



Malaria

Key Points

- | Malaria is an infection caused by a parasite that lives within the red blood cells and is acquired through the bite of mosquitoes which generally feed at night.
- | This infection occurs in tropical and subtropical countries, mostly in sub-Saharan Africa where risk is considerably higher than anywhere else.
- | Travelers who visit or live in rural areas of tropical countries where the disease is common are at high risk.
- | Symptoms always include fever and influenza-like symptoms (chills, sweats, muscle aches, headache). Vomiting, abdominal pain, diarrhea, cough, and jaundice (yellow skin and eyes) may occur.
- | Without immediate and proper treatment, severe malaria can progress to shock, lung and kidney failure, coma, and death. Some forms of malaria can persist for many months and can cause relapses.
- | Prevention includes medications taken during the trip and for a short period thereafter, as well as personal protective measures against mosquito bites.
- | Atovaquone-proguanil (Malarone or generic), doxycycline, and mefloquine are equally effective antimalarial drugs when taken as instructed.
- | For short-term travel (less than 2-3 weeks), atovaquone-proguanil may be preferable because travelers can stop taking the drug just 7 days after leaving the malarious area. Longer courses of atovaquone-proguanil appear safe but are more costly than mefloquine or doxycycline.
- | For long-term travel, mefloquine is preferable (if it is tolerated and if there is no resistance to the drug) due to the lower cost and once-weekly doses (rather than daily doses).
- | Chloroquine, an older drug, is the drug of choice in limited chloroquine-sensitive areas. Atovaquone-proguanil, doxycycline, and mefloquine are also completely effective in these areas and may be used when more convenient.
- | Mefloquine should not be used in areas of mefloquine resistance (i.e., Southeast Asia).

Introduction

Malaria is an infection caused by a parasite that lives within the red blood cells and is acquired through the bite of *Anopheles* mosquitoes which generally feed at night.

Malaria remains the most frequent infectious cause of death for persons traveling to tropical and subtropical countries.

There is no malaria vaccine available; however, malaria usually (but not always) can be prevented by the use of antimalarial drugs and personal protective measures against mosquito bites. (See *Insect Precautions*.)

Risk Areas

Malaria occurs in approximately 100 countries in Africa, Central and South America, South Asia, Southeast Asia, the Middle East, and South Pacific islands. Most of the world's malaria occurs in sub-Saharan Africa where risk is considerably higher than anywhere else.

In most parts of the world, malaria is a rural disease with minimal or no risk in urban areas. However, malaria risk occurs in both rural and urban areas of sub-Saharan Africa and South Asia. Malaria is less common above a certain altitude (usually around 8,200 ft / 2,500 m), during dry seasons, and among persons who stay in air-conditioned and/or screened accommodations.

The risk of getting malaria can vary greatly within a country depending on the intensity of transmission, the traveler's itinerary, season, duration and type of travel, the location (e.g., urban vs. rural), and where an individual spends the evening and nighttime hours. For example, short-term travelers living in urban centers and staying in air-conditioned hotels will be at much lower risk than long-stay, adventurous travelers living in rural areas. However, brief exposure, such as a 1-night stay in a malarious area or a night-time train trip through a malarious area, requires that protective measures be taken, including insect precautions and possibly a full course of prescription anti-malarial drugs. It is also possible to contract malaria during brief stopovers at airports in malarious zones if health officials have not taken proper measures to rid the area of mosquitoes. Airports off the main circuit of international travel are particularly suspect.

Country-specific malaria risk information is available from health care providers in the form of a Travax country report malaria recommendation map (where available).

Transmission

Malaria is usually transmitted between dusk and dawn, the time that *Anopheles* mosquitoes generally feed on humans.

Occasionally, malaria is transmitted through blood transfusion, transferal from mother to fetus, or contaminated needles and syringes.

Risk Factors

Travelers who visit or live in rural areas of tropical countries where the disease is common have greater risk of acquiring malaria. Very young and very old persons are at high risk, as are pregnant women.

Adults who grew up in malarious areas should be aware that immunity to malaria disappears within 6 months of the last exposure to malaria. Preventive medications are indicated for these individuals just as they are for first-time travelers to a malarious region.

Symptoms

Malaria symptoms usually develop within days after being exposed. Less commonly, symptoms can appear weeks, months, or even a few years after leaving a malarious area (when use of preventive drugs has been stopped).

Symptoms always include fever and influenza-like symptoms (chills, sweats, muscle aches, headache) that may come and go. Vomiting, abdominal pain, diarrhea, cough, and jaundice (yellow skin and eyes) can occur. The symptoms of malaria can mimic almost any other infection that causes fever.

