Warning:

Malaria: Health Information for International Travel

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MALARIA

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 transmission occurs by blood transfusion or congenitally from mother to fetus. The disease is characterized by fever and flu-like symptoms, including chills, headache, myalgias, and malaise; these symptoms may occur at intervals. 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. Information on malaria risk in specific countries (pp. 15-61) is derived from various sources, including the World Health Organization. While this is the most accurate information available at the time of publication, factors that may vary from year to year, such as local weather conditions, mosquito vector density, and prevalence of infection, can have a marked effect on local malaria transmission patterns.

Risk of Acquiring Malaria

Malaria transmission occurs in large areas of Central and South America, Hispaniola, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. The estimated risk of a traveler acquiring malaria varies markedly from area to area. This variability is a function of the intensity of transmission within the various regions and of the itinerary and time and type of travel. From 1980-1992, 2,548 cases of P. falciparum among U.S. civilians were reported to the CDC. Of these, 2,096 (82%) were acquired in sub-Saharan Africa; 191 (8%) were acquired in Asia; 129 (5%) were acquired in the Caribbean and South America; and 132 (5%) were acquired in other parts of the world. During this time period there were 45 fatal malaria infections among U.S. civilians; 44 (98%) were caused by P. falciparum - of which 36 (82%) were acquired in sub-Saharan Africa.

Thus, most imported P. falciparum malaria among American travelers was acquired in Africa south of the Sahara, even though only 130,000 arrivals from the United States were reported by countries in that region in 1991. In contrast, 20 million arrivals from the United States were reported that year in other countries with malaria (including 15 million travelers to Mexico, World Tourism Organization). This disparity in the risk of acquiring malaria reflects the fact that travelers to Africa tend to spend considerable time, including evening and nighttime hours, in rural areas where malaria risk is highest. Travelers to Asia and South America, however, spend most of their time in urban or resort areas where there is limited, if any, risk of exposure and travel to rural areas mainly during daytime hours when the risk of infection is limited.

Estimating the risk of infection for different categories of travelers is difficult and may be significantly different even for persons who travel or reside temporarily in the same general areas within a country. For example, tourists staying in air- conditioned hotels may be at lower risk than backpackers or adventure travelers. Similarly, longer-term residents living in screened and air-conditioned housing are less likely to be exposed than are missionaries or Peace Corps volunteers.

(Table 1)Checklist for Travelers to Malarious Areas

(Figure 1) Distribution of Malaria and Chloroquine-resistant Plasmodium falciparum, 1993

Drug Resistance

Resistance of P. falciparum to chloroquine has been confirmed or is probable in all countries with P. falciparum malaria except the Dominican Republic, Haiti, Central America west of the Panama Canal, Egypt, and most countries in the Middle East. In addition, resistance to both chloroquine and FansidarR (*) is widespread in Thailand, Myanmar (formerly Burma), Cambodia, and the Amazon basin area of South America, and resistance has also been reported in sub-Saharan Africa. Resistance to mefloquine has been confirmed in those areas of Thailand with malaria transmission.

(*)Use of names is for identification only and does not apply endorsements by the Public Health Service or the U.S. Department of Health and Human Services.

General Advice for Travelers to Malaria-Endemic Areas

All travelers to malarious areas of the world are advised to use an appropriate drug regimen and personal protection measures to prevent malaria; however, travelers should be informed that regardless of methods employed, malaria still may be contracted. Malaria 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,

after chemoprophylaxis has been terminated. Travelers should understand that malaria can be treated effectively early in the course of the disease, but that delay of appropriate therapy can have serious or even fatal consequences. Individuals who have symptoms of malaria should seek prompt medical evaluation, including thick and thin blood 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 should take protective measures to reduce contact with mosquitoes especially during these 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 before travel for use on exposed skin. 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 and can be as high as 95%. Repellents with DEET concentrations between 30% and 35% are quite effective and the effect should last for about 4 hours. Rarely, children exposed to DEET have had toxic encephalopathy. The possibility of adverse reactions to DEET will be minimized if the following precautions are taken: apply repellent sparingly and only to exposed skin or clothing; avoid applying high-concentration products to the skin; do not inhale or ingest repellents or get them in the eyes; avoid applying repellents to portions of children's hands that are likely to have contact with eyes or mouth; never use repellents on wounds or irritated skin; wash repellent-treated skin after coming indoors. If a reaction to insect repellent is suspected, wash treated skin and seek medical attention.

