Malaria is caused by an intracellular protozoan of the genus Plasmodium. The four species that cause human malaria are

- *P. malariae*
- *P. vivax*
- *P. falciparum*
- *P. ovale*

Epidemiology

Malaria is transmitted by the bite of an infected female *Anopheles* mosquito or through direct inoculation of infected red blood cells, i.e., congenital malaria, transfusion malaria and malaria from contaminated needles.

The life cycle of malaria is complex and certain aspects differ according to the *Plasmodium* species involved.

- The infective stages of plasmodia called sporozoites are injected during feeding from the salivary glands of the infected mosquito into the blood stream through subcutaneous capillaries.
- Human Pre-erythrocytic Phase (before becoming red blood cells): Sporozoites enter the liver cells, where they multiply asexually. There the nucleus undergoes repeated division, forming thousands of uninucleate merozoites. There is no inflammatory reaction in the surrounding liver tissue. After six to sixteen days from the time of infection, the hepatic cell containing the tissue schizonts ruptures and the merozoites enter the circulation.
- Human Exo-erythrocytic Phase (Outside the red blood cell):
  - → *P. falciparum* and *P. malariae* schizonts all rupture at about the same time, and none persist in the liver. The only “exo” erythrocytic phase for these two species occur before the invasion of RBC. There is NO continuous cycle in the liver.
  - → *P. vivax* and *P. ovale* have a continuous exoerythrocytic cycle: Some parasites that remain dormant in the liver (hypnozoites) for weeks, months, or even years before developing and resulting in relapses of erythrocytic infection.

All four species of malaria can cause chronic infections with fever occurring more than once.

- Human Erythrocytic Phase (in the red blood cell).
  Merozoites released from tissue schizonts invade erythrocytes.
- RBC Asexual Stages.
  The youngest stages in the RBC are small, rounded trophozoites, known as ring forms. During development, they use the hemoglobin, leaving as the product of digestion an iron-containing pigment, hematin or hemozoin, which can be seen in the cytoplasm of the parasite as dark granules. They grow in the red blood cell and when nuclear division occurs the parasite is called a schizont. This asexual multiplication is the erythrocytic schizogony. The infected erythrocytes rupture, liberating merozoites, which must invade new red cells. The erythrocytic cycle of schizogony is repeated over and over again. The periodicity of schizogony differs according to species.
- RBC Sexual Stages:
From three to fifteen days after the onset of symptoms, subpopulations of merozoites differentiate into sexual forms, gametocytes, i.e., female macrogametocytes and male microgametocytes. The duration of gametocytogony is assumed to be four days in *P. vivax* infections and ten or more days in *P. falciparum* infections.

**Vector phase**

When feeding on an infected human, the female *Anopheles* ingests gametocytes, which develop in the gut of the mosquito. The nucleus of the male gamocyte divides and forms long, thread-like flagellum which break free and produce microgametes. These fertilize the female macrogamete to produce a zygote.

The zygote gets wedged in the outer surface of the stomach and rounds up into a oocyst. An infected *Anopheles* may have ten to several hundred oocysts. The oocyst enlarges and the nucleus divides then forms finger-like processes, which become fusiform sporozoites. The oocyst ruptures, liberating thousands of motile sporozoites which migrate to the salivary glands. The female mosquito is now infectious.

Sporogony varies from eight to thirty-five days, depending on external temperature and on the malaria species.

**Epidemiologic classification of cases**

- **Autochthonous** malaria is contracted locally. Malaria is indigenous when naturally present in an area or country.
- **Imported** malaria is acquired outside a given area
- **Secondary** cases are those derived from imported cases and are referred to as introduced malaria,
- Malaria acquired by blood transfusions, sharing of needles, intentional inoculation, or accidental laboratory infections is known as **induced** malaria
- Cases with insufficient information to classify are **cryptic**

**Imported Malaria**: Increase in international air travel has resulted in the importation of malaria and other diseases to non-endemic areas. Regions where malaria has been eradicated are at continuing risk of imported cases. Patients often arrive during the incubation period and may not become ill until reaching home. Delays in diagnosis, misdiagnosis and inappropriate treatment may occur, resulting in excessive morbidity and mortality. Physicians and public health officials must remain aware of the possibility of imported malarial infections.

The **incubation period** varies according to species: usually twelve to eighteen days for *P.vivax* or *P.ovale*, slightly shorter for *P.falciparum*.

**Clinical Description**

Clinical symptoms and signs of malaria are associated with the release of merozoites, malarial pigment, and debris into the circulation following rupture of infected erythrocytes. Semi-immune patients are less likely to develop severe manifestations and complications when they become infected.

Some patients have vague **prodromal** symptoms before parasites can be detected in the blood. These manifestations, i.e., malaise, myalgia, headache, anorexia and slight fever, may persist for two or three days before an acute paroxysm begins. In the initial phase of illness, the fever can be erratic or continuous. If the infection continues for three to four days, a **synchronous cycle** may develop with afternoon temperature elevations approximately every 48 hours, the classic benign tertian periodicity. The fever can be as high as 40°C (104°F). The patient often feels much worse with falciparum malaria.

The **typical paroxysm** has an abrupt onset with a feeling of coldness and a chill. The teeth chatter and the patient covers himself. Within 30 to 60 minutes, the patient feels hot and has profuse sweating, usually a headache, malaise, and myalgia, along with a varying degree of other symptoms, e.g., nausea, vomiting, flushed face, dry and burning skin and convulsions. Temperatures of 40°C to 41°C (104°F to 106°F) are usual in primary falciparum infections, whereas with the other three species of plasmodia, fever peaks are
usually lower (39°C to 40°C). The hot stage lasts from two to six hours. The sweating stage, in which the patient's temperature falls rapidly, lasts two to three hours. The entire paroxysm, which often begins in the early afternoon, averages nine to ten hours. Between paroxysms, the patient may feel well.

