THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

SEP 13 2002

The Honorable John M. McHugh
Chairman, Subcommittee on Military Personnel
House Armed Services Committee
2120 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter regarding the Department of Defense's (DoD) use of mefloquine as an anti-malarial agent. Answers to the specific questions you raised are addressed in the enclosed document. The prevention and treatment of malaria is a matter of importance to all Americans who travel to areas where the disease exists; especially where the chloroquine-resistant *Falciparum* malaria, the most deadly form, is endemic.

For DoD, malaria prevention is of particular importance. When deployed to malaria endemic areas, our soldiers usually stay longer than most other American travelers and sometimes live under conditions where the risk of being bitten by a malaria infected mosquito is high. Because of malaria's potential impact on our forces and their ability to carry out their mission, DoD devotes considerable resources to malaria surveillance, control, and research. To effectively protect U.S. troops from malaria in current areas of operations, preventive malaria medications, their effectiveness, and any problems encountered with their use are monitored carefully.

As with all medications, health care providers, including those within DoD, must weigh the benefits of the drug against the possibility of adverse reactions in some individuals. They must also take into account the severity of the disease, characteristics unique to the patient to whom they are prescribing the drug, other medications the individual might be taking, and the probability that the patient will adhere to the drug regime prescribed.

In the case of malaria prevention and treatment, DoD health care providers use Food and Drug Administration (FDA) approved drugs, and follow the Centers for Disease Prevention and Control (CDC) recommendations, which list mefloquine, doxycycline, and malerone as medications effective in preventing infection with chloroquine-resistant *Falciparum* malaria.

While mefloquine remains a mainstay FDA approved anti-malarial drug within the United States, recent press articles and scientific studies have raised concerns regarding the adverse effects associated with mefloquine use. Recent peer-reviewed reports show adverse event rates at levels much higher than previously reported. Considerable debate has occurred within the scientific community regarding the implications of these findings. Some scientists point out that many of the recent reports relied on self-reported symptoms and were conducted in populations that differed greatly in age, time of medication use, and underlying co-morbidities which may have influenced the rate of adverse events.

DoD is part of the Interagency Working Group for Antimalarial Chemotherapy which is comprised of representatives from the Department of State, the Peace Corps, CDC, FDA, the United Kingdom, the Netherlands, and Germany. The subject matter experts within this Group meet periodically to exchange information and make recommendations regarding anti-malarial medication. Mefloquine was the subject of a recent Working Group meeting on April 16, 2002. The results of the meeting are summarized in the enclosed document.

In early 2001, CDC began planning and is now conducting an evidence-based review of the chemoprophylactic drugs they recommend, including mefloquine. When completed, the review findings will be used as a background document for a group of external experts, including scientists from universities and representatives from U.S. government agencies, who will review CDC's chemoprophylaxis guidelines.

Once the CDC findings and recommendations of the multi-agency panel are available, DoD will consider the need for more militarily-specific guidelines regarding the use of antimalarials, including mefloquine, during operational deployments. Because of the unique malaria exposures and demographics of the military, DoD will ask the Armed Forces Epidemiological Board to address the need for military-specific malaria prevention and treatment guidelines in addition to those set forth by the heretofore discussed multi-agency panel.

In summary, malaria prevention and control is of particular importance to DoD. Efforts are ongoing to develop improved methods of preventing and controlling the disease, including research on a vaccine and new medications. The current issues regarding the adverse effects of mefloquine have raised concerns within the DoD as well as within the health related scientific community worldwide. In concert with other federal agencies, DoD will continue to assess these issues. Future recommendations and use will be made based on scientific evidence and operational needs.

Thank you for your continued support of the health of the men and women who serve in our nation's military and for the Military Health System.

Sincerely,

William Winkenwerder, Jr., MD

Enclosure:
As stated

cc:
Representative Snyder

ENCLOSURE
DoD Operational Use of Mefloquine

Issue #1: The health risks to military personnel of continued mefloquine use.

Malaria strikes up to 500 million people and causes 2.7 million deaths per year around the world. It is caused by four species of Plasmodium parasites, which are transmitted to humans by infected female Anopheles mosquitoes. Symptoms include a spiking fever, shaking chills, and flu-like symptoms. Anemia or liver problems may develop. If treatment is delayed, severe infection may lead to kidney failure, coma, and death.

Mefloquine, which is approved by the Food and Drug Administration (FDA) and recommended by the Centers for Disease Control and Prevention (CDC), has been successfully used for the prevention and treatment of chloroquine-resistant *Falciparum* malaria in deployed DoD forces for over ten years. While adverse events have been reported among deployed personnel prescribed the drug, they have been few in number and generally of low severity. In the cases where adverse events have been reported, symptoms normally resolved when the drug was discontinued and the member switched to an alternative product.

A possible consequence of continued use of mefloquine within DoD is that the negative publicity surrounding the drug may lower compliance among deployed personnel, thereby increasing their risk for acquiring malaria. Existing disease surveillance systems in operational theaters, however, would quickly detect an increase in malaria infections rates and prompt investigations and action to resolve the issue.

The relatively low rate of mefloquine related adverse events is greatly outweighed by the drug's effectiveness in preventing the severe consequences of malaria infections among deployed United States service members. The drug's effectiveness and ease of administration will continue to make it a optimal choice for health care providers faced with ensuring the protection of personnel deploying to chloroquine-resistant *Falciparum* malaria endemic areas.

Issue #2: An assessment of applicable clinical studies and the Department's opinion on whether additional long or short-term study of service member use of mefloquine by either DoD or the Institute of Medicine is indicated.

Review of Recent Research

A valuable source for critical analyses of the currently available evidence regarding a variety of clinical situations is the Cochrane Database of Systematic Literature. The Cochrane Infectious Diseases Group has performed an extensive review of the medical literature.[1] The stated objective of the review was to "evaluate mefloquine chemoprophylaxis in non-immune adult travelers on preventing malarial infection and adverse events". This publication was updated in 2001 to incorporate reports published through July21, 2000.