Travelers should use a pyrethroid-containing flying-insect spray in living and sleeping areas during evening and nighttime hours. In addition, persons who will not be staying in rooms which are well-screened or air-conditioned should take additional precautions, which include sleeping under mosquito netting, i.e. bednets. Permethrin (PermanoneR) may be sprayed on clothing and bednets for additional protection against mosquitoes. Bednets are more effective if they are treated with permethrin or deltamethrin insecticides. In the United States permethrin spray can be used, while overseas permethrin or deltamethrin liquid may be purchased for the treatment of bednets.

Chemoprophylaxis

In choosing an appropriate chemoprophylactic regimen before travel, persons should consider several factors. The travel itinerary should be reviewed in detail and compared with the information on areas of risk within a given country (pp. 15-61) to determine whether the traveler will actually be at risk of acquiring malaria. Whether the traveler will be at risk of acquiring drug-resistant P. falciparum malaria should also be determined. In addition, it should be established whether the traveler has previously experienced an allergic or other reaction to the antimalarial drug of choice and whether medical care will be readily accessible during travel.

Malaria chemoprophylaxis should preferably begin 1-2 weeks before travel to malarious areas (except for doxycycline, which can begin 1-2 days before). This allows any potential side effects to be evaluated and treated by the traveler's physician before departure. Chemoprophylaxis should continue during travel in the malarious areas and for 4 weeks after leaving the malarious areas.

Chemoprophylactic Regimens

(to be used in conjunction with pp.15-61)

Regimen A: For travel to areas of risk where chloroquine- resistant P. falciparum has NOT been reported, once-weekly use of chloroquine alone is recommended. Chloroquine is usually well tolerated. The few people 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. Chloroquine prophylaxis should begin 1-2 weeks before travel to malarious areas. It should be continued weekly during travel in malarious areas and for 4 weeks after a person leaves such areas. (See (Table 2) for recommended dosages.)

Regimen B: For travel to areas of risk where chloroquine- resistant P. falciparum exists, use of mefloquine alone is recommended. Mefloquine is usually well tolerated but precautions should be observed as described in the section on adverse reactions. Mefloquine prophylaxis should begin 1-2 weeks before travel to malarious areas. It should be continued weekly during travel in malarious areas and for 4 weeks after a person leaves such areas. Mefloquine can be used for long-term prophylaxis. (See (Table 2) for recommended dosages.) Note: In some foreign countries a fixed combination of mefloquine and FansidarR is marketed under the name FansimefR+. FansimefR should not be confused with mefloquine, and it is not recommended for prophylaxis of malaria because of the severe adverse reactions associated with prophylactic use of FansidarR.

Alternatives to Mefloquine

Persons who travel to areas where drug-resistant P. falciparum is endemic and for whom mefloquine is not recommended may elect to use an alternative regimen, as follows: Doxycycline alone taken daily is an alternative regimen for travelers who cannot tolerate mefloquine or for whom the drug is not recommended. Doxycycline is as effective as mefloquine for travel to most malarious areas. However, it is also the only available effective prophylactic drug for prophylaxis for travelers to malaria endemic areas of Thailand. Travelers who use doxycycline should be cautioned about the possible side effects as described in the section on adverse reactions. Doxycycline prophylaxis should begin 1-2 days before travel to malarious areas. It should be continued daily during travel in malarious areas and for 4 weeks after the traveler leaves such areas. (See (Table 2) for recommended dosages.) Chloroquine alone taken weekly is only recommended for those travelers to areas with drug-resistant P. falciparum who cannot use mefloquine or doxycycline, for example pregnant women and children less than 15 kg. Limited data suggest that the combination of chloroquine with daily proguanil (PaludrineR+) is more effective than chloroquine alone in Africa, but not in Thailand and Papua New Guinea. Therefore, travelers to Africa who use chloroquine for prophylaxis should, if possible, also take 200 mg daily (adult) of proguanil. Proguanil is not available commercially in the United States but can be obtained in Canada, Europe and many African countries.