*P. falciparum* causes the most severe form of malarial infection. It may kill up to 25% of nonimmune adults within two weeks of a primary attack unless appropriate treatment is given.

All four species of malaria can cause chronic infections with fever occurring more than once. Recurrent parasitemia is due to proliferation of persistent erythrocytic forms and is known as recrudescence. Recrudescences occur for *P. falciparum* and *P. malariae* which have no persistent exoerythrocytic phase. For *P. vivax* and *P. ovale*, relapses are due to persistence of parasitic forms in the liver.

Congenital malaria is rare, and its occurrence is associated with low immunity in the mother. Therefore, most cases of congenital malaria appear in areas where the prevalence of malaria is low or involve non-immune mothers. Passive transfer of antibody across the placenta helps to protect neonates for the first six to twelve months of life. Malaria is an important cause of abortions, stillbirths and low birth weight, as well as neonatal and infant mortality.

Complications include:

- **Splenic Rupture**
- **Cerebral Malaria** is a frequent cause of mortality, especially in children and nonimmune adults. It usually develops slowly over several days but may occur early in the illness. A severe headache appears. The patient becomes increasingly drowsy and confused and, if not treated rapidly, becomes delirious and then comatose. Hallucinations occur and the patient may appear drunk. Inpatients with cerebral malaria, very high fever, i.e., 41°C to 42°C (106°F to 108°F), can occur. The skin is often flushed and dry, as in heat stroke. Hyperpyrexia requires immediate treatment to reduce the fever.
- **Hemolytic Anemia** can be severe in patients with high parasitemias (≥ 5%) and in non-immune individuals. Sudden intravascular hemolysis can lead to acute renal failure.
- **Renal Failure**: Mild proteinuria, azotemia and oliguria occur frequently in heavy *P. falciparum* infections. Acute renal failure often complicates severe falciparum infections with high parasitemia, and marked hemolysis in an acute tubular necrosis results from renal anoxia, a reduced renal blood flow, and deposition of hemoglobin in the renal tubules. Anuria is a poor prognostic sign, requiring peritoneal dialysis or hemodialysis.
- **Blackwater Fever**: Severe hemolysis, hemoglobinuria and renal failure make up the clinical triad of "blackwater fever."

**Treatment**

The choice of malaria chemotheraphy is based on the infecting species, possible drug resistance and the severity of disease. Severe malaria is defined as a parasitemia greater than 5%, signs of central nervous system or other end-organ involvement, shock, acidosis and/or hypoglycemia. Patients with severe malaria require intensive care and parenteral treatment until the parasite density falls below 1% and they are able to tolerate oral therapy. Exchange transfusion may be warranted when parasitemia exceeds 10%.

**Treatment of Chloroquine-Susceptible Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium falciparum**

Chloroquine-susceptible infections may be treated orally using a total dose of 25 mg chloroquine base/kg given over three days. Patients unable to take oral medications may be treated initially with parenteral chloroquine and then switched to oral chloroquine when they are able to take oral medications. Even for persons with central nervous system involvement, there are no advantages of quinine (or other antimalarial agents) over chloroquine for infections due to chloroquine-susceptible parasites. Halofantrine is contraindicated in pregnant or lactating women. Because of its arrhythmogenic potential, intravenous chloroquine must be given as a carefully controlled infusion to avoid a large bolus in the heart. Pruritus is an
important side effect of chloroquine (and halofantrine), and is particularly common in sub-Saharan Africa, although its pathogenesis is unclear.

**Treatment of Chloroquine-Resistant Plasmodium falciparum**

Persons able to take oral medications may be treated with quinine, mefloquine, halofantrine, or pyrimethamine sulfadoxine, assuming that they did not receive the same drug for chemoprophylaxis. Because most parasites resistant to mefloquine are also resistant to halofantrine, halofantrine should not be used to treat persons who acquire *P. falciparum* infection while receiving mefloquine chemoprophylaxis. Halofantrine can result in prolongation of the QT interval and ventricular arrhythmias in susceptible persons receiving higher than recommended doses as well as in those with recent or concurrent mefloquine therapy, QT prolongation, or thiamine deficiency. Because fatalities have occurred with halofantrine, alternative drugs are preferred when possible. Halofantrine is contraindicated in pregnant or lactating women. Because resistance to pyrimethamine sulfadoxine is common in areas with chloroquine resistance, persons given pyrimethamine sulfadoxine should be watched carefully to ensure that the drug is effective.

Although quinine may often produce side effects, it is effective in vivo against all strains of *P. falciparum* studied thus far. Because quinidine is two- to threefold more active than quinine, because its serum and plasma levels can be measured in most American hospitals and because parenteral quinine is no longer available in the United States, quinidine is preferable to quinine for parenteral use in the United States.

Artemisinin derivatives such as artemether are effective in children with *P. falciparum* infection; they may clear parasitemia and coma more rapidly than does quinine. A controlled study in Thailand has suggested that intravenous artesunate followed by mefloquine is more effective than either artesunate or mefloquine alone and may prevent the late recrudescences typically observed with artesunate alone. Additional controlled studies suggest that artemisinin suppositories may clear *P. falciparum* parasitemia as rapidly as intravenous artesunate, and that artemether is as effective as quinine for severe and cerebral malaria. Because artemisinin treatment is frequently associated with late recrudescences, additional drugs such as mefloquine, tetracycline, or pyrimethamine sulfadoxine are often given after the initial treatment with artemisinin to prevent recrudescence three to four weeks later. Anecdotal reports of embryo toxicity in rats and mice and pathologic evidence of neurotoxicity in dogs suggest that artemisinin derivatives should not be given to pregnant women and should be used with caution until these issues have been resolved. Note that comparative studies of artemether and quinine have not found an increase in neurotoxicity with artemether. As with quinine, there is no evidence of high-level resistance to artemisinin or its derivatives.