Malaria caused by the *P. falciparum* strain usually occurs about 10 to 12 days after infection and is a medical emergency. If falciparum malaria is not treated immediately and properly, it can proceed to shock, lung and kidney failure, coma, and death.

Malaria caused by milder strains (*P. vivax*, *P. ovale*, and *P. malariae*) is not usually life-threatening, but there may be serious health risks to very young or very old persons and to those with underlying illness. Malaria due to *P. vivax* and *P. ovale* may eventually resolve without treatment, but can relapse periodically until properly treated.

Malaria is always completely curable when the appropriate drug is used.

Consequences of Infection

Without immediate and proper treatment, severe malaria can progress to shock, lung and kidney failure, coma, and death. Some forms of malaria can persist for many months and can cause relapses.

Need for Medical Assistance

Individuals who think they might have symptoms of malaria (especially fever and/or influenza-like symptoms) should seek medical attention immediately because delay of appropriate treatment can lead to serious or fatal consequences. Inform the health care provider that risk of malaria exists and where travel occurred. Request "thick and thin blood films" or a malaria rapid diagnostic card test for diagnosis. One negative blood film does not rule out malaria; if symptoms persist, 2 additional films should be performed 12 to 24 hours apart. Similarly, a negative rapid malaria test should be followed with up to 3 thick/thin blood films.

- 1 Certain strains of malaria can lie dormant in the liver and cause malaria symptoms months or even years after leaving the malaria risk area and discontinuing malaria drugs. The development of fever or influenza-like symptoms is cause to seek medical attention and to advise the health care provider of previous travel to a malarious area.

Travelers should be aware that the medical management of malaria in countries where the disease routinely occurs may differ from their country of origin. However, in many countries where malaria is endemic, there may be a limited number of effective medications available for treatment. In fact, some of the drugs used may be ineffective for persons, such as travelers, without partial immunity to malaria or may be associated with unacceptable adverse effects.

Prevention

The use of preventive medications such as atovaquone-proguanil, doxycycline, or mefloquine (taken during the trip and for a short period thereafter), as well as personal protective measures against mosquito bites, are important safeguards for travelers to malarious areas. (See *Insect Precautions*.)

Drugs that are used for malaria prevention are listed below. The choice of drug depends on patient, itinerary, and economic factors; each drug has advantages and disadvantages.

There is always the risk of potential side effects no matter which medication is used to prevent malaria. However, any possible minor side effects of antimalarial medications must always be

weighed against the risk of severe and potentially fatal infection with *P. falciparum*. Disabling side effects are uncommon with most antimalarial drugs. If intolerable side effects arise, if at all possible, contact the original prescribing health care provider for advice. Should medications need to be changed mid-course due to side effects (or any desire to take a different medication for the next portion of the trip), special considerations apply with respect to duration of therapy. Travelers should obtain instruction on how to do this from a knowledgeable physician.

Although the use of preventive drugs and insect precautions will decrease the chance of getting malaria, such measures do not guarantee protection.

Travelers may encounter fellow travelers who have been prescribed regimens different from their own, some highly effective but many others much less so. They may include drugs that are not available in the U.S. Travelers should adhere to their own drug regimen at all times.

Timing of Antimalarial Drugs

Different drugs must be started at different times with respect to the beginning of travel. This has to do with the time it takes to build up effective blood levels as well as the need to assess for any serious side effects prior to departure.

Malarious countries may not have malaria in all areas. In determining antimalarial regimens, it is important to note that the first day in a malarious area may not correspond to the first day in that country, as many itineraries may begin in a nonmalarious area. An individual who will be in a nonmalarious area of the country for several days or weeks before entering a malarious area does not need to start taking the drug until the appropriate time before the actual malaria exposure starts. The traveler will need to continue to take antimalarials for as long as malaria risk occurs, in some cases months or even years, and then continue taking the antimalarial drugs for a specified period of time after leaving the malaria risk area. See below for information on the drugs that may be prescribed. Some long-term travelers or expatriates may travel into malarious areas only periodically and may need to take antimalarials only periodically. A health care provider can determine the best strategy.

Antimalarial Drugs

Atovaquone-Proguanil (Malarone and Generics)

Atovaquone-proguanil (Malarone or a generic version of the drug) is available in a single tablet.

The adult dose is a 250

mg/100 mg tablet, taken orally once a day. Start taking atovaquone-proguanil 1 day before arrival in a malaria risk area, take it daily while in the risk area, and continue taking it daily for 1 week after leaving the malarious area. Atovaquone-proguanil should be taken with a meal or milk at the same time each day.