Self-treatment

Travelers who elect to use chloroquine either alone or with daily proguanil (except those with histories of sulfonamide intolerance) should be given a treatment dose of FansidarR to be carried during travel. These travelers should take the FansidarR promptly if they have a febrile illness during their travel and if professional medical care is not ready available within 24 hours; however, they should be aware that this self-treatment of a possible malarial infection is only a temporary measure and that prompt medical evaluation is imperative. They should continue their weekly chloroquine prophylaxis after presumptive treatment with FansidarR. (See (Table 2) for recommended dosages for prophylaxis and (Table 3) for presumptive treatment with Fansidar.)

Mefloquine should not be used for self-treatment because of the frequency of serious side effects (e.g., hallucinations, convulsions) that have been associated with the high dosages of mefloquine used for treatment of malaria.

Halofantrine (Halfan) is an antimalarial drug which is licensed in the United States but is not commercially available, although the drug is available in many other countries. Halofantrine is not recommended for self-treatment of malaria because of potentially serious electrocardiogram changes which have been documented following treatment doses of halofantrine; these changes may be accentuated in the presence of other antimalarial drugs that can decrease myocardial conduction (for example mefloquine).

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

P. vivax and P. ovale parasites 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 and if they develop malaria symptoms after leaving a malarious area, they should report their travel history and the possibility of malaria to a physician as soon as possible. Primaquine decreases the risk of relapses by acting against the liver stages of P. vivax and P. ovale. Primaquine is administered after the traveler has left a malaria- endemic area, usually during the last 2 weeks of prophylaxis. 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. Prophylaxis with primaquine is generally indicated only for persons who have had prolonged exposure in malaria-endemic areas, e.g., missionaries and Peace Corps Volunteers. Although the actual risk to travelers with less intense exposure is difficult to define, most people can tolerate the standard regimen of primaquine, with the exception of individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) (see discussion of adverse reactions). (See (Table 2) for recommended dosages.)

Adverse Reactions and Contraindications to Antimalarials

The frequent or serious side effects of recommended antimalarials are discussed below. In addition, physicians should review the prescribing information in standard pharmaceutical reference texts and in the manufacturers' package inserts.

Chloroquine and hydroxychloroquine rarely cause serious adverse reactions when taken at prophylactic doses for malaria. Minor side effects that may occur include gastrointestinal disturbance, headache, dizziness, blurred vision, 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, but this serious side effect has not been associated with routine weekly malaria

prophylaxis. Chloroquine and related compounds have been reported to exacerbate psoriasis. Chloroquine may interfere with the antibody response to human diploid cell rabies vaccine when the vaccine is administered intradermally.

Mefloquine has rarely been associated with serious adverse reactions (e.g., psychoses, convulsions) at prophylactic dosage, but these reactions are more frequent with the higher dosages used in treatment. Minor side effects observed with prophylactic doses, such as gastrointestinal disturbance, insomnia, and dizziness, tend to be transient and self-limited.

Mefloquine is contraindicated for use by travelers with a known hypersensitivity to mefloquine and is not recommended for use by children < 15kg. (30 lbs.), pregnant women, and travelers with a history of epilepsy or psychiatric disorder. A review of the 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 until additional data is available. It has not been established that mefloquine is contraindicated for travelers involved in tasks requiring fine coordination and spatial discrimination, such as airline pilots. All studies to date confirm that mefloquine is well tolerated when used for prophylaxis; however, monitoring the occurrence of severe adverse reactions is important because such reactions are possible. Users of mefloquine prophylaxis who experience serious adverse reactions should consult their physician, and the reactions should be reported to the Malaria Section, CDC, telephone (404) 488-7760.