**Treatment of Chloroquine-Resistant Plasmodium vivax**

Thus far, all persons with chloroquine-resistant *P. vivax* infection have responded to treatment with oral mefloquine or halofantrine.

**Laboratory Tests**

**Blood Smears** Definitive diagnosis of malaria depends on microscopic demonstration of parasites in the peripheral blood film.

For detection of organisms, the thick blood film is superior because it concentrates the red blood cells by a factor of twenty to forty times. A thick film will yield three to four times as many positive findings as a thin smear and will reveal plasmodia in virtually all active clinical cases. Identification of species in the thick film is difficult because the red cells are lysed in the staining procedure and there is alteration of the morphologic features of the parasites. For positive identification of species, a thin blood film is often necessary. Thick and thin films can be made on the same slide. In doubtful cases, it may be necessary to repeat the thick blood smears every four to six hours until the diagnosis is made.

Timing: Symptoms may precede detectable parasitemia by one to two days. Timing of blood smears is less important than obtaining several smears daily in order to make the diagnosis. Quantitation of parasitemia is useful in following the response to therapy.
Blood smears should be stained with Giemsa stain. Leishman's stain and Wright's stain can also be used but are not as good. Rapid staining may be done with Field's stain, although this stain is less permanent.

The most important initial distinction to make is whether *P. falciparum* is present, because this parasite is frequently life threatening. Species identification may require expert opinion; many physicians are not sufficiently experienced in morphologic differentiation. *P. falciparum* is suggested by criteria such as small ring size, banana-shaped gametocytes, multiple parasites in a single erythrocyte, parasitemia greater than 2% of the red blood cells, and predominance of rings with few trophozoites and no schizonts.

The presence of granular brownish pigment in monocytes or leukocytes should alert physicians to malaria even in the absence of demonstrated parasitemia.

Parasites may also be demonstrated in a bone marrow specimen, but this is rarely required. Antibodies, demonstrable by IFA will appear after the first week of infection but may persist for years and is of limited use in diagnosis since it cannot differentiate between current and past infection. They are not useful for the diagnosis of acute illness.

**Surveillance**

Malaria is a condition reportable within one business day of the diagnosis.

**Case Definition**

**Clinical description**

Signs and symptoms are variable; however, most patients experience fever. In addition to fever, common symptoms include headache, back pain, chills, sweats, myalgia, nausea, vomiting, rarely diarrhea and cough. Untreated *Plasmodium falciparum* infection can lead to coma, renal failure, pulmonary edema and death. The diagnosis of malaria should be considered for any person who has these symptoms and who has traveled to an area in which malaria is endemic. Asymptomatic parasitemia can occur among persons who have been long-term residents of areas in which malaria is endemic.

**Laboratory criteria for diagnosis:**

Demonstration of malaria parasites in blood films

**Case classification:**

**Confirmed** - an episode of microscopically confirmed malaria parasitemia in any person (symptomatic or asymptomatic) diagnosed in the United States, regardless of whether the person experienced previous episodes of malaria while outside the country.

**Comment:**

A subsequent attack experienced by the same person but caused by a different *Plasmodium* species is counted as an additional case. A subsequent attack experienced by the same person and caused by the same species in the United States may indicate a relapsing infection or treatment failure caused by drug resistance.

Cases also are classified according to the following World Health Organization categories:

- **Indigenous:** malaria acquired by mosquito transmission in an area where malaria is a regular occurrence
- **Introduced:** malaria acquired by mosquito transmission from an imported case in an area where malaria is not a regular occurrence
- **Imported:** malaria acquired outside a specific area (e.g., the United States and its territories)
- **Induced:** malaria acquired through artificial means (e.g., blood transfusion, common syringes, or malarial-therapy)
Relapsing: renewed manifestation (i.e., of clinical symptoms and/or parasitemia) of malarial infection that is separated from previous manifestations of the same infection by an interval greater than any interval resulting from the normal periodicity of the paroxysms.

Cryptic: an isolated case of malaria that cannot be epidemiologically linked to additional cases.

Investigation

The purpose of investigation is to confirm suspected cases and identify species, to document recent travel history and to identify other travelers who may have been exposed and classify the case according to epidemiologic origin.

Upon receipt of a report of a malaria case, contact the physician and/or hospital to confirm the diagnosis. Verify the species of malaria. Investigate the source of exposure, i.e. recent travel history, blood transfusion, foreign residence, etc. and document the history of malaria chemoprophylaxis. Identify any other individuals at risk, (i.e., fellow travelers or blood bank, etc.)

If a history of needle sharing is obtained from the patient, investigate and refer all persons who shared the equipment for treatment.

If the malaria is a transfusion-induced case, all donors must be located and their blood examined for malarial parasites and for antimalarial antibodies. Those individuals that are parasite-positive donors should be referred for treatment.

Hospital precaution and isolation: Standard precautions

Malaria Prevention For Travelers

*P. falciparum* malaria is a life threatening disease for all persons infected but especially for those who have been recently infected and have no immunity to it. Every year, some 10,000 US travelers are infected during their travel and become sick when returning home. About one hundred die although prevention was possible. Globally, about two billion people are at risk of malaria, 270 million are infected and one million die from malaria each year.

