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RECOMMENDATIONS FOR THE PREVENTION OF MALARIA IN TRAVELERS - - PART I*

Malaria continues to be an important health risk to Americans who travel to malaria-endemic areas of the world. The continued extension of chloroquine resistant *Plasmodium falciparum* (CRPF) in Africa, Asia, South America, and Oceania has reduced the number of effective drugs for malaria prophylaxis. In addition, some alternative drugs to chloroquine have been found to be associated with serious adverse reactions, and thus their usefulness is limited. Guidelines for prophylaxis must take into account the risk of exposure to malaria, the effectiveness and safety of antimalarial drugs, and the use of personal protective measures. Recommendations for the prevention of malaria should be revised periodically because of geographic changes in the occurrence of drug-resistant *P. falciparum* malaria, new information on the efficacy or toxicity of drugs used for prophylaxis, and/or the availability of new drugs.

Malaria in humans is caused by one of four protozoan species of the genus *Plasmodium*: *P. falciparum, P. vivax, P. ovale, and P. malariae*. All are transmitted by the bite of an infected female *Anopheles* mosquito. Occasionally malaria is transmitted by blood transfusion or congenitally from mother to fetus. The disease is characterized by fever and influenza-like symptoms, which may occur at intervals and which include chills, headache, myalgia, and malaise. Malaria may be associated with anemia and jaundice, and *P. falciparum* infections may cause kidney failure, coma, and death. Deaths due to malaria are preventable.

Risk of Acquiring Malaria

Malaria transmission occurs in large areas of Central and South America, sub-Saharan Africa, the Indian Subcontinent, Southeast Asia,** the Middle East, and Oceania. The estimated risk of acquiring malaria varies markedly from area to area. This variability is a function of the intensity of transmission in both urban and rural areas within the various regions as well as a function of the itineraries of most travelers. For example, during the period 1983-1986, 634 cases of *P. falciparum* among American civilians were reported to CDC. Of these, 507 (80%) were acquired in sub-Saharan Africa; 44 (7%), in Southeast Asia; and 63 (10%), in the Caribbean and South America. Of the 28 fatal infections, 21 were acquired in sub-Saharan Africa. Thus, most cases of imported malaria among American travelers were acquired in sub-Saharan Africa, despite the fact that only an estimated 90,000 Americans travel to sub-Saharan Africa each year, whereas an estimated 900,000 Americans visit Southeast Asia and South America each year. This disparity in the risk of acquiring malaria stems from the fact that travelers to Africa are at risk in most rural and many urban areas. Moreover, travelers tend to spend considerable amounts of time, including evening and nighttime hours, in rural areas where malaria risk is highest. In contrast, most travelers to Southeast Asia and South America spend most of their time in urban or resort areas where risk of exposure, if any, is limited, and they travel to rural areas only during daytime hours, when risk is limited.

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**Thailand, Indonesia, Malaysia, People's Republic of China, the Philippines, Burma, Kampuchea, Vietnam, and Laos.

Drug Resistance

Resistance of *P. falciparum* to chloroquine has been reported from all countries with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America, the Middle East, and the following countries in West Africa: Chad, Equatorial Guinea, Guinea, Guinea-Bissau, Liberia, Senegal, and Sierra Leone. In addition, resistance to both chloroquine and pyrimethamine/sulfadoxine (Fansidar) is widespread in Thailand, Burma, and Kampuchea.

General Advice for Travelers to Malaria-Endemic Areas

All travelers to malaria-endemic areas are advised to use an appropriate drug regimen and personal protection measures to prevent malaria. However, travelers must be informed that, regardless of methods employed, malaria can still be contracted. Symptoms can develop as early as 8 days after initial exposure in a malaria-endemic area and as late as several months after departure from a malarious area. Travelers should understand that malaria can be treated effectively early in the course of the disease but that delaying appropriate therapy can have serious or even fatal consequences. Individuals who have the symptoms of malaria should seek prompt medical evaluation, including thick and thin malaria smears, as soon as possible.

Personal Protection Measures

Because of the nocturnal feeding habits of *Anopheles* mosquitoes, malaria transmission occurs primarily between dusk and dawn. Travelers must be advised of the importance of measures to reduce contact with mosquitoes during those hours. Such measures include remaining in well-screened areas, using mosquito nets, and wearing clothes that cover most of the body. Additionally, travelers should be advised to purchase insect repellent for use on exposed skin before travel. The most effective repellents contain N,N diethylmetatoluamide (DEET), an ingredient in many commercially available insect repellents. The actual concentration of DEET varies among repellents (ranging up to 95%); the higher the concentration, the longer-lasting the repellent effect. Travelers should also be advised to purchase a pyrethrum-containing flying-insect spray to use in living and sleeping areas during evening and nighttime hours.