A missed dose can be taken later the same day, but individuals should not double the next day's dose if a dose is missed completely. In the event of a missed dose occurring at a time when exposure to malaria is possible, atovaquone-proguanil must be continued for a minimum of 4 more weeks after resuming the medication and for a minimum of 1 week after the last day of exposure. In the event of a missed dose during the week after exposure, atovaquone-proguanil

must be continued for a minimum of 4 weeks after the last day of exposure.

When atovaquone-proguanil is used for malaria prevention, side effects are uncommon. However, nausea, vomiting, stomach pain, and diarrhea may occur.

Chloroquine (Aralen and Generics)

Chloroquine (Aralen) is a safe and effective medication that may be used to prevent malaria in the very few areas where chloroquine resistance has not occurred. The adult dose of chloroquine is 500 mg taken orally once a week. Start taking chloroquine 1 week before arrival in a malaria risk area, take it weekly while in the risk area, and continue taking it weekly for 4 weeks after leaving the malarious area. A missed dose should be taken as soon as possible that same week (but not the day before the next regularly scheduled dose), resuming the schedule on the next normally scheduled day. Do not take a double dose if a dose is completely missed one week. Most people find Sunday the most convenient and easy day to remember for weekly medication.

Serious side effects of chloroquine are uncommon. Minor side effects may occur, such as upset stomach, headache, dizziness, blurred vision, and itching (the latter most often in African Americans). Persons with epilepsy may be at risk for seizures.

Doxycycline

The adult dose of doxycycline is a 100 mg tablet, taken orally once daily. Start taking doxycycline 1 day before arrival in a malaria risk area, take it daily while in the risk area, and continue taking it daily for 4 weeks after leaving the malarious area. Late doses can be made up on the same day, resuming the normal schedule the following day. Do not double the dose the next day if a dose is completely missed one day. Doxycycline should be taken while sitting or standing in an upright position, and it should be taken with food or a liberal amount of fluid. Do not lie down for 30 minutes after taking this drug. Do not take Pepto Bismol or antacids while taking doxycycline, as they can interfere with absorption of the drug.

Skin sensitivity to sunlight is an uncommon side effect but can lead to severe sunburn. Risk of this complication can be lowered by using a sunscreen that blocks both UVA and UVB rays, avoiding prolonged exposure to sunlight, and wearing protective clothing, including a hat. Women who take doxycycline may develop vaginal yeast infections and should carry an antifungal drug for self-treatment.

Mefloquine (Lariam and Generics)

The adult dose of mefloquine is 1 tablet containing 250 mg taken orally once a week. Start taking mefloquine 2-3 weeks before arrival in a malaria risk area, take it weekly while in the risk area, and continue taking it weekly for 4 weeks after leaving the malarious area. A missed dose should be taken as soon as possible that same week (but not the day before the next regularly scheduled dose), resuming the schedule on the next normally scheduled day. Do not double the dose the next week if a dose is completely missed one week.

Mefloquine usually is well tolerated but may cause side effects affecting the gastrointestinal tract, nerves, and emotional and mental processes.

Minor side effects include headache, stomach upset, dizziness, and bad dreams, which tend to be mild or temporary. Individuals who plan to drive, pilot a plane, or operate machinery should be aware that mild dizziness is a possible side effect.

The FDA has added a warning to the packaging label for mefloquine, stating that it can cause serious neurological and psychiatric side effects. These reactions can persist for months, years, or permanently, even after discontinuation of mefloquine.

About 5% of users develop disabling anxiety, dizziness, depression, insomnia, or irritability that is bad enough to make them stop taking the drug. However, it is important to remember that about 95% of mefloquine users tolerate the drug without discontinuing it, and for long-stay travelers to chloroquine-resistant areas, this weekly medication is the most convenient regimen.

Severe adverse events, such as symptoms of insanity, seizures, and brain dysfunction may occur in about 1 out of 6,000 to 10,000 users. Adverse reactions affecting the nerves, emotional and mental processes, and the inner ear which helps control balance, can persist for months, years, or permanently, even after discontinuation of mefloquine.

Individuals should not take mefloquine if they have an allergy to the drug; a history of convulsions or epilepsy; conduction abnormalities of the heart; or current or recent history of depression, anxiety disorder, insanity (psychosis), schizophrenia, or any other major psychiatric disorder. Stop taking the drug if the following symptoms occur while taking the drug for malaria prevention: acute anxiety, depression, restlessness, or confusion. In this case, an alternative medication should be obtained from a health care provider.