The authors identified 38 controlled trials of mefloquine prophylaxis; ten of these were ultimately determined to be eligible for inclusion in the review. Inclusion criteria included:

adult, non-immune subjects traveling to endemic malarious regions; short-term drug regimens (<12 months); or randomized tolerability studies carried out on pre-travel or non-traveling volunteers. These trials represented a total of 2,750 participants randomized either to mefloquine prophylaxis or to control (placebo or alternative active drug). Five of the studies were field studies carried out in military personnel, over 99% of which were male. The intensity of malaria exposure ranged from nil to high. Only the trial with the highest intensity of malaria exposure yielded microscopically confirmed cases of malaria. Only two trials included detailed reporting of the symptoms experienced by all the participants. The manufacturer of mefloquine funded four of the ten studies, and the U. S. military funded three; this fact suggests at least the possibility of either commercial or institutional bias in the reporting of results.

Five of the reported trials compared outcomes between mefloquine and placebo. The high intensity malaria exposure trial mentioned above showed mefloquine to be highly effective in preventing malaria (no cases in 202 person-months of exposure compared to 53 cases in 109 person-months of exposure for placebo).[2] The other four studies, which measured withdrawals from therapy, showed a tendency for mefloquine-treated subjects to withdraw from therapy more frequently than subjects receiving placebo. The meta-analysis of this effect was statistically significant, but the absolute difference in withdrawal between mefloquine and placebo was only 3.3% (95% CI 1.1% to 4.4%).

Six trials compared outcomes between mefloquine and alternative chemoprophylaxis. Only the study mentioned above measured the relative incidence of malaria. In that study, mefloquine and doxycycline appeared equally efficacious in preventing the development of malaria, but the sample size was too small to allow one to draw meaningful conclusions regarding the relative efficacy of these two products. Another study comparing mefloquine to chloroquine-proguanil using antibody markers to Plasmodia as evidence of recent infection showed a tendency toward greater efficacy for chloroquine-proguanil, but again the study was insufficiently powered to provide conclusive evidence of superiority.[3]

Four trials compared non-adherence to the prescribed regimen; there was no significant difference noted when mefloquine was compared to other therapies. Withdrawal was higher in three of four studies, but the difference was small and non-significant when the data were pooled. Notably, the absolute risk of withdrawal ranged between 2.5% and 3.4% in the 4 reported studies. When the reporting of adverse events was analyzed, there was no difference noted between mefloquine and other chemoprophylactic agents. When neuropsychiatric symptoms were looked at specifically, mefloquine was significantly more likely to cause insomnia and fatigue than other agents; there was no difference noted in the frequency of other neurological or psychiatric adverse events. Other regimens were almost twice as likely to cause gastrointestinal upset, anorexia, and nausea as mefloquine. However, most of this effect appeared to be due to a single study comparing chloroquine-proguanil to mefloquine.[4]

Several studies performed a variety of psychometric tests on participants. Two studies demonstrated that patients taking mefloquine slept on average 20 minutes less than chloroquine users[5] and 34 minutes less than placebo users.[6] No other studies demonstrated significant differences between mefloquine and either placebo or other chemoprophylactic agents.

The review also discussed 328 case reports of adverse events attributed to mefloquine when used as prophylaxis, and 188 case reports of adverse events when mefloquine was used to treat confirmed cases of malaria. These were reported in 136 separate publications between 1976 and

2000. The authors comment specifically on the unexpected finding of 4 case reports that attribute patient deaths to mefloquine, and another citation that identifies 8 additional cases in which mefloquine has been associated anecdotally with a fatal reaction.[7]

In their discussion, the authors note that the strongest evidence for both the effectiveness and tolerability of mefloquine comes from studies performed with military participants. In fact, they question whether this evidence is generalizable to tourists and business travelers. They base this concern on: 1) the "fit subject" effect (healthy soldiers are less likely to have co-morbid conditions and concomitant medications); 2) gender bias (>99% of participants in military trials are male, while observational studies in tourists and experimental volunteers demonstrate that women experience worse adverse events from mefloquine prophylaxis than men[8-13]); 3) age bias (conclusions reached in studies of young persons cannot always be generalized to the elderly); and 4) ethnic differences (one military study was carried out in Indonesian soldiers, while some observational data suggest that Caucasians and African-Americans are more susceptible to adverse events from mefloquine than Asians[14]). They also point out that the importance of being able to quantify the risk of adverse events is paramount, since any adverse drug effect (real or perceived) can cause the user to discontinue their prophylaxis and be left unprotected against malaria. They suggest the possibility that well-tolerated regimens, even if less efficacious, may actually perform better in practice than regimens that are highly efficacious in carefully controlled trials but are poorly tolerated under actual conditions of use.

In their conclusions regarding implications for practice, the authors state that while tolerability is very important, no one appears to know for certain whether mefloquine is well or poorly tolerated. They do go on to conclude, however, that "current research evidence indicates that mefloquine prophylaxis is only demonstrably useful in fit, highly-motivated occupational subgroups or individual travelers at high risk of infection with chloroquine-resistant *P. falciparum*." Military personnel are included in this subgroup.

The Interagency Working Group on Anti-malarial Chemotherapy consists of subject matter experts from DoD, CDC, the Peace Corps, the Department of State, the Department of Veterans Affairs, FDA, the United Kingdom, the Netherlands, and Germany; who meet periodically to exchange information and make recommendation relative to malaria treatment and prevention. On April 16, 2002, the Working Group met to discuss the current issues regarding the use of mefloquine in the prevention and treatment of malaria. The Working Group findings are summarized below.

1. It is difficult to compare civilian and military experiences with anti-malarial drug usage. The military is generally a younger, healthier population. Certain subsets of the military, those most often deployed to malaria endemic areas for extended periods of time, have been screened psychologically for psychiatric disease. Civilian travelers, prescribed anti-malarials, would have unlikely to have received such screening. The non-military governmental agencies indicated that their screenings, when they do exist, are cursory. Their populations are older on average and not required to be as physically fit, which serves as yet another screening surrogate.

2. The in-country experience for military and civilian travelers is different. Soldiers often sleep in tents or on the ground under mosquito netting. Travelers, even Peace Corps workers, as a rule, do not. Military missions are often to areas where the entomological

inoculation rate (EIR) is excessive – areas infrequently traveled by civilians. Soldiers are often in malaria endemic areas for extended periods of time. In addition, subsets of soldiers are occasionally redeployed from one malaria endemic area to another geographic area where a different species predominates or the same species has developed drug-resistance. This requires a consistent and coherent plan of malaria chemoprophylaxis with guidance from the top down, but adapted and executed by the command assets in the field based on real-time findings.