Chemoprophylaxis

Malaria chemoprophylaxis is the use of drugs to prevent the development of the disease. Preferably, malaria chemoprophylaxis should begin 1-2 weeks prior to travel to malarious areas. In addition to assuring adequate blood levels of the drug, this regimen allows any potential side effects to be evaluated and treated by the traveler's own physician. The exception is doxycycline; because of its short half-life, its use should begin 1-2 days before entering a malarious area. Chemoprophylaxis should continue during travel in malarious areas and for 4 weeks after departure from these areas.

In choosing an appropriate chemoprophylactic regimen prior to travel, several factors should be considered. The travel itinerary should be reviewed in detail and compared with the information on areas of risk within a given country to determine whether the traveler will actually be at risk of acquiring malaria. The risk of acquiring CRPF malaria is another consideration. In addition, any previous allergic or other reaction to the antimalarial drug of choice and the accessibility of medical care during travel must be determined.

Chemoprophylactic Regimens

For travel to areas of risk where CRPF has **not** been reported or where only low-level or focal chloroquine resistance has been reported, once-weekly use of chloroquine **alone** is recommended. Chloroquine is usually well tolerated. The few individuals who experience uncomfortable side effects may tolerate the drug better by taking it with meals or in divided, twice-weekly doses. As an alternative, the related compound hydroxychloroquine may be better tolerated. (See Table 1 for recommended dosages for chloroquine and other chemoprophylactic regimens.)

For travel to areas of risk where CRPF **is** endemic, once-weekly use of chloroquine **alone** is recommended. In addition, travelers to these areas (except those with histories of sulfonamide intolerance) should be given a treatment dose of Fansidar to be carried during travel and should be advised to take the Fansidar promptly in the event of a febrile illness during their travel **when professional medical care is not readily available.** It must be emphasized to these

travelers that such presumptive self-treatment of a possible malarial infection is **only a temporary measure and that prompt medical evaluation is imperative.** They should be advised to continue their weekly chloroquine prophylaxis after presumptive treatment with Fansidar. (See Table 1 for recommended dosage.)

Alternative Chemoprophylactic Regimens

Doxycycline **alone**, taken daily, is an alternative regimen for short-term travel to areas with risk of CRPF. It is particularly appropriate for those individuals with a history of sulfonamide intolerance or for those, such as short-term travelers to forested areas of Thailand, Burma, and Kampuchea, who may be at risk in areas of chloroquine and Fansidar resistance. Travelers who use doxycycline should be cautioned about the possible side effects (see Part II, Adverse Reactions, PDN, Vol. 48, No. 29, July 23, 1988). Doxycycline prophylaxis can begin 1-2 days prior to travel to malarious areas. It should be continued daily during travel in malarious areas and for 4 weeks after departure from these areas.

Fansidar taken once weekly in combination with chloroquine may be considered in exceptional circumstances involving prolonged exposure in areas with intense transmission of CRPF and where medical care is not available. **If weekly use of Fansidar is prescribed, the traveler should be cautioned about the possible side effects as described in the section on adverse reactions.**

Proguanil (Paludrine) is, like pyrimethamine, a dihydrofolate reductase (DHFR) inhibitor. Resistance of *P. falciparum* to DHFR inhibitors is present in some endemic regions, but its distribution is not well delineated. Proguanil is not available commercially in the United States. Limited data suggest that it may be effective in Kenya, but not in Thailand and Papua New Guinea. No current data are available on the efficacy of proguanil in other areas of CRPF, especially West Africa. Travelers using proguanil should take a **daily** 200-mg dose (adult) in combination with a **weekly** regimen of chloroquine.

Mefloquine (Lariam), a new antimalarial similar in structure to quinine, is highly effective against both chloroquine- and Fansidar-resistant *P. falciparum* infections. Approval for use in the United States is pending; currently the drug is available in France and Switzerland. Mefloquine may be considered for use by travelers to areas where there is risk of CRPF infection and by travelers to areas where *P. falciparum* is resistant to both chloroquine and Fansidar. Currently available information suggests the adult prophylactic dose is 250 mg weekly. Mefloquine prophylaxis should begin 1 week before entry into the malarious area and should continue weekly while the traveler is there. Adverse reactions are infrequent at prophylactic dosage but may become more common with the higher doses used in treatment. Minor side effects observed with prophylactic doses, such as gastrointestinal disturbance and dizziness, tend to be transient and self-limited. Because mefloquine has occasionally been associated with asymptomatic sinus bradycardia and a prolonged QT interval, it should not be used by those receiving beta-blockers, calcium channel antagonists, or other drugs that may prolong or alter cardiac conduction.