Doxycycline may cause photosensitivity, usually manifested as an exaggerated sunburn reaction. The risk of such a reaction can be minimized by avoiding prolonged, direct exposure to the sun; using sunscreens that absorb long-wave ultraviolet (UVA) radiation; and by taking the drug in the evening. In addition, doxycycline use is associated with an increased frequency of monilial vaginitis. Gastrointestinal side effects (nausea or vomiting) may be minimized by taking the drug with a meal. Doxycycline is contraindicated in pregnancy and in children less than 8 years of age.

FansidarR is contraindicated in persons with a history of sulfonamide intolerance and in infants less than 2 months of age. Proguanil rarely causes serious adverse reactions at prophylactic dosage. Reported side effects include nausea, vomiting, mouth ulcers, and hair loss.

Primaquine may cause severe hemolysis in G6PD-deficient individuals. Before primaquine is used, G6PD deficiency should be ruled out by appropriate laboratory testing.

Chemoprophylaxis for Children

Children of any age can contract malaria. Consequently, the indications for prophylaxis are identical to those described for adults. Mefloquine is not indicated for children <15 kg. (30 lbs.). Doxycycline is contraindicated in children <8 years of age. (See recommended dosages in (Table 2). Children who cannot take mefloquine or doxycycline can be given chloroquine (with proguanil for travel to sub-Saharan Africa) for prophylaxis. Young children should avoid travel to areas with chloroquine-resistant P. falciparum, unless they can take a highly effective drug, such as mefloquine or doxycycline. Chloroquine phosphate is manufactured in the United States in tablet form only and has a very bitter taste. Pediatric doses should be calculated carefully according to body weight. Pharmacists can pulverize tablets and prepare gelatin capsules with calculated pediatric doses. Mixing the powder in food or drink may facilitate the weekly administration of chloroquine to children. Alternatively, chloroquine in suspension is widely available overseas. Parents should calculate the dose and volume to be administered based on body weight, because the concentration of chloroquine base varies in different suspensions.

OVERDOSE OF ANTIMALARIAL DRUGS CAN BE FATAL. THE MEDICATION SHOULD BE STORED IN CHILDPROOF CONTAINERS OUT OF THE REACH OF CHILDREN.

Prophylaxis During Pregnancy

Malaria infection in pregnant women may be more severe than in nonpregnant women. In addition, malaria may increase the risk of adverse pregnancy outcomes including prematurity, abortion, and stillbirth. For these reasons, and because chloroquine has not been found to have any harmful effects on the fetus when used in the recommended doses for malaria prophylaxis, pregnancy is not a contraindication for malaria prophylaxis with chloroquine or hydroxychloroquine. However, because no chemoprophylactic regimen is completely effective in areas with drug-resistant P. falciparum, women who are pregnant or likely to become so should avoid travel to such areas.

Mefloquine is not recommended for use during pregnancy according to the current FDA licensure agreement. A review of mefloquine use in pregnancy, from clinical trials or reports of inadvertent use of mefloquine during pregnancy, does not suggest that its use is associated with adverse fetal outcomes. Consequently, mefloquine can be considered by health care providers for prophylaxis in women in their

second or third trimester of pregnancy where exposure to chloroquine-resistant P. falciparum is unavoidable. Until more data is available, women of childbearing potential who are taking mefloquine for malaria prophylaxis should take reliable contraceptive precautions for the duration of prophylaxis and for 2 months after the last dose of mefloquine. Women exposed to mefloquine during the first trimester of pregnancy or their health care providers are asked to report the exposure to the Malaria Section, CDC, telephone 404-488-7760, for inclusion in a registry to assess pregnancy outcomes.

Doxycycline is contraindicated for malaria prophylaxis during pregnancy. Adverse effects of tetracyclines on the fetus include discoloration and dysplasia of the teeth and inhibition of bone growth. During pregnancy, tetracyclines are indicated only to treat life-threatening infections due to multidrug- resistant P. falciparum.

Proguanil has been widely used for several decades and no adverse effects on pregnancy or fetus have been established. Primaquine should not be used during pregnancy because the drug may be passed transplacentally to a G6PD-deficient fetus and cause hemolytic anemia in utero. Whenever radical cure or terminal prophylaxis with primaquine is indicated during pregnancy, chloroquine should be given once a week until delivery, at which time primaquine may be given.