Infants and Children

All children (including young infants) who travel to malaria risk areas should be protected against insects and should take drugs to prevent malaria. The dosage will depend on the child's age and/or weight.

Young children should avoid travel to areas of chloroquine-resistant falciparum malaria unless they can take an effective drug such as mefloquine, doxycycline, or atovaquone-proguanil.

- | Doxycycline should not be given to infants and children younger than 8 years in the U.S. or younger than 12 years in the U.K.
- | If a physician prescribes chloroquine or mefloquine for a child, the pharmacist can crush the tablets (which have a bitter flavor) and place the powder in gelatin capsules with calculated pediatric doses. Children may tolerate antimalarial medications more readily if the crushed powder is mixed in food (for example, honey or chocolate sauce) or drink.
- | Atovaquone-proguanil is available (in the U.S. and Canada) in a pediatric formulation that can be crushed and mixed with condensed milk for children who have difficulty swallowing tablets.
- | Medications should be stored in child-proof containers out of children's reach.
- | The dosage will need to be adjusted according to the increasing weight of a growing child if he or she is a long-term traveler or expatriate. A travel medicine provider can advise parents or guardians on adjusting the child's dosage before departing for long-term travel.

Travelers Taking Anticoagulants

Travelers taking warfarin or other coumarin derivatives should start the antimalarial drug 2-3 weeks before travel to a malaria risk area so that the health care provider can determine whether the warfarin dosage needs to be adjusted. A baseline international normalized ratio (INR) should be checked prior to starting the drug and rechecked 1 week after starting the drug to determine whether the warfarin dosage needs to be adjusted. Once the preventive medication has been completed, the INR should be checked again to restabilize anticoagulant therapy.

New oral anticoagulants such as dabigatran etexilate, rivaroxaban, and apixaban have a lower potential for drug interactions than do the coumarins, and no clinically significant interactions have occurred.

Travelers on extended trips should monitor their INR with periodic checks at the destination; however, the sensitivity of thromboplastin reagents used in different countries may vary. INR self-testing devices are readily available and can be used safely by experienced patients who may wish to stay in contact with their home anticoagulant clinic for dosage recommendations.

Self-Treatment of Presumptive Malaria

In most cases, travelers will not need to carry self-treatment drugs when using the recommended medication to prevent malaria. However, in rare situations in which a less effective medication must be used and access to medical care within 24 hours of developing a fever while in a malarious area may not be possible, it may be prudent to carry a drug for self-treatment. *The treatment drug should not be the same as the prevention drug.*

The traveler should stop taking the antimalarial drug for prevention while taking the antimalarial drug for treatment.

- | Resume the preventive medication immediately upon completion of self-treatment if atovaquone-proguanil will be used for ongoing prevention.
- | Resume the preventive medication 1 week after *initiating* self-treatment if another antimalarial (except atovaquone-proguanil) will be used for ongoing prevention.

Atovaquone-proguanil or co-artemether (artemether-lumefantrine combination; called Coartem in the U.S. and Riamet in Europe) can be used for emergency self-treatment as long as the same drug was not used for prevention.

Adult self-treatment using Coartem consists of 6 doses (a total of 24 tablets) taken over 3 days. On the first day, 4 tablets are taken, followed by 4 more tablets 8 hours later. On the second and third days, 4 tablets are taken every 12 hours.

- | Coartem needs to be taken with food. Do not take with grapefruit juice.
- | Coartem should not be used by persons with a heart condition called QTc prolongation, or those with an allergy to either component of the drug (artemether or lumefantrine).
- | The most frequently reported side effects in adults include loss of appetite, muscle aches, and joint pain. The most common side effects in children are fever, cough, vomiting, loss of appetite, and headache.

The adult self-treatment dose for atovaquone-proguanil consists of 4 tablets taken once daily for 3 days.

- | Atovaquone-proguanil should be taken with food.
- | Atovaquone-proguanil should not be used by pregnant women or persons who are allergic to either component of the drug.

The self-treatment drug should be taken promptly (according to a health care provider's instructions) if fever and illness occur during travel and medical care is not available within 24 hours. Remember that self-treatment is only a temporary measure and medical attention should be sought as soon as possible.

An alternative to Coartem or atovaquone-proguanil for self-treatment is quinine plus doxycycline, but this drug has a much more complex schedule of doses and is frequently associated with adverse effects.

Mefloquine should not be used for self-treatment unless there is no other alternative.