1-Inform the traveler about the degree of risk of malaria infection:

To advise travelers on malaria risk and prophylaxis it is necessary to know the distribution of malaria worldwide (see map). There are four zones of malaria risk. Prophylaxis has to be adapted to the area:

- Malaria free areas: Western and Eastern Europe, USA, Canada, former USSR, northern Asia (Korea, Japan), Australia, North Pacific Islands, most South Pacific Islands (from New Caledonia to Easter Islands).

- Low risk malaria, *Plasmodium vivax* and *P. malariae*, no chloroquine resistant *Plasmodium falciparum* (CRPF) or no *P. falciparum*: SW Saudi Arabia, Egypt and most of the Middle East, Iran, China, Peru and Bolivia. Malaria transmission is seasonal and low. There is no risk in urban and in high altitude areas.

- Low risk malaria but some CRPF: Southern part of the Arabian peninsula, Afghanistan, Pakistan, most of India and Philippines.

- High risk malaria and CRPF: Inter-tropical Africa, Amazon basin, the Indochinese peninsula, Indonesia, New Guinea, Solomon Islands and Vanuatu.
Malaria Endemic Areas

1 No malaria risk
2 Low risk, no chloroquine resistant *Plasmodium falciparum*
3 Low risk, some chloroquine resistant *Plasmodium falciparum*
4 High risk, chloroquine resistant *Plasmodium falciparum*

2-Recommend precautions against mosquito bites. This advice is as important as the prophylactic treatment.

- Avoid going out at night or wear long sleeve shirts and long trousers and avoid dark colors which attract mosquitoes.
- Apply insect repellent (with *N,N*-diethyl-*m*-toluamide -DEET- or dimethyl phtalate). Follow the instructions on the bottle. Do not exceed the dose, particularly in children.
- Spend nights in well maintained buildings with screened doors and windows. If the building is not insect-proof, sleep under a mosquito net. Make sure that the net is not torn and that no mosquitoes are trapped inside. Tuck the net under the mattress. Insecticide sprays, electric insecticide dispenser with pyrethroid tablets and pyrethroid mosquito coil are useful but do not replace a good mosquito net.

3-Prophylactic treatment:
The decision is based on the risk of malaria in the country AND the area traveled.

Travelers who spend a short stop over in a major city with sightseeing in the city are at very low risk and often prophylaxis is not recommended. Travelers who take trips to rural areas, particularly if they spend some nights in rural areas, should take some prophylaxis.

Prophylactic treatment should start a week before departure (loading dose and to check for any immediate serious side effects). Patients should understand that prophylactic treatment DOES NOT prevent infection, it only suppresses disease. It must be taken for the whole time the traveler is in the malarious area and continued for no less than four weeks (some recommend up to 8 weeks) after return to a malaria-free area. They must seek prompt medical attention if they become ill.

Prophylaxis recommendation according to malaria risk (see map)
<table>
<thead>
<tr>
<th>Malaria risk</th>
<th>Areas traveled</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Low, no CRPF</td>
<td>Urban, daytime rural</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Rural overnight</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>3 Low, some CRPF</td>
<td>Urban, daytime rural</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Rural overnight</td>
<td>Chloroquine or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proguanil (*)</td>
</tr>
<tr>
<td>4 High, CRPF</td>
<td>Stop-over in large urban</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>All other</td>
<td>Mefloquine or Chloroquine/Proguanil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Doxycycline Avotauquone/Proguanil</td>
</tr>
</tbody>
</table>

(*) If proguanil is not available, use mefloquine instead of chloroquine/proguanil

4-Stand-by treatment for travelers taking long trips (safaris, hiking trips) to rural areas during which prompt medical help will not be available. The treatment should be completed and prophylaxis resumed seven days after the first dose of stand-by treatment. The traveler must understand that stand-by treatment is only a temporary measure and that medical advice should be sought after self-treatment. Make sure that the traveler understands not to use the same dose in children.

5-Advise the traveler to seek immediate treatment in case of fever.

The traveler must understand that malaria can kill if treatment is delayed. (This is probably the most important message that the traveler should leave with). Any symptoms, even mild symptoms appearing one week or more after entry in a malaria endemic area and up to two months after return could be due to malaria: Headache, muscular ache (particularly back ache), sensation of fatigue or weakness, fever, nausea, vomiting or loose stools and cough could be the early signs of malaria. Prompt medical advice should be sought. Beware of physicians who rule out malaria without taking a blood smear (finger stick and application of a drop of blood on the slide). Be aware that at the early stages of malaria, a blood smear may be negative and that if symptoms persist, a repeat blood smear is necessary. The patient should always state that he/she has traveled through a malarious area when seeking medical attention.

Most malarial deaths among travelers have occurred because the traveler delayed seeking medical attention, or did not mention the history of travel in a malarious area, or the physician ignored that important clue, or the physician was falsely reassured by an early negative blood smear or the physician was misled by a false negative blood smear (early low density parasitemia are often missed if the lab does not perform a thick smear examination). When the diagnosis of malaria becomes obvious, it may be too late for antimalarials to prevent the fatal outcome.

**Antimalarial Drug Dosages, Schedules and Warnings**

Advise patients that anti-malarial drugs are most effective if taken exactly on schedule without skipping doses and that their drug should be continued post-travel for the most complete protection. Anti-malarial drugs should be purchased before travel; drugs purchased overseas may not be manufactured according to United States standards and may not be effective. They may also be dangerous, contain the wrong drug or an incorrect amount of active drug, or be contaminated.

