An Outbreak of *Plasmodium falciparum* Malaria in U.S. Marines Deployed to Liberia

Timothy J. Whitman,* Philip E. Coyne, Alan J. Magill, David L. Blazes, Michael D. Green, Wilbur K. Milhous, Timothy H. Burgess, Daniel Freilich, Sybil A. Tasker, Ramzy G. Azar, Timothy P. Eady, Christopher D. Clagett, Gregory A. Deye, G. Dennis Shanks, and Gregory J. Martin*

**Infectious Diseases Department, National Naval Medical Center, Bethesda, Maryland; Walter Reed Army Institute of Research, Silver Spring, Maryland; Infectious Diseases Clinical Research Program, Uniformed Services University, Bethesda, Maryland; Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; College of Public Health, University of South Florida, Tampa, Florida; Naval Medical Research Center, Silver Spring, Maryland; Infectious Diseases Division, Department of Medicine, State University of New York, Upstate Medical University, Syracuse, New York; U.S. Navy Environmental and Preventive Medicine Unit Seven, Naples, Italy; Australian Army Malaria Institute, Gallipoli Barracks, Australia**

**Abstract.** In 2003, 44 U.S. Marines were evacuated from Liberia with either confirmed or presumed *Plasmodium falciparum* malaria. An outbreak investigation showed that only 19 (45%) used insect repellent, 5 (12%) used permethrin-treated clothing, and none used bed netting. Adherence with weekly mefloquine (MQ) was reported by 23 (55%). However, only 4 (10%) had serum MQ levels high enough to correlate with protection (> 794 ng/mL), and 9 (22%) had evidence of steady-state kinetics (MQ carboxy metabolite/MQ > 3.79). Tablets collected from Marines met USP identity and dissolution specifications for MQ. Testing failed to identify *P. falciparum* isolates with MQ resistance. This outbreak resulted from under use of personal protective measures and inadequate adherence with chemoprophylaxis. It is essential that all international travelers make malaria prevention measures a priority, especially when embarking to regions of the world with high transmission intensity such as west Africa.

“Good doctors are of no use without good discipline. More than half the battle against disease is not fought by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine (anti-malarial chemoprophylactic drug used in WW II) is taken...if mepacrine was not taken, I sacked the commander. I only had to sack three; by then the rest had got my meaning.”

—Lieutenant General William Slim (1891–1970), Burma Campaign, 1943

**INTRODUCTION**

Military personnel frequently deploy to regions of the world endemic for tropical infectious diseases. One of the most important tropical diseases, malaria, has had a significant impact on the welfare of U.S. servicemen since the Revolutionary War.1,2 Failure to appreciate the importance of malaria led to disastrous results in many units fighting in the South Pacific during World War II.3 More recently, failure to properly use personal protective measures (i.e., topical insect repellent, bed netting, and permethrin-treated clothing) and chemoprophy laxis contributed to outbreaks of malaria in U.S. servicemen deployed to Somalia and Afghanistan.3,5 Physicians reporting these outbreaks concluded that an emphasis on proper adherence to personal protective measures and chemoprophylaxis is essential to prevent malaria during deployments to malaria-endemic regions.3,5

In response to civil unrest, 225 U.S. Marines were sent into Liberia in 2003 to augment the security of the U.S. Embassy and the major airport outside Monrovia.6 After deployment, a febrile illness with symptoms that included fever, headache, and diarrhea developed in approximately 80 Marines. After complicated malaria was diagnosed in several Marines, more than half were evacuated to U.S. military hospitals in Germany and Bethesda, Maryland. This report summarizes the clinical, laboratory, and epidemiologic features of an outbreak of malaria that was unique in severity of illness and attack rate after a brief exposure to a locale with high transmission intensity. It also discusses host and parasite factors that contributed to these apparent chemoprophylaxis failures.

