DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
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AFEB

JUL 3 1 2003

MEMORANDUM FOR

The Assistant Secretary of Defense (Health Affairs)
The Surgeon General, Department of The Army
The Surgeon General, Department of The Navy
The Surgeon General, Department of The Air Force

SUBJECT: Antimalarials and Current Practice in the Military – 2003 - 13

1. References:

a. Memorandum, Office of the Assistant Secretary of Defense for Health Affairs (Force Health Protection and Readiness), October 21, 2002, Antimalarials and Current Practice in the Military.

b. Centers for Disease Control and Prevention, *Health Information for International Travel,* 2003-2004, Drugs used in the Prophylaxis of Malaria, http://www.cdc.gov/travel/diseases/malaria/index.htm, revised May 5, 2003.

2. On 21 May 2003 the Armed Forces Epidemiological Board (AFEB) met to consider a request to the Board from the Assistant Secretary of Defense for Health Affairs (Force Health Protection and Readiness). Specifically, the AFEB was asked to review antimalarials and current practice in the military and provide comment on the efficacy and safety data for Malarone™ (Glaxo SmithKline) and make recommendations on how, or if, the availability of this new product should affect DoD antimalarial recommendations. The Board received briefings from Colonel Robert DeFraites from the Office of the Army Surgeon General, Colonel G. Dennis Shanks from the U.S. Army Center for Health Promotion and Preventive Medicine and from Captain Monica Parise from the Centers for Disease Control and Prevention (CDC).

3. The Department of Defense (DoD) currently follows national consensus guidelines for the prevention and treatment of malaria as published by the CDC in *Health Information for International Travel* (the "Yellow Book"). The recommended malaria chemoprophylactic drugs are attached. The recommendations in the Yellow Book are evidence based and developed by CDC in collaboration with a convened panel of experts from both outside and within the government. The Yellow Book does not recommend a single drug of choice, as different circumstances will require different chemoprophylactic choices. Some recommendations

from the CDC, including the indicated use of the drug or the dose of the drug, are off-label. This affects potential DoD use of the CDC-recommended guidelines. The DoD is subject to special requirements under section 1107 of Title 10, United States Code, concerning potential off-label use of any force health protection medications. For malaria chemoprophylaxis, this currently limits the CDC recommended prescribed use of primaquine for both prevention and post-exposure treatment of relapsing *P. vivax* and/or *P. ovale*, and the recommended loading dose of mefloquine for persons being deployed on short notice. These drugs, used in an off-label manner as recommended, may only be prescribed in the context of a doctor-patient relationship or as part of an investigational new drug protocol. Either option is burdensome and may be impractical in a military setting.

4. Although the DoD usually strives for "sameness," decisions regarding malaria chemoprophylaxis are highly complex. There is no single best choice. Military use of recommended drugs may differ from short-term recreational traveler use. Recommendations may vary based upon mission type (combat, peacekeeping, humanitarian assistance), troop population (flight crew vs. infantry), command climate (attitude and training/awareness), duration of exposure and seasonality (relationship to rainy seasons). In many military situations, to enhance compliance weekly dosing may be preferential to daily drug administration. Troops vary greatly in the need for and response to requirements for prophylaxis. In addition, malaria risk is cumulative (the longer the mission, the greater the malaria risk, especially for relapsing malaria). Long deployments almost always result in far less-than-optimal compliance with chemoprophylaxis (up to 60% noncompliance after five months with daily drug administration). Relapsing malaria is also a military problem with more than 80% of recent malaria cases reported in the Army due to *P. vivax* infection. (In CY 2002, 46 of the 59 cases of malaria reported among active duty Army soldiers were a result of infection with *P. vivax*.)

5. Protective measures to reduce contact with mosquitoes, especially between dusk and dawn, are the cornerstone of a complete malaria prevention program. Such measures include using insecticide-treated mosquito nets, wearing DEET impregnated BDUs, and insect repellent for use on exposed skin. Personnel deployed to malarious areas should start chemoprophylaxis prior to deployment and use chemoprophylaxis continuously while in malaria-endemic areas, and after redeployment as required, based upon the specific chemoprophylactic drug. Terminal prophylaxis with primaquine, the only drug available that kills liver stage parasites, is generally indicated only for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*, or both. Individuals for whom primaquine is indicated should be tested for G6PD deficiency prior to prescribing primaquine at the 30mg dose, as this dose is contraindicated in individuals who are G6PD deficient.