**Halofantrine (marketed as Halfan)** is widely used overseas to treat malaria. CDC does not recommend the use of Halfan because of serious cardiac complications, including death. Travelers should be advised to avoid Halfan unless they have been diagnosed with life-threatening malaria and no other options are immediately available.

Overdosage of anti-malarial drugs can be fatal. Parents should be advised to keep drugs in childproof containers out of the reach of children.
## Drugs Used in the Prophylaxis of Malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usage</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone/proguanil (Malarone™)</td>
<td>Prophylaxis in areas with chloroquine-resistant or mefloquine-resistant <em>Plasmodium falciparum</em></td>
<td>Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride.</td>
<td>Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride.</td>
<td>Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area, and for 7 days after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance &lt; 30mL/min). Atovaquone/proguanil should be taken with food or a milky drink. Not recommended for children &lt; 5 kg, pregnant women and women breastfeeding infants weighing &lt;5 kg.</td>
</tr>
<tr>
<td>Chloroquine phosphate (Aralen™ and generic)</td>
<td>Prophylaxis only in areas with chloroquine-sensitive <em>P. falciparum</em></td>
<td>300 mg base (500 mg salt) orally, once/week</td>
<td>5 mg/kg base (8.3 mg/kg salt) orally, once/week, up to maximum adult dose of 300mg base</td>
<td>Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. May exacerbate psoriasis</td>
</tr>
<tr>
<td>Doxycycline (Many brand names and generic)</td>
<td>Prophylaxis in areas with chloroquine-resistant or mefloquine-resistant <em>P. falciparum</em></td>
<td>100 mg orally, daily</td>
<td>8 years of age or more: 2 mg/kg up to adult dose of 100mg/day</td>
<td>Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children &lt; 8 years of age and pregnant women.</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate (Plaquenil™)</td>
<td>An alternative to chloroquine for primary prophylaxis* only in areas with chloroquine-sensitive <em>P. falciparum</em></td>
<td>310 mg base (400 mg salt) orally, once/week</td>
<td>5 mg/kg base (6.5 mg/kg salt) orally, once/week, up to maximum adult dose of 310 mg base</td>
<td>Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. May exacerbate psoriasis</td>
</tr>
<tr>
<td>Mefloquine (Lariam™ and generic)</td>
<td>Prophylaxis in areas with chloroquine-resistant <em>P. falciparum</em></td>
<td>228 mg base (250 mg salt) orally, once/week</td>
<td>≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/week 10-19 kg: ¼ tablet once/week 20-30 kg: ½ tablet, once/week 31-45 kg: ¾ tablet once/week ≥46 kg: 1 tablet, once/week</td>
<td>Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Contraindicated in persons allergic to mefloquine or related compounds (e.g. quinine and quinidine), and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities.</td>
</tr>
<tr>
<td>Drug</td>
<td>Usage</td>
<td>Adult dose</td>
<td>Pediatric dose</td>
<td>Comments</td>
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<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Primaquine</td>
<td>An option for prophylaxis in special circumstances. Call Malaria Hot-line (770-488-7788) for additional information.</td>
<td>30 mg base (52.6 mg salt) orally, daily</td>
<td>0.5 mg/kg base (0.8 mg/kg salt) up to adult dose, orally, daily</td>
<td>Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level. Use in consultation with malaria experts.</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease the risk of relapses of <em>P. vivax</em> and <em>P. ovale</em>.</td>
<td>30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area.</td>
<td>0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, once/day for 14 days after departure from the malarious area.</td>
<td>Indicated for persons who have had prolonged exposure to <em>P. vivax</em> and <em>P. ovale</em> or both. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level.</td>
</tr>
</tbody>
</table>

(1) Glucose-6-phosphate dehydrogenase. All persons who take primaquine should have a documented normal G6PD level prior to starting the medication.

**Travel to areas with Chloroquine-resistant *P. falciparum***

**Atovaquone/proguanil (Malarone™)**

Atovaquone/proguanil is a fixed combination of two drugs; in the United States, it is marketed as Malarone. Atovaquone/proguanil prophylaxis should begin one to two days before travel to malarious areas and should be taken daily, at the same time each day, while in the malarious area and daily for seven days after leaving such areas.

**Doxycycline (brand names and generics)**

Doxycycline prophylaxis should begin one to two days before travel to malarious areas. It should be continued once a day, at the same time each day, during travel in malarious areas and daily for four weeks after the traveler leaves such areas.

Note: There are insufficient data on the antimalarial prophylactic efficacy of related compounds such as minocycline (commonly prescribed for the treatment of acne). Optimally, for patients already on minocycline, it should be discontinued prior to travel and doxycycline started. Minocycline can be restarted after the four weeks of post-exposure doxycycline is completed.

**Mefloquine (Lariam™ and generic)**

Mefloquine prophylaxis should begin one to two weeks before travel to malarious areas. It should be continued once a week, on the same day each week, during travel to malarious areas and for four weeks after the traveler leaves such areas.

**Primaquine**

In special circumstances and after consultation with malaria experts available through the Malaria Hotline (770-488-7788), primaquine may be used for prophylaxis for travel to areas with or without chloroquine-resistant *P. falciparum*. This use should generally be reserved for travelers unable to take any of the other chemoprophylaxis regimens recommended for the region of travel.

Note: Travelers must be tested for G6PD deficiency (glucose-6-phosphate-dehydrogenase) and have a documented G6PD level in the normal range before primaquine use.