**MATERIALS AND METHODS**

In August 2003, 225 Marines with the 26th Marine Expeditionary Unit aboard U.S. Navy ships were deployed to Roberts International Airport outside the coastal city of Monrovia. Liberia has a tropical climate that includes frequent rainstorms (average rain fall is 78 cm/month) and daytime high temperatures average approximately 27°C in the summer months.8 Additionally, years of conflict and lack of a functioning government has led to the neglect of disease and vector control programs. As a result, Liberia is holoendemic for malaria and has an annual *Plasmodium falciparum* entomologic inoculation rate, defined as the product of the mosquito biting-rate times the proportion of mosquitoes carrying sporozoites in their salivary glands, as high as 62.05 infectious bites per year in some areas.9,10 Deployed Marines worked and slept in an abandoned airport warehouse that had standing water and was infested with rats and mosquitoes (Figure 1). They had already been at sea for several months, most serving briefly in Iraq (April) and Djibouti (July) before arriving in Liberia in August. For malaria chemoprophylaxis during deployment, Marines were issued a supply of generic mefloquine (MQ) hydrochloride (250 mg tablets; Geneva Pharmaceuticals, Dayton, NJ), which were foil-wraped in blister packs. Each Marine was given several blister packs before going ashore in the Middle East and Africa. Adherence with weekly MQ was based on the honor system, not directly observed therapy (DOT). None of the Marines used doxycycline or atovaquone/proguanil as chemoprophy laxis. The unit spent 10 days in Liberia. Within one day after returning to their ships, a febrile illness developed in the first of what amounted to 80 Marines.
In 2003, 44 U.S. Marines were evacuated from Liberia with either confirmed or presumed Plasmodium falciparum malaria. An outbreak investigation showed that only 19 (45%) used insect repellent, 5 (12%) used permethrin-treated clothing, and none used bed netting. Adherence with weekly mefloquine (MQ) was reported by 23 (55%). However, only 4 (10%) had serum MQ levels high enough to correlate with protection (> 794 ng/mL), and 9 (22%) had evidence of steady-state kinetics (MQ carboxy metabolite/MQ > 3.79). Tablets collected from Marines met USP identity and dissolution specifications for MQ. Testing failed to identify P. falciparum isolates with MQ resistance. This outbreak resulted from under use of personal protective measures and inadequate adherence with chemophrophylaxis. It is essential that all international travelers make malaria prevention measures a priority, especially when embarking to regions of the world with high transmission intensity such as west Africa.
The broad differential diagnosis of a febrile illness in these individuals was narrowed when shipboard physicians identified *P. falciparum* in peripheral blood smears of several Marines. Considering the limited diagnostic resources available to rapidly evaluate a large number of patients, the remainder of the febrile Marines were presumed to have malaria and empirically treated with oral quinine sulfate and doxycycline until supplies of atovaquone/proguanil could be flown to the ship (Figure 2). However, the possibility of other febrile diseases associated with such an outbreak in the tropics (e.g., leptospirosis, rickettsial diseases, or Lassa fever) remained a concern. Because of the severity of symptoms in the first Marines in which illness developed, 40 were evacuated to the National Naval Medical Center (NNMC) in Bethesda, Maryland, and 4 to Landstuhl Regional Medical Center in Germany. Remaining Marines with presumptive malaria were in a sufficiently stable condition to receive treatment on ship. Knowing that Liberia is endemic for Lassa fever, there was a possibility

---

**Figure 1.** Warehouse that housed U.S. Marines at Roberts Interactional Airport in Monrovia, Liberia demonstrating numerous risk factors for contracting an arthropod-borne illness including broken windows, persons sleeping on the roof, standing water, and tall grass in the surrounding area, for contracting an arthropod-borne illness. This figure appears in color at www.ajtmh.org.