3. Study designs to date on Mefloquine are flawed, for example, the Barrett study (Barrett PJ et al, BM; 313: 525-528). The design of the study cannot meet its stated objectives, symptoms are self-reported, there is sampling bias, the studies are not randomized, and the studies are not controlled. Also, not to be discounted is the timing of the study in relation to adverse publicity regarding the prescribing of mefloquine in Britain.

4. The true barriers to a scientific evaluation of the drug mefloquine, given the subjective nature of many of the side effects attributed to it are the suggestible nature of human beings, the bias created by the media and the internet, and the difficulty in credibly communicating health risks when "expert" assessments are pitted in the lay press against "public" assessment.

5. Different military services, with different lengths and types of exposures, in the course of their duties establish different chemoprophylaxis regimens. The Naval Service of the Netherlands, for instance, which maintains on-board a regular complement of healthcare providers experienced in the treatment of malaria, prefers for short duties ashore to treat disease that presents in its service members rather than prophylax them. However, for longer duties ashore, they use chemoprophylaxis regimens like the US forces do. The bottom line is that the chemoprophylaxis must be tailored to the medical threats of the mission and the availability of treatment.

6. Finally, there is a historical problem with DoD credibility which regrettably could become entwined with a dangerous precedent of DoD medical policy being unduly influenced or established not by scientific fact or by the realities of the operational milieu, but by the most sensational or best marketed information about a circumscribed population that has no validity for or correlation with the military population.

In summary, sufficient evidence exists to raise the question whether the neuropsychiatric adverse events of mefloquine are frequent enough and severe enough to warrant limiting its use for the prevention and treatment of chloroquine-resistant malaria. However, sufficient evidence does not exist to answer the question, especially in the case of military personnel. The most compelling evidence for effectiveness and acceptable tolerance is derived from studies performed on military patient populations. One of mefloquine's specific advantages is its dosing schedule of once per week. This greatly simplifies the unit commander's task of ensuring his troops' compliance with their prescribed prophylactic regimen. The evaluation of the neuropsychiatric adverse events possibly related to mefloquine must take into consideration the baseline rate of neuropsychiatric events occurring in individuals under similar circumstances who are not taking the drug, an analysis that to date has not been undertaken. In light of the

current safety questions and the substantial value of mefloquine as a prophylactic agent for the prevention of chloroquine-resistant malaria, there does appear to be a need for additional well-conceived and well-organized controlled studies to answer the questions regarding the safety and tolerability of the currently designed prophylactic regimens. As the majority of severe adverse events reported with mefloquine have occurred during its use as treatment for documented infection with chloroquine resistant *P. falciparum*, other treatment regimens should be carefully considered before mefloquine is used at the doses required for treatment.

Future Research

The CDC began planning and is now conducting an evidence-based based review of the chemoprophylactic drugs they recommend, including mefloquine. When completed, the review findings will be used as a background document for a group of external experts including scientists from universities and representatives from US government agencies who will review CDC's chemoprophylaxis guidelines.

Once the CDC findings and recommendations of the multi-agency panel are available, DoD will consider the need for additional research in the form or short- and long- term studies of anti-malarials, including mefloquine. DoD will ask the Armed Forces Epidemiological Board to weigh the available evidence and address the specific areas where additional DoD research is indicated while taking into consideration militarily- unique malaria exposure and demographic factors.

Issue #3: Options regarding substitutes to mefloquine.

When considering the appropriate role for mefloquine in the management of malaria among active duty personnel, one principal issue that must be addressed is which *Plasmodia* species are most likely to be encountered in the operational theater, and what is the likely resistance pattern of the common species. The vast majority of malaria infections are caused by either *P. vivax* or *P. falciparum*. *P. vivax* is most prevalent in Central America, the Middle East, and India; *P. falciparum* is most prevalent in tropical Africa, Southeast Asia, Oceania, Haiti, the Amazon basin of South America, and the Dominican Republic.[15] This is important because: 1) *P. falciparum* is much more likely to cause death, 2) it is the only species to cause certain serious complications such as cerebral malaria, renal failure, pulmonary edema/ARDS, hypoglycemia, hemorrhage, and gastroenteritis, and 3) it is much more likely to be resistant to drugs used commonly for both prophylaxis and treatment. While clinically significant chloroquine resistance for *P. vivax* has been described only in Papua New Guinea and Irian Jaya, chloroquine-resistant *P. falciparum* is widespread in all countries where *P. falciparum* malaria occurs commonly.[16] As a result, most infections caused by *P. falciparum* require alternative therapy. *P. falciparum* is also commonly resistant to antifolates and quinine.[16] Mefloquine resistance has been identified in strains of *P. falciparum*, but to date these have been confined to certain areas in Thailand.[17] For this reason, chloroquine is now considered the first line chemoprophylactic agent only in areas where *P. vivax* is the likely infecting species of Plasmodium, and transmission of *P. falciparum* is unlikely, while mefloquine is recommended as the primary chemoprophylactic agent in other malaria-endemic areas.[18]

Other alternative chemoprophylactic agents include pyrimethamine-sulfadoxine (Fansidar), doxycycline, proguanil, primaquine, and atovaquone-proguanil (Malarone). Fansidar has been associated with severe mucocutaneous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, with a fatality rate of 1:11,000 to 1:20,000 among U.S. travelers. For this reason, it is used primarily as "self-care" therapy in patients who develop symptoms after taking second line prophylactic therapy if they are unable to obtain medical evaluation within 24 hours of the onset of symptoms.

Doxycycline, as indicated above, has been shown to be as effective as mefloquine in preventing chloroquine-resistant malaria. However, it must be given on a daily basis in order for it to be effective. This has been associated with a lower rate of compliance when compared to medications administered on a weekly basis, such as mefloquine.[19, 20] It has also been associated with the development of gastrointestinal side effects including esophageal ulcerations[21-23], and phototoxic skin reactions[24, 25]. The latter can be particularly significant given the potential for unavoidably excessive sun exposure during field operations, and the fact that using sunscreens may not prevent this phototoxic reaction.

Proguanil is not available in the U.S., must be taken daily along with weekly chloroquine, and is less effective than mefloquine against *P. falciparum* malaria.[26] Its use as a single agent is not appropriate.