Primaquine prophylaxis should begin one to two days before travel to the malaria-risk area. It should be continued once a day, at the same time each day, while in the malarious area and daily for seven days after leaving the malaria-risk area.
In those who are G6PD deficient, primaquine can cause hemolysis, which can be fatal. Be sure to document a normal G6PD level before prescribing primaquine.

**Travel to Areas with Mefloquine-resistant *P. falciparum***

Mefloquine-resistant *P. falciparum* is present in eastern Burma (states of Shah, Kayin and Kayah), the western provinces of Cambodia that border Thailand and all malaria-risk areas in Thailand. Either atovaquone/proguanil or doxycycline can be used by travelers to these areas.

**Travel to Areas with Chloroquine-sensitive *P. falciparum***

**Chloroquine (Aralen™, Plaquenil™ and generic)**

In areas where chloroquine-resistant *P. falciparum* has not been reported, either chloroquine phosphate (Aralen and generic) or hydroxychloroquine sulfate (Plaquinil) may be used. Less evidence exists on hydroxychloroquine sulfate’s effectiveness as an antimalarial drug. Chloroquine prophylaxis should begin one to two weeks before travel to malarious areas. It should be continued once a week, on the same day of the week, during travel to malarious areas and for four weeks after a traveler leaves such areas.

Travelers unable to take chloroquine should take atovaquone/proguanil, doxycycline, mefloquine, or primaquine; these drugs are also effective against chloroquine-sensitive *P. falciparum*.

**Adverse Reactions and Contraindications**

Most anti-malarial drugs are well-tolerated; most travelers do not need to stop taking their drug because of side effects. However, if the traveler is particularly concerned about side effects, discuss the possibility of starting their drug early (3-4 weeks in advance of their trip). If the drug cannot be tolerated, another anti-malarial drug should be prescribed.

**Atovaquone/proguanil**

The most common adverse effects reported in persons using atovaquone/proguanil for prophylaxis are abdominal pain, nausea, vomiting and headache. Atovaquone/proguanil should not be used in infants <5kg, pregnant women, women breast-feeding infants <5kg, or patients with severe renal impairment (creatinine clearance <30mL/min).

**Chloroquine phosphate and Hydroxychloroquine sulfate**

Side effects that can occur include gastrointestinal disturbance, headache, dizziness, blurred vision, insomnia and pruritus, but generally these effects do not require that the drug be discontinued. High doses of chloroquine, such as those used to treat rheumatoid arthritis, have been associated with retinopathy; this serious side effect appears to be extremely unlikely when chloroquine is used for routine weekly malaria prophylaxis. Chloroquine and related compounds may exacerbate psoriasis.

**Doxycycline**

Doxycycline can cause sun sensitivity, usually manifested as an exaggerated sunburn reaction. Travelers on doxycycline should be advised to protect themselves by avoiding prolonged sun exposure and by using sunscreen that absorbs long-wave UVA radiation.

Doxycycline use may be associated with an increased frequency of *Candida* vaginitis. Travelers should be advised to take an over-the-counter yeast medication or a prescription drug or cream. Gastrointestinal side effects (nausea or vomiting) may be minimized by taking the drug with a meal and a full glass of water. Travelers should be advised not to take doxycycline before going to bed to avoid esophagitis.

Doxycycline should not be taken by persons allergic to tetracyclines, pregnant women and by children less than eight years of age.
Vaccination with the oral typhoid vaccine Ty21a should be delayed for more than twenty-four hours after taking a dose of doxycycline.

**Mefloquine**

Mefloquine has been associated with rare serious adverse reactions (e.g. psychoses or seizures), at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Other side effects that occur with prophylactic doses include gastrointestinal disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder and dizziness. Other more severe neuropsychiatric disorders occasionally reported during post-marketing surveillance include sensory and motor neuropathies (including paraesthesia, tremor and ataxia), agitation or restlessness, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, paranoia and encephalopathy. On occasions, psychiatric symptoms have been reported to continue long after mefloquine has been stopped. During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness, or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative drug substituted.

Mefloquine is contraindicated for use by travelers with a known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders. Mefloquine is contraindicated in persons with a history of seizures (not including the type of seizure caused by high fever in childhood). It should be used with caution in persons with psychiatric disturbances or a previous history of depression. A review of available data suggests that mefloquine may be used in persons concurrently on beta blockers, if they have no underlying arrhythmia. However, mefloquine is not recommended for persons with cardiac conduction abnormalities. Any traveler receiving a prescription for mefloquine must also receive a copy of the FDA Medication Guide which can be found at the FDA website: [http://www.fda.gov/cder/foi/label/2003/19591s19lbl_Lariam.pdf](http://www.fda.gov/cder/foi/label/2003/19591s19lbl_Lariam.pdf) (PDF format only)

**Primaquine**

The most common adverse event in G6PD-normal persons is gastrointestinal upset if primaquine is taken on an empty stomach—this problem is minimized or eliminated if primaquine is taken with food. Primaquine can cause hemolysis in G6PD-deficient persons, which can be fatal. Before primaquine is used, G6PD deficiency MUST be ruled out by appropriate laboratory testing.

Changing Medications during Chemoprophylaxis as a Result of Side Effects

Anti-malarial drugs have different modes of action that affect the parasite at different stages of the life cycle. If medications need to be changed because of side effects, there are some special considerations. Travelers who start with medications such as mefloquine or doxycycline but must switch to atovaquone/proguanil during or after travel should continue their atovaquone/proguanil for four weeks after switching or one week after returning, whichever is longer, but not beyond four weeks after return. Assistance with the management of travelers who need to discontinue their anti-malarial drug and switch to another is available at the CDC Malaria Hotline (770-488-7788).

