

# The Medical Letter<sup>®</sup>

## On Drugs and Therapeutics

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The latest recommendations.

### Prevention of Malaria

Many patients planning to travel seek advice about prevention of malaria.<sup>1</sup> No drug is 100% effective for this indication; travelers should be told to take other protective measures as well. Malaria in pregnancy is particularly serious for both mother and fetus; prophylaxis is indicated if travel cannot be avoided. Countries with a risk of malaria are listed in the table on page 102. Some countries with endemic malaria transmission may not have malaria in the most frequently visited major cities and rural tourist resorts.

**CHLOROQUINE-SENSITIVE MALARIA** — **Chloroquine** is the drug of choice for prevention of malaria in the few areas that still have only chloroquine-sensitive malaria: Central America (west of the Panama Canal Zone), Paraguay, northern Argentina, Mexico, Haiti, the Dominican Republic, North and South Korea, Armenia, Georgia and some countries in the Middle East (chloroquine resistance has been reported in Iran, Yemen, Oman, and Saudi Arabia). In rural areas of China where malaria occurs, it is generally chloroquine sensitive. Only Hainan and Yunnan provinces have chloroquine resistance.

**CHLOROQUINE-RESISTANT MALARIA** — Three drugs with similar efficacy, listed with their dosages in the table on page 101, are available in the US for prevention of chloroquine-resistant malaria. **Malarone**, a fixed-dose combination of atovaquone and proguanil taken once daily, is generally the best

tolerated.<sup>2</sup> It can cause gastrointestinal (GI) disturbances and has been associated with Stevens-Johnson syndrome.<sup>3</sup> Atovaquone/proguanil should not be given to patients with severe renal impairment (CrCl <30 mL/min).

**Mefloquine** has the advantage of once-a-week dosing, but it is contraindicated in patients with a history of depression, anxiety, psychosis, schizophrenia or other major psychiatric disorders, and also in those with a history of seizures or cardiac conduction abnormalities. Dizziness, headache, insomnia and disturbing dreams are the most common CNS adverse effects. The drug's adverse effects in children are similar to those in adults.<sup>4</sup> If a patient develops anxiety, depression, restlessness or confusion while taking mefloquine, it should be stopped. The drug should not be given together with quinine, quinidine or halofantrine due to potential prolongation of the QT interval; caution is required when using these drugs to treat patients who have taken mefloquine prophylaxis. Mefloquine can be given to patients taking beta-blockers if they do not have an underlying arrhythmia.

**Doxycycline**, which frequently causes GI disturbances and can cause photosensitivity and vaginitis, offers an inexpensive once-daily alternative for travelers  $\geq 8$  years old who are not pregnant. Taking the drug with food may ameliorate GI upset. Doxycycline should not be taken concurrently with antacids, oral iron or bismuth salts.

For patients unable to take other antimalarial drugs, several studies have shown that daily **primaquine phosphate** begun one day before departure and continued until 3-7 days after leaving the malarious area can provide effective prophylaxis against chloroquine-resistant *Plasmodium falciparum* and *P. vivax*.<sup>5</sup> Primaquine can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, which is most common in African, Asian, and Mediterranean peoples. Travelers should be screened for G-6-PD deficiency

## DRUGS OF CHOICE FOR PREVENTION OF MALARIA

DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE	DURATION
<b>CHLOROQUINE-RESISTANT AREAS†:</b>			
<b>Drug of Choice<sup>1</sup>:</b>			
Atovaquone/proguanil <sup>2</sup> – <i>Malarone, Malarone Pediatric</i>	1 adult tablet once/d <sup>3</sup>	11-20 kg: 1 peds tab/d <sup>3</sup> 21-30 kg: 2 peds tabs/d <sup>3</sup> 31-40 kg: 3 peds tabs/d <sup>3</sup> >40 kg: 1 adult tab/d <sup>3</sup>	Start: 1-2d before travel Stop: 1 wk after leaving malarious zone
OR Mefloquine <sup>4</sup> – <i>Lariam, and others</i>	1 tablet once/wk <sup>5</sup>	5-10 kg: 1/8 tablet once/wk <sup>5,6</sup> 11-20 kg: 1/4 tablet once/wk <sup>5,6</sup> 21-30 kg: 1/2 tablet once/wk <sup>5,6</sup> 31-45 kg: 3/4 tablet once/wk <sup>5,6</sup> >45 kg: 1 tablet once/wk <sup>5,6</sup>	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone
OR Doxycycline <sup>8</sup> – <i>Vibramycin, and others</i>	100 mg once/d	2 mg/kg/d <sup>9</sup> (up to 100 mg/d)	Start: 1-2d before travel Stop: 2 wks after leaving malarious zone
<b>Alternatives<sup>10</sup>:</b>			
Primaquine phosphate <sup>7,11</sup>	30 mg base daily <sup>12</sup>	0.5 mg/kg base/d <sup>12</sup>	Start: 1d before travel Stop: 3-7d after leaving malarious zone
<b>CHLOROQUINE-SENSITIVE AREAS†:</b>			
<b>Drug of Choice<sup>1</sup>:</b>			
Chloroquine phosphate <sup>13,14</sup> <i>Aralen, and others</i>	300 mg base <sup>15</sup> once/wk	5 mg/kg base once/wk, up to adult dose of 300 mg base	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone

† Chloroquine-resistant *Plasmodium falciparum* occurs in all malarious areas except Central America (including Panama west of the Canal Zone), Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, Armenia, most of rural China and some countries in the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia and Iran).