Primaquine is used primarily in the treatment of *P. vivax* or *P. ovale* infection, since it clears the persisting hepatic stages of these forms of malaria. It is used for prophylaxis primarily in individuals with potentially heavy exposure to *P. vivax* or *P. ovale*, such as Peace Corps volunteers. However, it is also effective as prophylaxis against chloroquine-resistant *P. falciparum*.[26] Its use is limited by the need for daily therapy and the risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. However, it has the advantage of needing to be continued for only one week following departure from a malarious area, compared to four weeks for other agents. The general consensus is that primaquine would be a more popular choice if it were not for the requirement for daily use and the problem of hemolysis seen in G-6-PD deficient patients.

The final option currently available for prophylaxis is the combination product atovaquone-proguanil (Malarone). The FDA approved Malarone in July 2000 for "the prevention and treatment of acute, uncomplicated *P. falciparum* malaria". When used for prophylaxis, it is begun 1-2 days prior to entering a malaria-endemic area and continued on a daily basis during the stay and for 7 days following return. The shorter post-exposure treatment period (7 days vs. 28 days) results from its effectiveness in treating the early liver phase of the disease. When used for treatment, the usual adult dose is 4 tablets taken as a single dose daily for three days.

Malarone has been shown to be as efficacious as mefloquine for preventing *P. falciparum* infection when taken as directed. Several studies have also compared the tolerability of these agents, with mixed results. One fairly large study comparing the incidence of adverse events among patients treated with either Malarone or mefloquine demonstrated that the overall incidence of adverse events was the same in both groups (71.4% for Malarone versus 67.3% for mefloquine; difference, 4.1%; 95% confidence interval, -1.71 to 9.9). However, the rate of neuropsychiatric adverse events was significantly lower for Malarone (14% versus 29%; P=.001), as was the rate of moderate or severe AEs (10% versus 19%; P=.001) and AEs severe enough to lead to discontinuation of prophylaxis (1.2% versus 5.0%; P=.001). Except for the

fact that Malarone must be taken daily, it could be considered an attractive alternative to mefloquine for anti-malarial chemoprophylaxis in areas where *P. falciparum* is endemic.

However, consideration must be paid to developing an overall strategy for management of the risk of *P. falciparum* infection. This includes decisions regarding both prophylaxis of all individuals entering a malaria-endemic area, and treatment of those individuals who become infected, whether or not they complied with their regimen of prophylaxis. This requires an appreciation of several realities related to prophylaxis and treatment:

1. The same drugs, with the exception of doxycycline, may be used for either prophylaxis or treatment of malaria..
2. At the present time the best available options for chemoprophylaxis against P. falciparum malaria are mefloquine, Malarone, and doxycycline, while the best options for treatment of established infection are Malarone and mefloquine.
3. Since different regimens are used for prophylaxis and treatment, the incidence and severity of side effects for a given drug differ depending on which regimen is being used for a particular drug.
4. Individuals developing malaria despite the use of a prophylactic agent should be treated with a different agent due to the possibility that the infecting agent is resistant to the drug being used for prophylaxis.
5. The incidence of severe adverse events is much higher when mefloquine is used for treatment of *P. falciparum* infection than when used for prophylaxis[20].
6. Malarone is effective and well-tolerated when used to treat established *P. falciparum* infection.

These realities strongly suggest that Malarone should be the drug of choice for treatment of malaria caused by chloroquine-resistant *P. falciparum.* Given reality number 4, Malarone should not be used as a first line agent for prophylaxis in this scenario, as patients who contract malaria despite Malarone prophylaxis will require treatment with an agent (mefloquine) with a much higher incidence of adverse events when used at treatment doses. Mefloquine or doxycycline should be chosen as first-line agents for prophylaxis against *P. falciparum* malaria. The decision regarding which of these agents to use is not straightforward, and remains controversial. The fact remains that *P. falciparum* malaria is a serious and potentially fatal disease that is almost completely preventable when an effective program of infection prevention is followed, including effective chemoprophylaxis. The keys to effective chemoprophylaxis are an effective drug and compliance to the recommended schedule. When deciding between two drugs that are equally effective, compliance becomes the deciding factor. A drug that is administered weekly has a clear advantage over a drug that must be administered daily. Therefore, the daily drug must have clear advantages that outweigh the disadvantage of daily dosing. Doxycycline does not have sufficient advantages relative to prophylactic doses of mefloquine to justify a policy decision to mandate the use of doxycycline as the first-line prophylactic agent.

Issue #4: The operational and force health implications of changing to an alternative drug.

The operational and force health protection implications of changing to an alternative drug regime to prevent malaria relate to the effectiveness of the alternative drug and the willingness of deployed personnel to take the medication at the prescribed dose schedule. A medication that is less effective, either because of reduced efficacy or because the population potentially at risk for infection does not adhere to the dose schedule, would lead to an increase in malaria cases and ultimately impact the ability of United States force to carry out their mission. Additionally, the adverse events of the alternative medication must be considered. While other available medications appear to have good efficacy, the rate of adverse events is comparable to mefloquine.

Issue #5: The cost of changing to other drugs.

As noted in the above discussion of Issue #4, cost is a fairly low priority issue when making policy decisions regarding the most appropriate method of prophylaxis or treatment of malaria, particularly chloroquine-resistant malaria.

The current Federal Supply Schedule (FSS) prices for the drugs currently available for use for the prevention of malaria are outlined in Table 1. The cost per week of prophylactic therapy is based on the unit cost of the medication and the recommended dosing regimen for the drug.

Table 1. Relative cost of prophylactic regimens for chloroquine-resistant *P. falciparum*.

Drug Name	Manufacturer	Tablet / Capsule size (mg)	Quantity in Package	Package Price ($)	Price per Unit ($)	Units per Week	Cost per Week ($)
Mefloquine	Roche	250	25	137.82	5.51	1	5.51
	Geneva	250	25	135.74	5.43	1	5.43
Malarone	Glaxo	250/100	100	293.18	2.93	7	20.52
Doxycycline	Pfizer	100	50	106.60	2.13	7	14.92
	West-Ward	100	500	15.08	0.03	7	0.21
	West-Ward	100	100	7.96	0.08	7	0.56
	IVAX	100	500	16.00	0.03	7	0.22
	IVAX	100	100	8.03	0.08	7	0.56
	Schein	100	500	22.86	0.05	7	0.32
	Qualitest	100	500	21.56	0.04	7	0.30
	Imiren	100	500	19.60	0.04	7	0.27

As seen, mefloquine is substantially less expensive than Malarone. However, it is significantly more expensive than doxycycline, except when the brand-name product is used. While doxycycline is less expensive, it has other shortcomings that make it a less than optimal substitute for mefloquine for malaria prevention, as discussed above.

