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REVISED RECOMMENDATIONS FOR PREVENTING MALARIA IN TRAVELERS TO AREAS WITH CHLOROQUINE-RESISTANT PLASMODIUM FALCIPARUM*

Since 1982, CDC has recommended the combined use of chloroquine and Fansidar® (pyrimethamine-sulfadoxine) as the primary chemoprophylactic regimen for travelers to areas with transmission of chloroquine-resistant *Plasmodium falciparum* (CRPF). Based on preliminary reports of serious adverse cutaneous reactions associated with the use of Fansidar®, in January 1985, CDC issued interim guidelines that limited areas for which the prophylactic use of the drug was recommended. Since then, additional information that has been used to formulate revised recommendations for travelers to specific areas with CRPF (Table 1) has become available. These recommendations, presented below, differ significantly from those previously issued.

Since Fansidar® became available in the United States in 1982, 20 cases of severe cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) have been documented among American travelers using Fansidar®; 19 of these reactions occurred among persons simultaneously using chloroquine. Six of these reactions were fatal. Based on IMS America Ltd† data, the US Food and Drug Administration (FDA) estimates that, for the United States, between 109,000 and 156,000 persons have been exposed to the drug since 1982. These data indicate that the incidence of fatal cutaneous reactions associated with the prophylactic use of Fansidar® among American travelers ranges from 1/18,000 to 1/26,000 users.

These reactions have been associated only with multiple (two to five) doses of Fansidar® when used as weekly prophylaxis, and none of these serious reactions have been associated with single-dose Fansidar® therapy as used in treating malaria. In addition to these cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, other adverse reactions associated with Fansidar® use have also been reported to CDC and FDA. These include serum sickness-type reactions, urticaria, exfoliative dermatitis, and hepatitis.

Because of the risk of these adverse reactions, it is no longer recommended that all travelers to areas with CRPF use Fansidar® combined with chloroquine for chemoprophylaxis. The following recommendations have been formulated with the assistance of an *ad hoc* panel of expert consultants convened at CDC in February 1985. They are based on the estimated risk of acquiring a *P. falciparum* infection in various geographic areas and on CDC malaria surveillance data and travel industry data on the number of Americans who travel to these areas each year. **Of necessity, these revised recommendations place increased emphasis on individualized recommendations for travelers and increased responsibility on individual travelers and their physicians.**

GENERAL ADVICE FOR TRAVELERS TO MALARIA-ENDEMIC AREAS

Travelers must be informed that, regardless of the malaria prophylactic regimen employed, it is still possible to contract malaria. The symptoms of malaria, such as fever with chills and headache, demand medical attention **as soon as possible** and should not be presumptively ascribed by either the physician or traveler to a "flu-like" illness. Malaria symptoms can develop as early as eight days after initial exposure in a malaria-endemic area and can appear months after departure from a malarious area, even after chemoprophylaxis is discontinued. It is important for travelers to understand that malaria can be effectively treated early in the course of the disease but that delays before the institution of appropriate therapy can have serious or even fatal consequences.

*Adapted from: CDC. MMWR 1985;34:185-190, 195.

†A private firm that conducts comprehensive marketing surveys of pharmaceutical products.

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 before travel to use on any exposed areas of skin. The most effective repellent is N,N diethylmetatoluamide (deet), an ingredient in many commercially available insect repellents. Travelers may also be advised to purchase a pyrethrin-containing flying insect spray to use in living and sleeping areas during evening and nighttime hours.

RATIONALE FOR USING CHLOROQUINE IN AREAS WITH CRPF

Because of its record of safety and efficacy, chloroquine remains the primary prophylactic drug of choice for travelers to all malarious areas, including areas with CRPF. In all areas with CRPF, there is malaria caused by one or more other species of *Plasmodium* (*P. vivax, P. ovale, P. malariae*) that remain sensitive to chloroquine. In addition, chloroquine-sensitive *P. falciparum* may coexist with chloroquine-resistant parasites within a geographic area.

TRAVELERS TO AREAS IN AFRICA WITH CRPF

In general, travelers to malaria-endemic Africa are at considerable risk of exposure to *Plasmodium* because of the high level of malaria transmission in many areas. Of 358 reports to CDC of *P. falciparum* infections imported into the United States by American civilian travelers during 1982-1984, 256 (72%) were acquired in Africa. Nine of these were fatal (three fatal cases were acquired in areas of east Africa with CRPF). An estimated 90,000 Americans travel to sub-Saharan Africa each year. Except for the city of Nairobi, where the level of malaria transmission is very low, there is considerable risk of acquiring CRPF in areas in east Africa frequented by tourists.