- For prevention of attack after departure ("terminal prophylaxis") from areas where *P. vivax* and *P. ovale* are endemic, some experts prescribe in addition primaquine phosphate 30 mg base/d or, for children, 0.5 mg base/kg/d for 14 days after departure from the malarious area. Others prefer to rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 11.
- Safety in pregnancy is unknown; outcomes were normal in 24 women treated with the combination in the 2nd and 3rd trimester (R McGready et al, Eur J Clin Pharmacol 2003; 59:545). There have been several isolated reports of *P. falciparum* resistance in Africa (E Schwartz et al, Clin Infect Dis 2003; 37:450; A Farnert et al, BMJ 2003; 326:628).
- Available as a fixed-dose combination: adult tablets (*Malarone*; 250 mg atovaquone/100 mg proguanil) and pediatric tablets (*Malarone Pediatric*; 62.5 mg atovaquone/25 mg proguanil). To enhance absorption, it should be taken with food or a milky drink.
- Not approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the second or third trimester of pregnancy and possibly during early pregnancy as well (CDC, Health Information for International Travel, 2005-2006, page 205; BL Smoak et al, J Infect Dis 1997; 176:831). Resistance to mefloquine is a significant problem in the malarious areas of Thailand and in the areas of Myanmar and Cambodia that border on Thailand.
- In the US, a 250-mg tablet of mefloquine contains 228 mg mefloquine base. Outside the US, each 275-mg tablet contains 250 mg base.
- For pediatric doses <1/2 tablet, it may be advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There is no data for use in children <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.
- Not approved for this indication by the FDA, but recommended for use by the CDC.
- Contraindicated in pregnancy.
- Not recommended for children <8 years old.
- The combination of weekly chloroquine (300 mg base) and daily proguanil (200 mg) is recommended by the World Health Organization (www.WHO.int) for use in selected areas. The combination is no longer recommended by the CDC. Proguanil (*Paludrine* – Wyeth Ayerst, Canada; AstraZeneca, United Kingdom) is not available alone in the US but is widely available in Canada and Europe. Prophylaxis is recommended during exposure and for 4 weeks afterwards. Proguanil has been used in pregnancy without evidence of toxicity (PA Phillips-Howard and D Wood, Drug Saf 1996; 14:131).
- Patients should be screened for G-6-PD deficiency before treatment. Primaquine should not be used during pregnancy.
- In the US, a 26.3 mg tablet of primaquine phosphate contains 15 mg primaquine base. Nausea and abdominal pain can be diminished by taking with food.
- Has been used extensively and safely for prophylaxis during pregnancy.
- Atovaquone/proguanil, mefloquine, doxycycline or primaquine may be used in patients who are unable to take chloroquine.
- In the US, a 500 mg tablet of chloroquine phosphate contains 300 mg chloroquine base.

before treatment. Primaquine should be taken with food to reduce GI effects. The drug should not be used during pregnancy.

**MEFLOQUINE-RESISTANT MALARIA** — Doxycycline or atovaquone/proguanil are recommended for prophylaxis against mefloquine-resistant malaria, which occurs in the malarious areas of Thailand and in

the areas of Myanmar and Cambodia that border on Thailand.

**PREVENTION OF RELAPSE** — For travelers with a high risk of infection with *P. vivax* and *P. ovale*, such as those with prolonged stay in regions where these species are highly endemic, which includes almost all areas where malaria is found (except Haiti and the

## COUNTRIES WITH A RISK OF MALARIA<sup>1</sup>

### AFRICA

Angola	Equatorial Guinea	Namibia
Benin	Eritrea <sup>3</sup>	Niger
Botswana	Ethiopia <sup>3</sup>	Nigeria
Burkina Faso	Gabon	Rwanda
Burundi	Gambia, The	São Tomé and Príncipe
Cameroon	Ghana	Senegal
Cape Verde <sup>2</sup>	Guinea	Sierra Leone
Central African Republic	Guinea-Bissau	Somalia
Chad	Kenya	South Africa <sup>3</sup>
Comoros	Liberia	Sudan
Congo	Madagascar	Swaziland
Côte d'Ivoire	Malawi	Tanzania
Democratic Republic of the Congo	Mali	Togo
Djibouti	Mauritania	Uganda
	Mauritius <sup>3</sup>	Zambia
	Mayotte	Zimbabwe <sup>3</sup>
	Mozambique	