6. Given these considerations, the Board makes the following findings and recommendations regarding the question before the Board on antimalarials and current practice in the military:

a. The consensus guidelines for the prevention and treatment of malaria as published by the Centers for Disease Control and Prevention in the *Health Information for International Travel* (the "Yellow Book") are appropriate guidelines for use by the Department of Defense. Operational considerations should always be considered and malaria chemoprophylactic recommendations should be based upon the best available information, including the most recent medical intelligence from the Armed Forces Medical Intelligence Center on the endemnicity and drug-resistance patterns of malaria in the area of operations. For military deployments to areas of risk where chloroquine-resistant *P. falciparum* exists, three efficacious options exist:

- **Malarone™ is a fixed combination of the two drugs, atovaquone and proguanil, and is indicated for primary prophylaxis in areas where chloroquine-resistant or mefloquine-resistant *P. falciparum* is present. Atovaquone/proguanil should not be used in children <11 kg, pregnant women, women breast-feeding infants weighing <11 kg, or patients with severe renal impairment (creatinine clearance <30 mL/min). Atovaquone/proguanil primary prophylaxis should begin 1–2 days before travel to malarious areas and should be taken daily, at the same time each day, while in the malarious area and daily for seven days after leaving such areas. This short dosage interval after return from a malaria endemic area is an advantage over the recommended, but rarely used, one month post return prophylaxis with doxycycline and mefloquine. The requirement for daily administration may limit the military use of Malarone™ in certain instances, but Malarone™ should be available in the military drug armamentarium as a malaria chemoprophylactic drug. The Board notes that Malarone™ was available in the deployment formulary for Operation IRAQI FREEDOM.**

- **Mefloquine is indicated for primary prophylaxis in areas with chloroquine-resistant *P. falciparum*. Mefloquine has been associated with rare, serious adverse reactions (e.g., psychoses or seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Mefloquine is contraindicated in persons with active depression and in those with a history of psychosis or seizures, and should be used with caution in persons with psychiatric disturbances. Mefloquine primary prophylaxis should begin 1–2 weeks before deployment to malarious areas. It should be continued once a week, on the same day of the week, during deployment in malarious areas and for 4 weeks after redeployment from such areas. Mefloquine should continue to be available in the military drug armamentarium as a malaria chemoprophylactic drug.**

- **Doxycycline is indicated for primary prophylaxis in areas with chloroquine-resistant *P. falciparum*. Doxycycline may cause photosensitivity and can predispose women to vaginal yeast infections. Doxycycline should not be used during pregnancy. Doxycycline primary prophylaxis should begin 1 or 2 days before arrival in the malaria-risk area, once a day, at the same time each day, in the malaria-risk area, and once a day for 4 weeks after leaving the malaria-risk area.**

b. DoD routinely provides information to armed forces personnel when they are issued antimalarials. The recent FDA requirement to provide the Lariam™ (Roche Laboratories Inc.) Medication Guide to all personnel prescribed Lariam™ for malaria prophylaxis may require a different risk communication approach than now in place for DoD, as there is no similar requirements (nor level of concern) by FDA for other antimalarials. The concern among military personnel that mefloquine should be avoided is not evidence based. DoD should consider conducting a survey looking at the knowledge, attitudes and beliefs among military personnel on this issue, e.g. focus groups and anonymous questionnaires, to document actual beliefs and behaviors, and how they vary by age, sex, service and other factors. Such information might help craft communication tools and messages that would improve compliance with chemoprophylaxis in general, especially for mefloquine. DoD should encourage implementation of an educational effort to help address this issue. A randomized trial of the major malaria prophylactic regimens focusing on side effects is warranted.

c. Terminal prophylaxis with primaquine is indicated only for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. Primaquine can cause fatal hemolysis in those who are G6PD deficient. At the currently recommended dose of 30 mg, primaquine is contraindicated in individuals who are G6PD deficient. Therefore, documentation of a normal G6PD level should be available before prescribing primaquine.

7. The above recommendations were unanimously approved.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

STEPHEN M. OSTROFF, M.D.
AFEB President

JAMES R. RIDDLE, D.V.M., M.P.H.
Colonel, USAF, BSC
AFEB Executive Secretary

AFEB
SUBJECT: Antimalarials and Current Practice in the Military – 2003 – 13

2 Enclosures
1. Memorandum, Office of the Assistant Secretary of Defense for Health Affairs (Force Health Protection and Readiness), 21 October 2002, Antimalarials and Current Practice in the Military.
2. Drugs used in the prophylaxis of malaria, *Health Information for International Travel,* 2003.