Prophylaxis While Breast-feeding

Very small amounts of antimalarial drugs are secreted in the breast milk of lactating women. The amount of drug transferred is not thought to be harmful to a nursing infant. Because the quantity of antimalarials transferred in breast milk is insufficient to provide adequate protection against malaria, infants who require chemoprophylaxis should receive the recommended dosages of antimalarials listed in (Table 2).

Malaria Hotline

Detailed recommendations for the prevention of malaria are available 24 hours a day by phone or fax by calling the CDC Malaria Hotline at (404) 332-4555.

POINT OF CONTACT FOR THIS DOCUMENT:

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JANE R ZUCKER
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Table 1

Table 1:Checklist for Travelers to Malarious Areas

The following is a checklist of key issues to be considered in advising travelers. The numbers in parentheses refer to those pages in the text where these issues are discussed in detail.

- Risk of malaria (pages 15-61, 103)
  Travelers should be informed about the risk of malaria infection and the presence of drug-resistant P. falciparum malaria in their areas of destination.
- Anti-mosquito measures (page 106)
  Travelers should know how to protect themselves against mosquito bites.
- Chemoprophylaxis (pages 108-112)
  Travelers should be:
  - Advised to start prophylaxis before travel, and to use prophylaxis continuously while in malaria-endemic areas, and for four weeks after leaving such areas.
  - Questioned about drug allergies and other contraindications for use of drugs to prevent malaria.
  - Advised which drug to use for prophylaxis, and, if chloroquine is used, whether FansidarR(+) should be carried for presumptive self-treatment.
  - Informed that antimalarial drugs can cause side effects; if these side effects are serious, medical help should be sought promptly and use of the drug discontinued.
  - Warned that they may acquire malaria even if they use malaria chemoprophylaxis.
- In case of illness (pages 103, 106, 109)
  Travelers should be:
  - Informed that symptoms of malaria may be mild, and that they should suspect malaria if they experience unexplained fever or other symptoms such as persistent headaches, muscular aching and weakness, vomiting, or diarrhea.
  - Informed that malaria may be fatal if treatment is delayed. Medical help should be sought promptly if malaria is suspected, and a blood sample should be taken and examined for malaria parasites on one or more occasions.
  - Reminded that self-treatment should be taken only if prompt medical care is not available and that medical advice should still be sought as soon as possible after self-treatment.
- Special categories (pages 111-112)
  - Pregnant women and young children require special attention because they cannot use some drugs (mefloquine and doxycycline).

(Adapted from International Travel and Health, World Health Organization, Geneva, 1991)

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

Table 2

Table 2. Drugs Used for The Prophylaxis of Malaria

Drug	Adult dosage	Pediatric dosage
Mefloquine (Lariam)R	228 mg base (250 mg salt) orally, once/week	15-19 kg: 1/4 tab/week 20-30 kg: 1/2 tab week 31-45 kg: 3/4 tab week > 45 kg: 1 tab/week
Doxycycline	100 mg orally, once daily	> 8 years of age: 2 mg/kg orally, once daily up to adult dose of 100 mg/day
Chloroquine phosphate (Aralen)R	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
Hydroxychloroquine sulfate (Plaquenil)R	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
Proguanil (Paludrine)R	200 mg orally, once/day in combination with weekly chloroquine	< 2 years: 50 mg/day 2-6 years: 100 mg/day 7-10 years: 150 mg/day > 10 years: 200 mg/day
Primaquine	15 mg base (26.3 mg salt) orally, once/day for 14 days	0.3 mg/kg base (0.5 g/kg salt) orally, once/day for 14 days