Primaquine: Prevention of Relapses of *P. vivax* and *P. ovale*

Unlike *P. falciparum* and *P. malariae*, *P. vivax* and *P. ovale* have forms that can persist in the liver and cause relapses for as long as 4 years after routine chemoprophylaxis is discontinued. Travelers to malarious areas should be alerted to this risk; if they develop malaria symptoms after they return home, they should report their travel history and the possibility of malaria to a physician as soon as possible. Primaquine prevents relapses by acting against the liver stages of *P. vivax* and *P. ovale*; however, its use is not indicated for all travelers. Primaquine is administered after the traveler leaves an endemic area and usually in conjunction with chloroquine during the last 2 weeks of the 4-week period of prophylaxis after exposure in an endemic area has ended.

Since most malarious areas of the world (except Haiti) have at least one species of relapsing malaria, travelers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*. However, this risk is extremely difficult to quantify. Prophylaxis with primaquine is generally indicated for persons who have had prolonged exposure in malaria-endemic areas, eg, missionaries and Peace Corps volunteers. While the actual risk to the traveler with less intense exposure is difficult to define, with the exception of individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) (see Part II, Adverse Reactions, PDN, Vol. 48, No. 29, July 23, 1988), most individuals can tolerate the standard regimen of primaquine.

Table 1.

Drugs used in the prophylaxis and presumptive treatment of malaria

Drug	Prophylaxis: Adult Dose	Prophylaxis: Pediatric Dose	Presumptive Treatment for Travelers to Areas of Chloroquine Resistance
Chloroquine phosphate (Aralen®*)	300 mg base (500 mg salt) orally, once/week	5 mg/kg base (8.3 mg/kg salt) orally, once/week, up to maximum adult dose of 300 mg base	Chloroquine is not recommended for the presumptive treatment of malaria acquired in areas of known chloroquine resistance.
Hydroxy-chloroquine sulfate (Plaquenil®*)	310 mg base (400 mg salt) orally, once/week	5 mg/kg base (6.5 mg/kg salt) orally, once/week, up to maximum adult dose of 310 mg base	Hydroxychloroquine is not recommended for the presumptive treatment of malaria acquired in areas of known chloroquine resistance.
Doxycycline	100 mg orally, once/day	>8 years of age: 2 mg/kg of body weight orally, once/day up to adult dose of 100 mg/day	Tetracyclines are not recommended for the presumptive treatment of malaria.
Proguanil (Paludrine®*)	200 mg orally, once/day, in combination with weekly chloroquine	<2 yrs: 50 mg/day 2–6 yrs: 100 mg/day 7–10 yrs: 150 mg/day >10 yrs: 200 mg/day	Proguanil is not recommended for the presumptive treatment of malaria.
Pyrimethamine-sulfadoxine (Fansidar®*)	1 tablet (25 mg pyrimethamine and 500 mg sulfadoxine) orally, once/week	2–11 mos: ⅛ tab/wk 1–3 yrs: ¼ tab/wk 4–8 yrs: ½ tab/wk 9–14 yrs: ¾ tab/wk >14 yrs: 1 tab/wk	**Adult Dose**: 3 tablets (75 mg pyrimethamine and 1,500 mg sulfadoxine), orally, as a single dose **Pediatric Dose**: 2–11 mos: ¼ tab; 1–3 yrs: ½ tab; 4–8 yrs: 1 tab; 9–14 yrs: 2 tabs; >14 yrs: 3 tabs as a single dose
Primaquine	15 mg base (26.3 mg salt) orally, once/day for 14 days, or 45 mg base (79 mg salt) orally, once/week for 8 weeks	0.3 mg/kg base (0.5 mg/kg salt) orally, once/day for 14 days, or 0.9 mg/kg base (1.5 mg/kg salt) orally, once/week for 8 weeks	Primaquine is only recommended for use after leaving an endemic area to prevent relapses of *Plasmodium vivax* and *P. ovale*.

*Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the Public Health Service.

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