**Chemoprophylaxis for Infants, Children and Adolescents**

Children of any age can contract malaria; all children traveling to a malaria-risk area should take an anti-malarial drug. In the United States, anti-malarial drugs are available only in tablet form and may taste quite bitter. Pediatric dosages should be carefully calculated based on the child’s current weight; children’s dosages should never exceed adult dosage. Full-service (compounding) pharmacists can pulverize tablets, weigh out the precise dose and place the dose in a gelatin capsule. Advise parents to open the gelatin capsule and mix the drug with something sweet such as applesauce, chocolate syrup, or jelly and to give the drug on a full stomach to minimize stomach upset and vomiting. Parents should allow sufficient time before travel to allow preparation of these dosages.
Overdosage of anti-malarial drugs can be fatal. Medication should be stored in childproof containers out of the reach of infants and children.

**Chemoprophylaxis during Pregnancy and Lactation**

Malarial infection in pregnant women can be more severe than in non-pregnant women. In addition, malaria can increase the risk for adverse pregnancy outcomes, including prematurity, abortion and stillbirth. Because malaria is such a serious illness in pregnancy and because no chemoprophylactic regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to a malaria-risk area. If travel cannot be avoided, then use of an effective anti-malarial drug is essential.

Travel during Pregnancy to Areas with Chloroquine-sensitive *P. falciparum*

Chloroquine phosphate or hydroxychloroquine sulfate are recommended for pregnant women traveling to areas with chloroquine-sensitive *P. falciparum*. Chloroquine has not been found to have any harmful effects on the fetus when used in the recommended doses for weekly prophylaxis.

Travel during Pregnancy to Areas with Chloroquine-resistant *P. falciparum*

Mefloquine is currently the only medication recommended for prophylaxis during pregnancy. Studies indicate that prophylactic use during second and third trimesters is not associated with adverse fetal or pregnancy outcomes. More limited data suggest it is also safe during the first trimester. Because of insufficient data regarding the use during pregnancy, atovaquone/proguanil is not currently recommended for the prevention of malaria in pregnant women. Doxycycline is contraindicated during pregnancy because of the known risks of tetracycline on fetal development, including discoloration and dysplasia of the teeth and inhibition of bone growth. Primaquine should not be used during pregnancy because the drug may pass to a G6PD-deficient fetus and cause hemolytic anemia in utero.

**Lactation**

Very small amounts of chloroquine and mefloquine are excreted in breast milk; the amount of drug is not sufficient to harm the infant nor is the quantity sufficient to protect the child from malaria. Breastfeeding infants should receive the recommended dosages of antimalarials found in the table above. Very limited data are available on the use of doxycycline in lactating women; most experts consider the theoretical possibility of adverse events to be remote. Primaquine should only be given to lactating women if both the woman and her infant have been tested for G6PD deficiency and have documented normal G6PD levels. Because safety data is not yet available, atovaquone/proguanil is not currently recommended for women breastfeeding infants < 5kg.

**Educate Patients on the Signs and Symptoms of Malaria**

Advise your patients that they can still contract malaria despite prophylaxis and anti-mosquito measures. Inform travelers that fever or flu-like illness, either while traveling or after returning home (for up to 1 year or more), may be malaria and that they should seek immediate medical evaluation, including thick and thin smears.

**Self-Treatment**

Malaria can be effectively treated early in the course of the disease; however, delay of appropriate treatment can have serious or even fatal consequences. Travelers who choose not to take an anti-malarial drug or who are on a less than effective regimen (chloroquine in a chloroquine-resistant risk area) or who may be in very remote areas can be given a self-treatment course of atovaquone/proguanil. Travelers on atovaquone/proguanil as their anti-malarial drug regimen should not use atovaquone/proguanil as their self-treatment drug and should use an alternative self-treatment regimen.
Presumptive Self Treatment of Malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose</th>
<th>Pediatric dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone/proguanil (Malarone)</td>
<td>4 tablets</td>
<td>Daily dose to be taken for 3 consecutive days: 5-8 kg: 2 pediatric tablets 9-10 kg: 3 pediatric tablets 11-20 kg: 1 adult tablet 21-30 kg: 2 adult tablets 31-40 kg: 3 adult tablets ≥41 kg: 4 adult tablets</td>
<td>Contraindicated in persons with severe renal impairment (creatinine clearance &lt;30mL/min). Not recommended for self-treatment in persons on atovaquone/proguanil prophylaxis. Not currently recommended for children &lt;5kg, pregnant women, and women breastfeeding infants &lt;5kg.</td>
</tr>
</tbody>
</table>

Travelers should be advised to take their presumptive self-treatment promptly if they have a fever, chills, or other influenza-like illness and if professional medical care is not available within 24 hours. Travelers should be advised to seek medical care immediately after self-treatment.

Treatment: General Approach

Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory confirmation).

Once the diagnosis of malaria has been confirmed, appropriate anti-malarial treatment must be initiated immediately. Treatment should be guided by three main factors: the infecting Plasmodium species, the clinical status of the patient and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired.

Determination of the infecting Plasmodium species for treatment purposes is important for three main reasons:

- *P. falciparum* infections can cause rapidly progressive severe illness or death while the non-falciparum (*P. vivax, P. ovale,* or *P. malariae*) species rarely cause severe manifestations;
- *P. vivax* and *P. ovale* infections require treatment for the hypnozoite forms that remain dormant in the liver and can cause a relapsing infection
- and *P. falciparum* and *P. vivax* species have different drug resistance patterns in differing geographic regions

For *P. falciparum* infections, the urgent initiation of appropriate therapy is especially critical.