Short-Term Travel. For short-term travelers (3 weeks or less) to areas of Africa with CRPF, the weekly use of chloroquine alone is recommended. In addition, these travelers (except those with histories of sulfonamide or pyrimethamine intolerance) should be given a single treatment dose of Fansidar® (Table 2) to be kept in their possession during travel and should be advised to take the Fansidar® promptly in the event of a febrile illness during or after their travel when professional medical care is not readily available. It must be emphasized to travelers that such presumptive self-treatment of a possible malarial infection is only a temporary measure and that professional medical follow-up care as soon as possible is imperative. They should also be advised to continue weekly chloroquine prophylaxis after presumptive treatment with Fansidar .

Longer-Term Travel. Because persons with prolonged exposure in areas of CRPF transmission are at higher risk of acquiring malaria, the use of combined weekly prophylaxis with chloroquine and Fansidar® (Table 2) can be considered. Physicians who advise such travelers and expatriate residents must take into consideration individual living conditions while in Africa, the availability of local medical care, and when possible, local malaria transmission patterns. The suitability of the regimen described above for short-term travelers, and alternatives discussed below, should also be assessed. The potential benefit of the routine prophylactic use of Fansidar® for these travelers must be weighed against the risk of a possible serious or fatal adverse reaction. If weekly use of Fansidar® is prescribed, the traveler should be advised to discontinue it immediately in the event of a possible ill effect, especially if any mucocutaneous signs or symptoms, such as pruritis, erythema, rash, orogenital lesions, or pharyngitis, develop.

Alternatives. Alternatives to these regimens have shortcomings either because of less than conclusive efficacy data and/or unavailability in the United States. One alternative for travelers to areas of Africa with CRPF is the use of daily doxycycline alone (Table 2). This drug could be considered for use in short-term travelers, such as those with previous histories of sulfonamide intolerance. Limited studies conducted in the early 1970s indicated that tetracyclines, when used alone, were effective against *P. falciparum*. Tetracyclines are contraindicated in pregnancy and in children under 8 years of age. Persons who use doxycycline as prophylaxis must be made aware of the possible side effects associated with tetracyclines; of particular concern in travelers to tropical climates is the possibility of 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.

The use of proguanil (Paludrine®) alone or in combination with other antimalarials has been suggested for travelers to east Africa. Because adequately controlled efficacy trials have yet to be reported, the use of this drug cannot be recommended.

PDN Editorial Note: The April 12, 1985,MMWR article, which represents the body of this PDN article, included a recommendation for the use of amodiaquine (Camoquine®, Flavoquine®) as an alternative prophylaxis for travel to areas with CRPF. However, several reports of agranulocytosis associated with the use of amodiaquine have led the CDC to conclude that "any possible prophylactic advantage that amodiaquine may afford is not justified by the possible risk of agranulocytosis associated with the use of the drug. CDC, therefore, no longer recommends that amodiaquine be used for prophylaxis." (MMWR 1986;35:165-6, March 14, 1986.)

For travelers to Africa, the importance of using the general protection measures outlined previously and the absolute necessity for prompt recognition and treatment of possible malaria cannot be overemphasized.

TRAVELERS TO AREAS IN CHINA AND SOUTHEAST ASIA WITH CRPF

An estimated 500,000 Americans travel to China and Southeast Asia each year. In contrast to travelers to Africa, they are at very low risk of acquiring malaria. Of the 358 reported *P. falciparum* infections among American civilians during 1982-1984, only 11 (3%) were acquired in these areas; none were fatal. Malaria transmission in China and Southeast Asia is largely confined to rural areas that are not visited by most travelers; furthermore, travelers who do visit rural areas usually do so only during daytime hours when there is minimal risk of exposure.

Therefore, malaria chemoprophylaxis is not recommended for travelers who will visit only urban centers of Asia or who will have only daytime exposure in rural areas. This includes most travelers to China, Indonesia, Malaysia, the Philippines, and Thailand. Such travelers should, however, be advised to observe general precautions to minimize mosquito contact as outlined previously and to seek prompt medical attention in the event of a febrile illness either during or after their trip.

Travelers who veer from the usual tourist routes of these areas and who will have outdoor exposure in rural, malarious areas during evening and nighttime hours should be given consideration similar to travelers to CRPF areas of Africa as previously described. Special consideration should be given to travelers who will have substantial exposure in rural areas of Thailand, where widespread resistance to both chloroquine and Fansidar® has been reported. Regimens for these travelers should be made in consultation with local or state health departments or CDC.

TRAVELERS TO AREAS OF SOUTH AMERICA WITH CRPF

Travelers to malaria-endemic regions of South America are at minimal risk of exposure to *Plasmodium.* Only seven (2%) of the 358 reported *P. falciparum* infections among American civilians were acquired in South America; one case was fatal. Malaria transmission in South America occurs primarily in rural areas, except for certain urban areas of the interior Amazon River basin and urban coastal areas of Ecuador.

Therefore, travelers to areas of South America with CRPF should be advised in the use of chemoprophylaxis regimens as previously described for China and Southeast Asia.