The current regimen of choice for treatment of chloroquine-resistant *P. falciparum* malaria in patients able to tolerate oral medication is quinine sulfate in combination with pyrimethamine-sulfadoxine (fansidar), doxycycline, or mefloquine. Other alternative regimens include

Malarone, mefloquine, halofantrine, atovaquone, artemisinin, and fansidar. The relative costs of these different regimens are outlined in Table 2.

Table 2. Relative cost of treatment regimens for chloroquine-resistant *P. falciparum*.

Drug Name	Manufacturer	Tablet / Capsule size (mg)	Quantity in Package	Package Price ($)	Price per Unit ($)	Units per Treatment Course	Cost per Treatment Course ($)
Quinine and	Liberty (quinine)	325	100	9.80	0.10	42	4.12
Fansidar	Roche (fansidar)	25/500	25	53.88	2.16	3	6.47
							10.59
Quinine and	Liberty (quinine)	325	100	9.80	0.10	42	4.12
Doxycycline	West-Ward (deoxycycline)	100	500	15.08	0.03	14	0.42
							4.54
Mefloquine	Roche	250	25	137.82	5.51	5	**27.56**
	Geneva	250	25	135.74	5.43	5	**27.15**
Malarone	Glaxo	250/100	100	293.18	2.93	12	**35.18**
Fansidar	Roche	25/500	25	53.88	2.16	3	**6.47**

The combination of quinine/doxycycline is the most well-tolerated, efficacious, and cost-effective therapy available for treatment of chloroquine-resistant *P. falciparum* infection. It can be administered orally, or quinine can be administered intravenously in more critically ill patients who cannot tolerate oral therapy. Malarone, although substantially more expensive, should be considered second-line therapy given the frequency and severity of adverse events associated with alternative treatment regimens.

Issue #6: Prospects for new, replacement drugs currently in development.

Efforts in malarial prevention are two-fold; the development of new anti-malarial drugs and the creation of an effective malaria vaccine for deployed forces.

New Anti-Malarial Drugs

Despite the widespread recognition that growing resistance to currently available anti-malarial drugs is a major contributing factor in the rising incidence of both malaria cases and malaria-related deaths worldwide, there currently appear to be very few new anti-malarial drugs being developed by pharmaceutical companies with a stated intent to apply for FDA approval for use in the United States. DoD Directive 6200.2 establishes that non-FDA approved drugs will not be used for Force Health Protection except under an approved Investigational New Drug (IND) request, and that use of non-FDA approved drugs under INDs should be limited to situations where "no FDA-approved product is available to meet a foreseeable threat". Therefore, the remainder of this discussion will concentrate on the two products that currently are in the pipeline for eventual FDA approval.

Tafenoquine is an analog of primaquine that is being developed in a collaborative arrangement between the Walter Reed Army Institute of Research (WRAIR) and Glaxo SmithKline. It has the same spectrum of activity as primaquine; its major therapeutic advantage is its substantially longer half-life, which allows it to be dosed on a weekly rather than a daily basis. Like

primaquine, it is contraindicated in patients with severe G-6-PD deficiency, although it can be used in individuals with the milder variant forms of G-6-PD deficiency. Glaxo SmithKline reports that they anticipate filing an NDA for FDA approval of tafenoquine in 2004.

Artemisinin or **Qinghaosu** refers to a family of compounds derived from *Artemisia annua*, a plant endemic to China and other areas of Southeast Asia. Chinese researchers first discovered Artemisinin in 1972 found it to have excellent anti-malarial properties. Three additional compounds (artesunate, artemether, and arteether) were subsequently isolated and noted to also be effective in treating chloroquine-resistant as well as mefloquine-resistant *P. falciparum*. These drugs have different routes of administration and somewhat different adverse effect profiles; one adverse effect that they share with each other and with mefloquine is the potential for neurological toxicity. Despite this concern, these products are rapidly gaining favor in a number of malaria-endemic areas. The Swiss company Mepha has submitted an NDA for artesunate rectocaps to the FDA for approval; the FDA's Anti-Infective Drugs Advisory Committee will review the application on July 10th 2002. If recommended for approval, the FDA could approve this drug within 6-12 months. This family of drugs is used only for treatment of established malaria; they have no role in prophylaxis.