The second factor affecting treatment is the clinical status of the patient. Patients diagnosed with malaria are generally categorized as having either uncomplicated or severe malaria. Patients diagnosed with uncomplicated malaria can be effectively treated with oral anti-malarials. However, patients who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions and/or parasitemia of > 5%) are considered to have manifestations of more severe disease and should be treated aggressively with parenteral anti-malarial therapy.

Finally, knowledge of the geographic area where the infection was acquired provides information on the likelihood of drug resistance of the infecting parasite and enables the treating clinician to choose an appropriate drug or drug combination and treatment course. If the diagnosis of malaria is suspected and cannot be confirmed, or if the diagnosis of malaria is confirmed but species determination is not possible, anti-malarial treatment effective against *P. falciparum* must be initiated immediately.
After initiation of treatment, the patient's clinical and parasitologic status should be monitored. In infections with *P. falciparum* or suspected chloroquine-resistant *P. vivax*, blood smears should be made to confirm adequate parasitologic response to treatment (decrease in parasite density followed by clearance).

**Treatment: Uncomplicated Malaria**

*P. falciparum* or Species Not Identified

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haiti, the Dominican Republic and most of the Middle East, patients should be treated with oral chloroquine. A chloroquine dose of 600 mg base (= 1,000 mg salt) should be given initially, followed by 300 mg base (= 500 mg salt) at 6, 24, and 48 hours after the initial dose for a total chloroquine dose of 1,500 mg base (=2,500 mg salt). As a second line alternative for treatment, a hydroxychloroquine dose of 620 mg base (=800 mg salt) po can be given immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours after the initial does for a total hydroxychloroquine dose of 1,550 mg base (=2,000 mg salt).

For *P. falciparum* infections acquired in areas with chloroquine-resistant strains, three treatment options are available. The first two treatment options are quinine sulfate plus doxycycline, tetracycline, or clindamycin; or atovaquone-proguanil (Malarone). Both of these options are very efficacious. For the quinine sulfate combination options, quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there are more data on the efficacy of quinine plus doxycycline or tetracycline. Quinine treatment should continue for seven days for infections acquired in Southeast Asia and for three days for infections acquired in Africa or South America. The third option, mefloquine, is associated with a higher rate of severe neuropsychiatric reactions when used at treatment doses. We recommend this third option only when the quinine sulfate combination or atovaquone-proguanil options cannot be used.

For pediatric patients, the treatment options are the same as for adults except the drug dose is adjusted by patient weight. The pediatric dose should never exceed the recommended adult dose. For children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine (given alone for a full seven days regardless of where the infection was acquired or given in combination with clindamycin as recommended above), and atovaquone-proguanil are recommended treatment options for chloroquine-resistant *P. falciparum* infections; mefloquine can be considered if these options are not available. In rare instances, doxycycline or tetracycline can be used in combination with quinine in children less than eight years old if other treatment options are not available or are not tolerated, and the benefit of adding doxycycline or tetracycline is judged to outweigh the risk.

If infections initially attributed to “species not identified” are subsequently diagnosed as being due to *P. vivax* or *P. ovale*, additional treatment with primaquine should be administered (see *P. vivax* and *P. ovale*, below).

*P. malariae*

There has been no widespread evidence of chloroquine resistance in *P. malariae* species; therefore, chloroquine remains the drug of choice for all *P. malariae* infections. As a second line alternative for treatment, hydroxymellarine may be given instead.

*P. vivax* and *P. ovale*

Chloroquine (hydroxychloroquine as second line alternative for treatment) remains the treatment of choice for all *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia. Reports have confirmed a high prevalence of chloroquine-resistant *P. vivax* in these two specific areas. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and South America. Persons acquiring *P. vivax* infections from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine. If the patient does not respond
to chloroquine, treatment should be changed to one of the two regimens recommended for chloroquine-resistant \textit{P. vivax} infections.

Persons acquiring \textit{P. vivax} infections in Papua New Guinea or Indonesia should initially be treated with a regimen recommended for chloroquine-resistant \textit{P. vivax} infections. The two treatment regimens for chloroquine-resistant \textit{P. vivax} infections are quinine sulfate plus doxycycline or tetracycline, or mefloquine. These two treatment options are equally recommended. There are no adequate, well-controlled studies to support the use of atovaquone-proguanil to treat chloroquine-resistant \textit{P. vivax} infections.

In addition to requiring blood stage treatment, infections with \textit{P. vivax} and \textit{P. ovale} can relapse due to hypnozoites that remain dormant in the liver. To eradicate the hypnozoites, patients should be treated with a 14-day course of primaquine phosphate. CDC has recently changed its recommendations for treating hypnozoites by increasing the recommended primaquine phosphate dose to 30 mg (base) by mouth daily for fourteen days. Because primaquine can cause hemolytic anemia in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency, persons must be screened for G6PD deficiency prior to starting primaquine treatment. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given at the dose of 45 mg (base) orally one time per week for eight weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

For pediatric patients, the treatment options are the same as for adults except the drug dose is adjusted by patient weight. The pediatric dose should never exceed the adult recommended adult dose. For children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine (given alone for 7 days) or mefloquine are recommended treatment options for chloroquine-resistant \textit{P. vivax} infections. In rare instances, doxycycline or tetracycline can be used in combination with quinine in children less than 8 years old if other treatment options are not available, are not being tolerated and the benefit of adding doxycycline or tetracycline is judged to outweigh the risk. Primaquine should be given to pediatric patients only after they have been screened for G6PD deficiency.