CF:
Board Members and Consultants (w/encls)
J4-MRD (w/encls)
OASD(HA)/FHP&R (w/encls)
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OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

21 OCT 2002

MEMORANDUM FOR EXECUTIVE SECRETARY, ARMED FORCES EPIDEMIOLOGICAL BOARD

SUBJECT: Antimalarials and Current Practice in the Military

On 14 July 2000, the U.S. Food and Drug Administration (FDA) approved Malarone, a new combination drug for the prevention and treatment of acute, uncomplicated P. falciparum malaria. The FDA has also recently approved the addition of new safety data to the prescribing information of Malarone, demonstrating that it has fewer adverse events overall, than mefloquine (Lariam) and chloroquine/proguanil. According to the new prescribing information, studies show that travellers taking Malarone for malaria prevention experienced significantly fewer neuropsychiatric side effects (14% vs. 29%), such as strange or vivid dreams, insomnia, dizziness or vertigo, anxiety and depression, than those who took mefloquine. Additionally, fewer gastrointestinal adverse experiences, such as vomiting, nausea and diarrhoea, occurred in subjects receiving Malarone than chloroquine/proguanil (12% vs. 20%).

In light of this new safety data and the recent FDA and Roche announcement to strengthen the contraindications, warnings, precautions, and adverse reactions sections of the label for Lariam, I would like the AFEB to review antimalarials and current practice in the military and provide comment on the efficacy and safety data for Malarone and make recommendations on how or if the availability of this new product should affect DoD anti-malarial recommendations.

Ellen P. Embrey
Deputy Assistant Secretary of Defense
(Force Health Protection and Readiness)

Attachments
As stated

Drugs used in the prophylaxis of malaria[1,2]				
Drug	**Usage**	**Adult Dose**	**Pediatric Dose**	**Comments**
Atovaquone/ proguanil (Malarone™)	Primary prophylaxis in areas with chloroquine-resistant or mefloquine-resistant *P. falciparum*	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily	Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride. 1–20 kg: 1 tablet 21–30 kg: 2 tablets 31 –40 kg: 3 tablets 40 kg or more: 1 adult tablet daily	Contraindicated in persons with severe renal impairment (creatinine clearance < 30 mL/min). Atovaquone/proguanil should be taken with food or a milky drink. Not recommended for children <11 kg, pregnant women, and women breastfeeding infants weighing <11 kg
Chloroquine phosphate (Aralen® and generic)	Primary prophylaxis only in areas with chloroquine-sensitive *Plasmodium falciparum*	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	May exacerbate psoriasis
Doxycycline (Many brand names and generic)	Primary prophylaxis in areas with chloroquine-resistant or mefloquine-resistant *P. falciparum*	100 mg orally, daily	8 years of age or older: 2 mg/kg up to adult dose of 100 mg/day	Contraindicated in children <8 years of age and pregnant women
Hydroxychloro-quinesulfate (Plaquenil®)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive P. falciparum	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	
Mefloquine (Lariam® and generic)	Primary prophylaxis in areas with chloroquine-resistant Plasmodium falciparum	228 mg base (250 mg salt) orally, once/week	15 kg and under: 4.6 mg/kg base (5 mg/kg salt) orally, once/week 15–19 kg: 1/4 tablet once/week 20–30 kg: 1/2 tablet once/week 31–45 kg: 3/4 tablet once/week 46 kg and over: 1 tablet once/week	Contraindicated in persons allergic to mefloquine and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Not recommended for persons with cardiac conduction abnormalities

Drugs used in the prophylaxis of malaria[1,2]				
Drug	**Usage**	**Adult Dose**	**Pediatric Dose**	**Comments**
Primaquine	An option for primary prophylaxis in special circumstances. Call Malaria Hotline (770-488-7788) for additional information.	30 mg base (52.6 mg salt) orally, daily	0.6 mg/kg base (1.0 mg/kg salt) up to adult dose orally, daily	Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level. Use in consultation with malaria experts.
Primaquine	Used for terminal prophylaxis to decrease the risk of relapses of *P. vivax* and *P. ovale*	30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area	0.6 mg/kg base (1.0 mg/kg salt) up to adult dose orally, once/day for 14 days after departure from the malarious area	Indicated for persons who have had prolonged exposure to *P. vivax* and *P. ovale* or both. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level.
Abbreviations: mg - milligram; kg - kilogram. Kilogram = 2.2 pounds. *Glucose-6-phosphate dehydrogenase.				

1. Adopted from *Health Information for International Travel* (the "Yellow Book") http://www.cdc.gov/travel/diseases/malaria/index.htm
2. Start chemoprophylaxis before travel and use prophylaxis continuously while in malaria-endemic areas and for 4 weeks (chloroquine, doxycycline, or mefloquine) or 7 days (atovaquone/proguanil) after leaving such areas.
3. Primaquine primary prophylaxis and terminal prophylaxis at 30mg base are off-label indications.