Vaccine Development

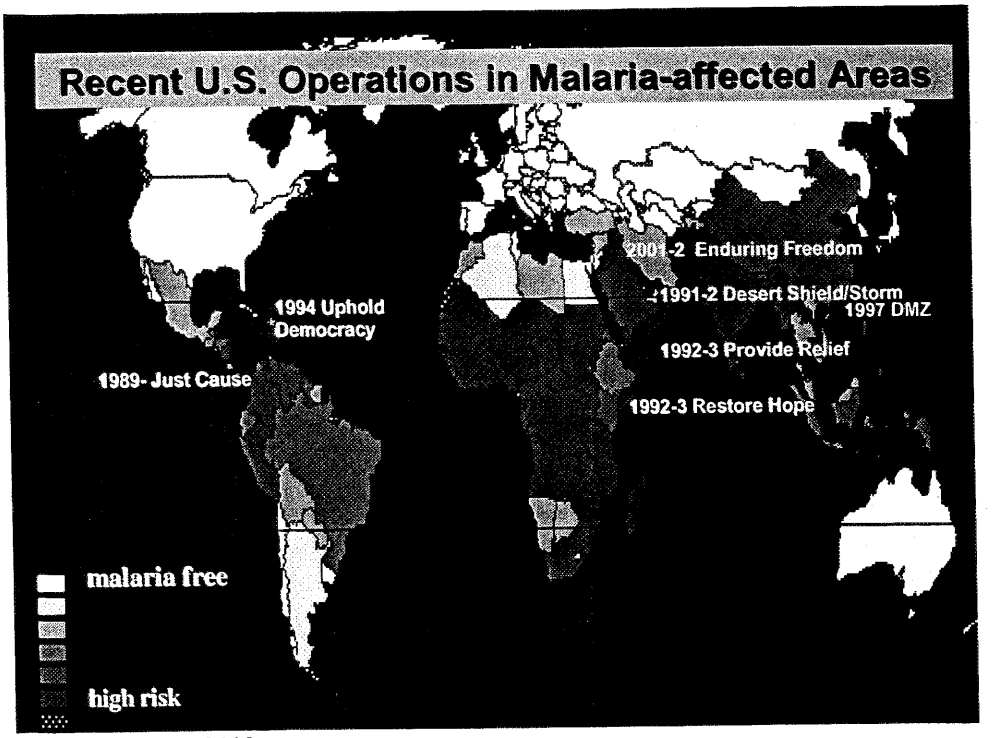
In addition to the research underway to develop new anti-malarial drugs, DoD is substantially involved in developing a safe, well tolerated malaria vaccine which would prevent malaria in deployed forces. The DoD goals of vaccine development are to prevent disease by killing the malaria parasite in the liver and thereby preventing blood-stage infection in non-immune adults. Researchers the Walter Reed Army Institute of Research (WRAIR) in Washington D.C. were the first in the world to validate the proof of concept that a malaria vaccine could protect malaria exposed individuals and conducted studies ranging from antigen discovery, to Phase 1 clinical trial of potential vaccines. At overseas laboratories in Bangkok, Thailand, Jakara, Indonesia, Lima, Peru, and Nairobi, Kenya, WRAIR scientists have made important steps towards the goal of producing an effective malaria vaccine. Field trials of a prototype vaccine, conducted in Gambia in conjunction with a United States commercial vaccine manufacturer, have showed a well-tolerated vaccine can be produced. In the field trial, the prototype vaccine yielded a 2/3 reduction in new malaria cases for a two month period following administration. While these results would not be considered sufficient to protect American forces deployed to a malaria endemic area, they represent the first demonstration of a successful malaria vaccine anywhere in the world. The promising results to date in vaccine development make the availability of effective malaria vaccine within the next 10 years a reasonable reality. Given the malaria organism's proven ability to develop resistance to medications, the need for a vaccine will remain a critical DoD goal.

Item 7: Data regarding the use of mefloquine, including the numbers of service member and locations and time frames used, and the availability of health data on mefloquine's side effects on those members.

Geographic Locations Requiring Malaria Medication Use

The number of DoD operations where the anti-malarial drug mefloquine was or currently is in use is extensive. As personnel move about geographic regions because of operational requirements, deployed personnel may find themselves in multiple operations at different times. DoD personnel in small numbers may also be assigned specific missions that are not of sufficient size to be named as an operation; for example Special Operations Forces.

The major operations carried out in malaria endemic areas where mefloquine may be prescribed to deployed forces are depicted in the graphic below. Information on geographic regions within Combatant Commands where *Falciparum* malaria is endemic is also provided in the following paragraphs.



Magill, WRAIR, 2002

a. USPACOM. USAPCOM has conducted literally hundreds of operational deployments requiring anti-malarial prophylaxis during the past 5 years. The most frequent and routine deployments requiring anti-malarial prophylaxis occurred in East Timor, Thailand, South Korea, and the Philippines. In Korea, only those soldiers assigned to the area near the demilitarized zone are prescribed anti-malarial drugs. The list of other countries in USPACOM's area of responsibility (AOR) currently requiring anti-malarial prophylaxis includes:

Bangladesh	Bhutan
Burma (Myanmar)	Cambodia
East Timor	India
Indonesia	Lao People's Democratic Republic
Papua New Guinea	Philippines
Solomon Islands	Sri Lanka
South Korea	Thailand
Vanuatu	Vietnam

b. USSOUTHCOM. Virtually all deployments into USSOUTHCOM's AOR require such medications. Malaria is not a threat in Guantanamo Bay.

c. USSOCOM. USSOCOM and its component commands, as force providers to all combatant commanders, have supported thousands of deployments to malaria endemic areas (Africa, Asia, Central America, Middle East and South America) over the last 5 calendar years. All deployments (regardless of length of time or number of troops deploying) to a geographic location that is suspected of having malaria requires a decision to be made with regards to the use of malaria chemoprophylaxis.

d. USJFCOM. There have been no operational deployments in the USJFCOM AOR over the past 5 years that have required use of anti-malarial prophylaxis.

e. USCENTCOM. There have been no operational deployments in the USCENTCOM AOR in the past 5 years that have required force-wide anti-malarial prophylaxis. Individual and/or unit analysis of the mission area may have determined some sub-populations (i.e., SOF, Marines, etc.) use prophylaxis in certain malaria-endemic areas.

f. USEUCOM. Every USEUCOM deployment and nearly every temporary duty to sub-Saharan Africa has required use of such medications - including medical red flag exercises, Operation FOCUS RELIEF in Nigeria, Mozambique flood relief operations, and others too numerous to list.

Malaria Medications Prescribed

The data below show the prescription for chloroquine outnumber those for mefloquine. Malarone is prescribed at 3 percent the rate of mefloquine. Because doxycycline is used prescribed for many conditions other than malaria, it is not depicted.

Table 3. Number of active duty military personnel receiving a prescription for malaria medications, July 2001 – May 2002.

	HYDROXY-CHLOROQUINE SULFATE	MALARONE	MEFLOQUINE	PRIMAQUINE
July 2001	1,054	16	389	651
August	1,058	21	609	653
September	1,032	12	613	466
October	1,139	17	675	465
November	1,083	9	931	786
December	1,069	28	865	532
January 2002	1,150	34	1,036	786
February	1,051	31	837	687
March	1,117	88	1,512	1,547
April	1,185	99	1,458	1,346
May	1,185	42	1,654	1,168
TOTALS	**12,123**	**397**	**10,579**	**9,087**

DoD Pharmacoeconomic Center, 2002

Information on health events among service members is available from two major sources. Outpatient medical encounter data are available through the Ambulatory Data System (ADS). Inpatient data is available through the Standard Impatient Data Record (SIDR). Other systems for data collection including the Theatre Medical Information Program (TMIP) are used during deployments to collect patient-level medical information.