TRAVELERS TO THE INDIAN SUBCONTINENT

Nineteen (5%) of the 358 reported *P. falciparum* infections among American civilians were acquired in India; none were fatal. Approximately 100,000 American residents visit the Indian subcontinent each year. Since transmission occurs in both urban and rural areas of Bangladesh, India, and Pakistan, travelers to these areas must be considered at risk of acquiring malaria. While there have been reports of chloroquine resistance from multiple areas of these countries, it has generally been low-level resistance in areas not frequented by tourists.

Chloroquine prophylaxis alone is, therefore, recommended for travelers to the Indian subcontinent (Table 2). These travelers should be advised to observe general precautions to minimize mosquito contact as outlined previously and to seek prompt medical attention in the event of a febrile illness either during or after their trip.

TRAVELERS TO OCEANIA

Malaria transmission in many areas of Papua New Guinea, Irian Jaya, the Solomon Islands, and Vanuatu is intense and in some areas may approximate that found in malarious areas of Africa. Travelers to these areas should, therefore, be advised in the use of the chemoprophylaxis regimens previously described for travelers to CRPF areas of Africa.

Table 1. Areas with reported chloroquine-resistant Plasmodium falciparum (CRPF)*

AFRICA†	ASIA	SOUTH AMERICA	INDIAN SUBCONTINENT †
Angola	Burma	Bolivia	Bangladesh (north and east)
Burundi	China (Hainan Island and southern provinces)	Brazil**	India
Central African Republic	Indonesia §	Colombia	Pakistan (Rawalpindi)
Comoros	Kampuchea †	Ecuador ††	
Gabon	Laos ¶	French Guiana	OCEANIA †
Kenya	Malaysia	Guyana	Papua New Guinea
Madagascar	Philippines (Luzon, Basilan, Mindoro, Palawan, and Mindanao Islands; Sulu Archipelago)	Panama (east of the Canal Zone, including the San Bias Islands)	Solomon Islands
Malawi	Thailand	Peru (northern provinces)	Vanuatu
Mozambique	Vietnam	Surinam	
Namibia		Venezuela	
Rwanda			
Sudan (northern provinces)			
Tanzania			
Uganda			
Zaire (northeastern)			
Zambia (northeastern)			

*There is no malaria risk in urban areas unless otherwise indicated. This table should be used in conjunction with the text in determining appropriate prophylaxis.
†Malaria risk exists in most urban areas.
§Malaria risk exists in urban areas of Timor and Kalimantan provinces. Irian Jaya should be considered as Oceania.
¶Malaria risk exists in all urban areas except Vientiane.
**Malaria risk exists in urban areas of interior Amazon River region.
††Malaria risk exists in urban areas of Esmeraldas, Manabi, El Oro, and Guayas provinces (including city of Guayaquil).

Table 2. Drugs used in the prophylaxis and presumptive treatment of malaria acquired in areas with CRPF

Drug	Routine prophylaxis		Presumptive treatment	
	Adult dose	Pediatric dose	Adult dose	Pediatric dose
Chloroquine phosphate (Aralen®)	300 mg base (500 mg salt) orally, once/week, beginning 1 week before and continuing 6 weeks after last exposure in an endemic area	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.	
Pyrimethamine-sulfadoxine (Fansidar®)*	1 tablet (25 mg pyrimethamine and 500 mg sulfadoxine) orally, once/week, beginning 1 week before and continuing 6 weeks after last exposure in an endemic area	2-11 mos: 1/8 tab/wk 1-3 yrs. 1/4 tab/wk 4-8 yrs: 1/2 tab/wk 9-14 yrs: 3/4 tab/wk >14 yrs: 1 tab/wk	3 tablets (75 mg pyrimethamine and 1500 mg sulfadoxine), orally, as a single dose	2-11 mos: 1/4 tab 1-3 yrs: 1/2 tab 4-8 yrs: 1 tab 9-14 yrs: 2 tabs >14 yrs: 3 tabs as a single dose
Doxycycline †	100 mg orally, once/day, beginning 1 week before and continuing 6 weeks after last exposure in an endemic area	>8 years of age: 2 mg/kg of body weight, orally/day, up to adult dose of 100 mg/day	Tetracyclines are not recommended for the presumptive treatment of malaria.	

*The use of Fansidar® is contraindicated in persons with histories of sulfonamide or pyrimethamine intolerance, in pregnancy at term, and in infants under 2 months of age. Physicians who prescribe the drug to be used as presumptive treatment in the event of a febrile illness when professional medical care is not readily available should ensure that such prescriptions are clearly labeled with instructions to be followed in the event of a febrile illness. If used as weekly prophylaxis, travelers should be advised to discontinue the use of the drug immediately in the event of a possible adverse effect, especially if any mucocutaneous signs or symptoms develop.
†The use of doxycycline is contraindicated in pregnancy and in children under 8 years of age. FDA considers the use of tetracyclines as antimalarials to be investigational. Physicians who prescribe doxycycline as malaria chemoprophylaxis should advise their patients to limit direct exposure to the sun to minimize the possibility of a photosensitivity reaction.

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