere; doxycycline and clindamycin are administered for 7 days.

Side effects—Headache and tinnitus (ringing in the ears) are the most common side effects of quinine. Cinchonism—nausea, vomiting, abdominal pain, blurred vision, vertigo, and tremors—is common during the first several days of treatment. Serious, occasionally fatal side effects (hypotension, convulsions, heart block, ventricular fibrillation) can occur with too rapid intravenous injection of the drug. Slow IV administration, or oral administration, is usually safe but can cause minor ECG changes (prolongation of the QT interval and T-wave flattening). Quinine can also cause hypoglycemia (low blood sugar) from stimulation of the insulin producing cells of the pancreas; therefore, the parenteral preparation should be administered with glucose, and blood glucose levels must be measured frequently during therapy.

Quinine can be used, if necessary, during pregnancy. On the third day of parenteral therapy, the dose should be reduced by one-half to one-third. Although quinine has been thought to induce abortion, the doses used in malaria treatment are not associated with this side effect.

Quinidine

Quinidine, the d-isomer of quinine, is a commonly used cardiac drug. It can also be used either intravenously or orally to treat chloroquine-resistant falciparum malaria. It is particularly useful in Thailand for the treatment of multidrug-resistant malaria.

Dosage—A loading dose of quinidine gluconate, 10 mg/kg (salt), in normal saline is given intravenously over 1–2 hours, followed by a constant infusion at 0.02 mg/kg/min (1.0–1.5 mg/kg/hour). As soon as the parasite density drops below 1% of red cells infected, intravenous quinidine should be stopped and oral quinine sulfate started and continued for a total of 5 days (7 days in Thailand). Tetracycline, doxycycline, or clindamycin should be given for 7 days.

Side effects—Intravenous quinidine therapy should be administered in an intensive care unit. ECG monitoring is essential. Cardiac effects are similar to those caused by quinine, dose-related QT interval prolongation, and QRS widening.

Artemisinin (Qinghaosu) and Derivatives

Artemisinin (qinghaosu) and its two derivatives, artesunate (water soluble) and artemether (oil soluble), are the most rapidly acting antimalarial drugs. Artemisinin is found in the medicinal herb *Artemeisia annua* (sweet wormwood), a plant used by traditional Chinese practitioners since A.D. 341 for the treatment of fever. Artemisinin was isolated in 1972 and is a sesquiterpene lactone peroxide chemically unrelated to any other currently used antimalarial drug.

Artemisinin is effective against *P. vivax* as well as chloroquine-resistant strains of *P. falciparum*, but recrudescence of infection is common when the drug is used as sole therapy. To prevent recrudescent infections, artemisinin should always be given in conjunction with another antimalarial such as doxycycline or mefloquine. Artemisinin is produced for clinical use in China and Vietnam and is presently available in those countries as well as several others in Asia and Africa. It is now being widely used in Africa, on its own, for the treatment of falciparum malaria.

Oral dosage—3 gm (or 50 mg/kg) given over 3 to 5 days.

Intramuscular dosage—1.0 to 1.2 gm (adult dose) over 3 to 5 days.

Suppositories—2,800 mg total dose given over 3 days.

Side effects—Nausea, vomiting, rash, fever, transient first-degree heart block.

There are several semisynthetic derivatives of artemisinin.

• **Artesunate** is an oral, water-soluble derivative of artemisinin and has been combined with single-dose mefloquine to treat drug-resistant *P. falciparum* in Southeast Asia.

Dosage (Oral, IV, IM, suppository)—100 mg, then 50 mg every 12 hours for three to six days.

• **Artemether** is an oil-soluble compound that is rapidly effective in severe malaria. Oral artemether given over 5 days was found to have a higher cure rate, with fewer side effects, than mefloquine against multidrug-resistant *P. falciparum* in Thailand. In studies done in Malawi, intramuscular artemether acted more rapidly than intravenous quinine in clearing coma and reducing parasite counts in children with cerebral malaria. In Vietnam, intramuscular artemether was as effective as intramuscular quinine in curing severe falciparum malaria. Quinine, however, acted more rapidly in reducing fever and was associated with a shorter hospital stay.

Oral dosage—700 mg given over 5 days.

Intramuscular dosage—3.2–4 mg/kg initially, then 1.6–2 mg/kg every 24 hours for five to seven days. Artemether, dissolved in oil, is supplied in 1.0-ml ampoules containing 80 mg of the drug for intramuscular injection. The average treatment for adults is six ampoules.

Side effects—Oral artesunate and artemether appear to be among the safest and best-tolerated antimalarial drugs, but their side-effect profile has not been fully delineated. These drugs should therefore be used with caution, especially when repeat courses are being administered. Recent studies have shown that brain stem damage may occur from repeated or prolonged artemisinin use in laboratory animals, including primates.

• **Co-artmether (Riamet)** combines the fast-acting artemether with the prolonged action of lumefantrine. The drug is currently available in Switzerland. Unlike halofantrine, lumefantrine is not associated with adverse cardiac effects, such as prolongation of the QT interval. There have been no reports of significant neurological symptoms. A 6-dose regimen over 3 days is reported to cure over 95% of acute uncomplicated multidrug-resistant

Table 5.4

Self-Treatment Options (Adults)

Drug	Dose
chloroquine	1,000 mg initially, followed by 500 mg 6, 24, and 48 hours later
Malarone	4 tablets once daily for 3 days
Fansidar	3 tablets at once
mefloquine	3–5 tablets (750 mg–1,250 mg) in divided doses over 12 hours
Riamet	2 tablets daily for 3 days
quinine	650 mg every 8 hours for 5 to 7 days
quinine plus	650 mg every 8 hours for 5 to 7 days
tetracycline*	250 mg 4 times daily for 7 days
quinine plus	650 mg every 8 hours for 5 to 7 days
clindamycin*	900 mg 3 times daily for 7 days

* Doxycycline, 100 mg twice daily, can be used in place of tetracycline or clindamycin.

falciparum malaria. Because of its rapid onset of action, co-artmether may prevent progression to cerebral malaria. In countries where it is available, the drug is currently recommended as first-line treatment for acute *P. falciparum* malaria and for standby emergency treatment.

SELF-TREATMENT

Several studies have shown that travelers who carry a self-treatment drug rarely use it appropriately and often do not seek medical attention after use as is recommended in all cases. Self-treatment should be considered a last resort since it may delay treatment of another cause of fever. For this reason, medical attention is recommended ASAP whenever self-treatment is initiated.

To date, sulfadoxine-pyrimethamine (Fansidar) has been the drug recommended by the Centers for Disease Control and Prevention (CDC) for presumptive self-treatment for persons with illness suspected to be malaria who are not on optimal prophylaxis regimens. This might be a traveler taking chloroquine in an area with chloroquine-resistant *P. falciparum* who cannot reach medical care within 24 hours. Other travelers who should consider the self-treatment options include:

- Travelers who will be traveling or living in remote areas with chloroquine resistance where they will not have access to medical care within 24 hours and travelers who are unable to tolerate an optimal chemoprophylactic regimen.

- Travelers whose exposure to malaria is likely to be so low that chemoprophylaxis is not desirable. Some North American experts, however, feel that even a single exposure in a high-risk area such as Africa or Oceania requires preventive medication.

Malarone is a new option for self-treatment and is the drug of choice for presumptive self-treatment for travelers to areas with Fansidar-resistant malaria, including the following areas:

- Amazon Basin of South America
- Southeast Asia
- Some countries in eastern and southern Africa: specifically, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Uganda.

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