### AMERICAS

Argentina <sup>3</sup>	Ecuador <sup>3</sup>	Nicaragua <sup>3</sup>
Belize <sup>3</sup>	El Salvador <sup>3</sup>	Panama <sup>3</sup>
Bolivia <sup>3</sup>	French Guiana	Paraguay <sup>3</sup>
Brazil	Guatemala <sup>3</sup>	Peru <sup>3</sup>
Colombia <sup>3</sup>	Guyana	Suriname <sup>3</sup>
Costa Rica <sup>3</sup>	Haiti	Venezuela <sup>3</sup>
Dominican Republic <sup>3</sup>	Honduras <sup>3</sup>	
	Mexico <sup>3</sup>	

### ASIA

Afghanistan	Indonesia <sup>3</sup>	Philippines <sup>3</sup>
Armenia <sup>3</sup>	Iran <sup>3</sup>	Saudi Arabia <sup>3</sup>
Azerbaijan <sup>3</sup>	Iraq <sup>3</sup>	Sri Lanka
Bangladesh <sup>3</sup>	Korea, North <sup>3</sup>	Syria <sup>3</sup>
Bhutan <sup>3</sup>	Korea, South <sup>3</sup>	Tajikistan
Cambodia <sup>3</sup>	Kyrgystan <sup>3</sup>	Thailand <sup>3</sup>
China, People's Republic <sup>3</sup>	Laos <sup>3</sup>	Turkey <sup>3</sup>
East Timor	Malaysia <sup>3</sup>	Turkmenistan <sup>3</sup>
Georgia <sup>3</sup>	Myanmar <sup>3</sup>	Uzbekistan
India	Nepal <sup>3</sup>	Vietnam <sup>3</sup>
	Pakistan	Yemen <sup>3</sup>

### OCEANIA

Papua New Guinea	Solomon Islands	Vanuatu
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1. Only includes countries for which prophylaxis is recommended. Regional variation in risk may exist within a county. More detailed information is available at [www.cdc.gov/malaria](http://www.cdc.gov/malaria) and by phone for medical personnel from the Malaria Branch of the CDC at 770-488-7788.

2. Island of Saõ Tiago only (limited risk).

3. No malaria in major urban areas.

Dominican Republic), some Medical Letter consultants add “terminal prophylaxis” with primaquine phosphate. Others prefer to rely on surveillance to detect cases.

**PROTECTION AGAINST MOSQUITO BITES** — To minimize insect bites, travelers should wear light-colored, long-sleeved shirts, pants, socks and cov-

ered shoes. They should sleep in screened areas and avoid going out after sunset when the mosquitoes that transmit malaria are most active. Dusk and dawn are the peak biting times.

The most effective topical insect repellent is N, N-diethyl-m-toluamide (DEET).<sup>6,7</sup> Applied on exposed skin, DEET repels mosquitoes, as well as ticks, chiggers, fleas, gnats and some flies. DEET is available in formulations of 5-40% and 100%. Concentrations of 30-35% are preferred by Medical Letter consultants; higher concentrations do not improve efficacy, but usually protect longer. A long-acting DEET formulation originally developed for the US Armed Forces (US Army Extended Duration Topical Insect and Arthropod Repellent – EDTIAR) containing 25-33% DEET (*Ultrathon*) can provide protection for 6-12 hours. DEET in concentrations of up to 50% is probably safe in children and infants >2 months old; it should not be used in infants <2 months old. One study found that applying DEET regularly during the second and third trimesters of pregnancy did not result in any adverse effects on the fetus.<sup>8</sup> DEET may decrease the effectiveness of sunscreens; when they are used together, a sunscreen with a higher SPF should be used. Using a sunscreen and insect repellent together apparently does not reduce the effectiveness of the insect repellent.<sup>9</sup>

Picaridin is an insect repellent that has been available in Europe and Australia for many years. The 7% formulation (*Cutter Advanced*) currently sold in the US<sup>10</sup> might be as effective against mosquitoes as low concentrations of DEET, but no data are available. Higher concentrations are sold in Europe and protect against mosquitoes for up to 8 hours.<sup>11-13</sup>

Permethrin (*Duranon*, *Permanone*, and others) is an insecticide available in liquid and spray form for use on clothing, mosquito nets, tents and sleeping bags for protection against mosquitoes. After application to clothing, it remains active for several weeks through multiple launderings. Using permethrin-impregnated mosquito nets while sleeping can be helpful when rooms are not screened or air-conditioned. If bednets or tents are immersed in the liquid, the effect can last for about 6 months. It can also be used in combination with DEET for increased protection.

**CONCLUSION** — No drug regimen guarantees protection against malaria. Insect repellents, insecticide impregnated bed nets and proper clothing are important adjuncts for malaria prophylaxis. Travelers to

malarious areas should be reminded to seek medical attention if fever develops after they return. □

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