Item 8: Policy issues, especially the level of the authority that determines theatre policy regarding which anti-malarial drug is to be used; and whether the decision is done a the most appropriate level using the best infectious disease expertise available?

In accordance with the Goldwater Nichols Act, Combatant Commander-In-Chief (CINC) is responsible for the command and control of all military activities within his area of operations. This responsibility includes ensuring the health and welfare of the assigned service members. With respect to malaria the CINC must ensure appropriate medical measures are available to prevent infection and to provide for the appropriate of those with acquire the disease.

The Command Surgeon or Chief Medical Officer to the Combatant Commander recommends to the CINC appropriate medical actions taking into consideration the diseases endemic to the area, including malaria. The medications, and alternatives in the case of allergies, sensitivities, or contraindications due to duty position (e.g., aviation), are stipulated in the Annex Q of the Operational Orders published for each deployment.

With respect to malarial prevention, Command surgeons select and determine malaria chemoprophylaxis requirements based on a decision matrix considering the following issues:

(1) Level of endemicity of the disease in the indigenous population.
(2) Presence of the vectors.
(3) The health of the deploying Service members.
(4) The potential of drug resistance in the disease.
(5) The potential of Service members to interact with the vectors of the disease.

(6) The ability to control the presence of the vectors (pesticides, repellents, barriers).
(7) Evidence of pesticide resistance in the vectors.
(8) Efficacy of the chemo-prophylaxis (potential for breakthrough).
(9) The potential health effects of the medication on Service members.
(10) The impact and/or risk on the mission without implementation of countermeasures.
(11) The impact and/or risk on the mission with implementation of countermeasures.

The CINC and the Command Surgeon have at their disposal a wealth of information on the disease threats in theatre and the preventive measure available to mitigate risk to health. In particular, the Armed Forces Medical Intelligence Center (AFMIC) is an important source of information.

Located at Fort Detrick, Maryland, AFMIC is a field production activity of the Defense Intelligence Agency and the sole DoD producer of medical intelligence. The Center provides all-source intelligence on:

- Worldwide infectious disease and environmental health risks.
- Foreign military and civilian healthcare systems and infrastructure.
- Foreign biomedical developments and life science technologies of military medical significance.

AFMIC also maintains extensive data bases, monitors foreign research, development, production and transnational flow of medical materiel for military interest, provides intelligence liaison services to key customers, conducts in-house and mobile training including a medical intelligence fellowship program, serves on numerous intelligence committees and working groups, and trains military reservists for mobilization assignments. These intelligence products provide direct support to U.S. military customers for operational planning; development of policy, doctrine, and training priorities; and medical research and development.

AFMIC has developed an evidence-based framework that is used to provide Commanders and other decision makers with an estimate of the level of impact a specific disease may have during a military operation in a specific country or area. The threat assessment model information including the endemicity of the disease in the country or area under question, the expected number of Service members who could be affected, and the typical severity of disease among those who acquire infection to derive the probability that individuals will become ill or die within a stated period of time. Based on the information, Commanders can derive an estimate of operational impact from the disease and determine the applicability of appropriate preventive countermeasures.

Deploying commanders through their Command Surgeons or preventive medicine professionals may acquire additional medical intelligence for malaria protection decisions from an abundance of sources including:

(1) *Military Sources*

(a) Commander, USPACOM Force Health Protection Branch, Camp H.M. Smith, Hawaii
(b) Joint Intelligence Center, Pacific, Honolulu, Hawaii
(c) Armed Forces Medical Intelligence Center, Fort Detrick, Maryland
(d) Navy Environmental & Preventive Medicine Unit 6, Pearl Harbor, Hawaii
(e) US Navy Medical Research Unit No. 2, Jakarta, Indonesia
(f) US Army Center for Health Promotion and Preventive Medicine Pacific, Camp Zama, Japan
(g) Tripler Army Medical Center, Travel Medicine Clinic, Honolulu, Hawaii
(h) Walter Reed Army Institute of Research, Travel Medicine Clinic, Bethesda, Maryland
(i) Service-Specific Preventive Medicine Personnel (Organic to the deploying unit)

(2) Civilian Sources

(a) Centers for Disease Control and Prevention, Atlanta, Georgia
(b) TravaxTM Shoreland, Incorporated, Milwaukee, Wisconsin
(c) Travel CareTM Care Ware, Incorporated, La Jolla, California

(3) Internet Sites Commonly Visited

(a) CDC: http://www.cdc.gov/travel/travel.html
(b) PROMED: http://www.fas.org.promed/
(c) Shoreland Travel Health Information Service: http://www.shoreland.com

(4) Commonly Used Textbooks and Publications

(a) *Medical Products for Supporting Military Readiness: Vaccines and Drugs*, US Army Medical Research & Materiel Command, Fort Detrick, Maryland
(b) *Pocket Book of Infectious Disease Therapy*, Bartlett JG, Williams & Wilkins, 1996
(c) *Control of Communicable Diseases Manual (FM8-33)*, Benenson, ed., American Public Health Association, 1995
(d) *Manson's Tropical Diseases*, Cook, ed., Saunders, 1996
(f) *The Sanford Guide to Antimicrobial Therapy*, Sanford, ed., Antimicrobial Therapy, Inc., yearly
(g) *Travel and Routine Immunizations*, Thompson RF, Shoreland, Inc., yearly

(5) Other sources of useful medical intelligence include: after-action reports maintained at each operational headquarters; direct contact with medical personnel in the location hosting the deployment; interface with the US State Department's medical staff; and interface with non-governmental organizations in humanitarian assistance scenarios.

For operations into malaria endemic areas, Annex Q of the Operational Orders specifies whether malaria prophylaxis is required and may list specific preventive measures such as the use of bed nets and insect repellents. While Annex Q generally lists anti-malarial medications applicable to the deployment, the documents does not require that any-specific drug from the list is to be

prescribed. For example a deployment into a chloroquine resistant malaria endemic area will generally list, mefloquine, doxycycline, and malerone as appropriate medication, Annex Q does not mandate that all personnel take mefloquine.

The final decision of the appropriate anti-malarial for each deployed service member is made by the prescribing physician, who takes into account information regarding the effectiveness of the drug, the patient's co-morbidities, possible drug interactions, and the willingness of the patient to adhere to the drug regime. This is done on a case-by-case basis under a doctor-patient relationship.