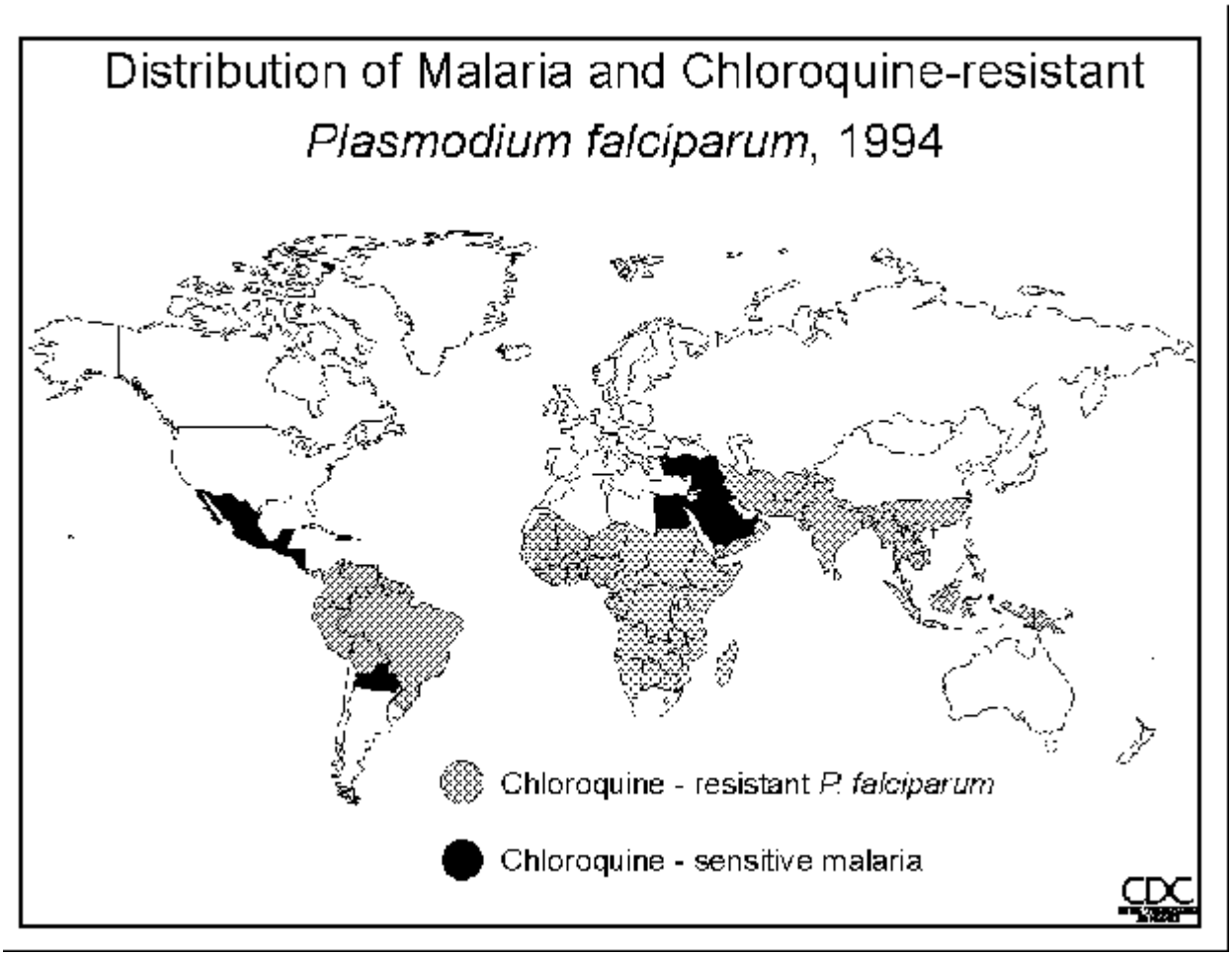
Table 3

Table 3. Drug Used in The Presumptive Treatment of Malaria

Drug	Adult dosage	Pediatric dosage Weight (kg): tablet(s)
Pyrimethamine-sulfadoxine (Fansidar)R	3 tablets (total:75 mg pyrimethamine and 1,500 mg sulfadoxine), orally as a single dose	5-10: 1/2 11-20: 1 21-30: 1 1/2 31-45: 2 > 45: 3

Figure 1

Distribution Of Malaria And Chloroquine-resistant Plasmodium



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