Item 9: What risk communications effort is in place to inform members of the risks and benefits of mefloquine use? If mefloquine is indeed as valuable to force health protection as some officials have suggested, is a risk communication effort similar to the Anthrax Vaccine Program indicated?

Communicating the health risks associated with deployments, including the use of operationally indicated medications such as mefloquine, is of high importance within DoD. By definition, deployments are risky. It is incumbent upon commanders to ensure the troops are aware of the risks and know how to prevent or minimize them. To this end DoD has devoted considerable efforts toward health risk communication through the creation of health risk communication centers, training programs and research. Rather than taking the approach of developing a program to specifically address health risk communication for one disease or one drug, a more comprehensive approach is desired that addresses health risk communication as it relates to risk associated with deployments, including anti-malarial medications.

The United States Army Center for Health Promotion and Preventive Medicine (USACHPPM) is a center of excellence for health risk communication and publishes a wide variety of fact sheet and other communication tools.

For Special Operations Forces within the Army, the benefits and risks associated with the use of anti-malarial drugs are discussed with the deploying group during the threat and countermeasure briefing. For deploying conventional forces, health risk information specific for anti-malarials is provided during the Soldier Readiness Process (SRP). (As an example, see the attached Deployment Medication Information Sheet (DMIS) for Mefloquine.) Medical personnel are available during the processing to answer soldiers' questions about immunization, keeping healthy in foreign areas, and about specific health threats and their prevention. "Keeping Fit" handbooks, handouts about disease and environmental hazards, explanations about immunizations, and a whole range of other topics are available in hard copy from USACHPPM on request and are made available to soldiers at the SRP. The individual soldier or medical/ command assets can access these same information products at the USACHPPM website.

DoD Deployment Health Clinical Center (DHCC) at Walter Reed Medical Center serves as an invaluable resource for health care providers as they deal with the health concerns for deployed personnel and their families. The DHCC mission includes developing and implementing clinical practice guidelines pertaining to post-deployment care, providing specialized care for veterans with persistent health concerns or potentially military related exposures after deployment, and collaborating with the VA to establish the congressionally mandated clinical

center for war-related illnesses. The DHCC assists unit commanders and leaders with deployment health risks and post-deployment health care. Through the deployment health web site, http://www.pdhealth.mil, DHCC provides excellent up-to-date information on the health risks associated with specific deployments, to include the risk for malaria. The web site also provides information regarding the adverse events of operationally required medications, including mefloquine, to assist providers in making clinical decisions on which anti-malarial is appropriate for individual patients.

Health risk communication training for providers as an ongoing program is highlighted in upcoming conferences in distant learning projects. The DoD-wide conference on risk communication and terrorism will be held in Alexandria, Virginia on September 9 - 11, 2002. The purpose of the conference is to present and discuss cutting-edge information on clinical risk communication and strengthen health provider-patient relationships. Following the conference, USACHPPM in conjunction with Veterans Affairs and the DoD Deployment Health Clinical Center (DHCC) is conducting health risk communication training program via satellite broadcast. The training is designed to provide health care professionals with the tools they need to effectively communicate risks and technical information to a non-technical, anxious and sometimes frightened audience including patients.

In addition to on-going training efforts, DoD is involved in two research studies aimed at developing better techniques for accomplishing health risk communication among those involved in deployments. Researchers from the DHCC and Rutgers University are conducting the research over the next two year at locations across the Department of Defense. DoD is also soliciting research in the area of health risk communication. Ten grants of approximately $500,000 each are currently available to interested researchers.

Specific health risk communication regarding malaria and anti-malarial medications, programs and processes established by the Combatant Commands are outlined in the following paragraphs.

a. USPACOM. USPACOM's Force Health Protection Plan for Deployments requires that all deploying individuals receive a medical threat briefing delineating the risk potential for that operation. Included in that briefing is information regarding the risks of acquiring malaria if preventive measures are not effectively employed. The possibility of adverse reactions to the anti-malarial drugs is commonly a part of this briefing. Individuals are advised of appropriate preventive measures to avoid these effects (drink plenty of water, avoid too much direct sunlight, etc.). The Travel Medicine Clinic, Tripler Army Medical Center, provides each individual with benefit and risk information when prescribing anti-malarial drugs, a common practice in the medical community.

b. USSOUTHCOM. USSOUTHCOM Regulation 40-10, "Force Health Protection" specify health risk communication actions to be taken by the task force commanders and their JTF surgeons.

c. USSOCOM. Pre-deployment medical threat briefings are given to all deploying Service members. Medical threat briefings are typically focused at three target audiences: leaders, troops, and medical care providers.

d. USJFCOM. During pre-deployment force health protection briefings, Service members are advised of the threat and the risk. The drugs used are discussed, to include benefits and risks as well as the need for other personal protective measures.

e. USCENTCOM. Service member briefing occurs along with an explanation of the medical threat during the pre-deployment process. Service members receive a series of pre-deployment briefings at their home stations.

f. USEUCOM. It is the commander's responsibility to emphasize the dangers posed by malaria and to enforce the requirement so that the troops will take the medication. The medical staff is responsible for individual risk evaluation (as, for example, the risk posed by primaquine to those with glucose –6 phosphate dehydrogenase deficiency (G6PD)) and provide advice to the commander. As the anti-malarials are not investigational new drugs, special steps are not taken to inform Service members of the risks beyond the normal discussion that the attending physician would give anyone for whom he or she is writing a prescription. USEUCOM has had no reports of adverse reactions to taking mefloquine. The Services would have records of any such reactions.

Item 10: Whether it is advisable to conduct a study of communication strategies regarding medications such as mefloquine and the impact of the "nocebo effect" or the power of suggestion.

As mentioned in response to item 9, DoD is currently actively involved in studying strategies for health risk communication towards deployed service members. These activities include studies led by DoD's Deployment Health Clinical Center and the provision of $5 million to fund research proposals from the scientific community. This research may serve as an ideal vehicle to promote additional study of the nocebo phenomenon. This phenomenon may have relevance to many military health issues beyond mefloquine, including the use of other pharmaceuticals, recovery following surgical procedures, and even low-level environmental exposures.

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