**Figure 2.** Flow diagram of U.S. Marines ashore in Liberia. † Doxycycline administered for malaria treatment as well as concern for possibility of co-infection with leptospirosis or rickettsial disease.
260 WHITMAN AND OTHERS

some Marines were infected, or co-infected, with Lassa virus
after exposure to rat excreta and as a safety measure, they
were initially cared for with contact and droplet isolation
precautions.12–14

Upon admission, each Marine answered a standard out-
break questionnaire (not anonymous) to obtain data on
symptoms and adherence to personal protection measures
and chemoprophylaxis. Clinical data, which included physi-
cal examination findings and admission laboratory results,
were recorded. Thick and thin peripheral blood smears were
prepared on admission (approximately 48 hours after initia-
tion of treatment with antimalarial drugs while aboard ship).
To facilitate rapid diagnosis of malaria in an outbreak setting,
the NOW ICT Malaria P.f/P.v test (Binax, Inc., Portland, ME)
cards were concurrently used for the first 32 Marines arriv-
ing at NNMC. At the time of this outbreak, this test was not
yet approved by the Food and Drug Administration (FDA)
(Silver Spring, MD) and was used only in conjunction with
standard microscopy.15

Serum levels of MQ and its carboxy metabolite (MMQ)
were measured using previously described methods in 41 of the
44 Marines by the Centers for Disease Control and Prevention
(Atlanta, GA).16,17 The serum level of MQ estimated to pre-
vent clinical illness (breakthroughs in MQ chemoprophylaxis)
is based on observations in U.S. Peace Corps volunteers serv-
ing in west Africa in the early 1990s.18 In that report, a mean
(SD) whole blood MQ level of 384 (174) ng/mL was seen in
25 persons in whom levels were obtained. Probit analysis pre-
dicted 99% prophylactic efficacy could be achieved at a blood
MQ concentration of approximately 915 ng/mL, 95% efficacy
at a concentration of 620 ng/mL, and 90% efficacy at a concen-
tration of 462 ng/mL.18 The serum to whole blood MQ ratio is
1.28.16 Therefore, protection (95% efficacy) against malaria is
associated with serum MQ levels > 794 ng/mL (this value was
determined by multiplying the prophylactic efficacy of MQ in
whole blood [620 ng/mL] by the MQ serum-to-whole blood
ratio of 1.28).16 A ratio of MMQ:MQ in serum greater than
3.79 (95% confidence interval = 3.48–4.10) represents prior
dosing associated with steady-state kinetics but does not cor-
relate with protection.16

To ensure that the tablets provided to the Marines were
actually composed of MQ hydrochloride and met industry
standards for identity and dissolution, five tablets in blister
packs collected from the pockets of Marines with complicated
malaria were sent to an FDA reference laboratory in St. Louis,
Missouri, for analysis.

To evaluate the possibility of MQ-resistant malaria, the
Walter Reed Army Institute of Research (Silver Spring, MD)
cultured isolates of P. falciparum from 10 Marines. Parasites
were expanded in culture in human erythrocytes, and MQ sus-
ceptibility testing was performed by using 1H-hypoxanthine
incorporation assays using standard methods.19 Assays were
performed in duplicate and results reflected mean 50%
hibitory concentration (IC50) values of at least three sepa-
rate assays performed on different dates using control
clones from west Africa and Indochina.20 In addition, we per-
formed polymerase chain reaction (PCR) for these parasites
to detect an increase in copy number of the P. falciparum
multidrug resistance 1 (pfmdr1) gene according to standard
methods.21

With the concern for Lassa virus infection or co-infection,
enzyme-linked immunosorbent assays for IgM and IgG
against Lassa virus and PCR were performed according
to an established method on serum samples from the first
32 Marines arriving in Bethesda at the U.S. Army Medical
Research Institute of Infectious Diseases.22,23

RESULTS

Complete clinical, laboratory, and epidemiologic data were
available for 32 of the 44 Marines. The mean (SD) time spent
ashore was 9.9 (2.6) days, and the mean time for development
of symptoms was 15.4 days after arriving in Liberia (Figure 3).

Figure 3. Epidemic curve showing the onset of symptoms in days after first possible exposure in Liberia. † The symptoms this U.S. Marine reported on day 1 in Liberia were not considered related to malaria.
All patients were men (age range = 19–43 years, median age = 24 years). Anemia, an increase in the level of alanine aminotransferase, and prolonged prothrombin and partial prothrombin times were the most common laboratory findings (Table 1). Fever, headache, and diarrhea were the most common symptoms. Stool studies (culture and examination for ova and parasites) were performed for five Marines with continued complaints of diarrhea on admission in Bethesda; one patient (who also had a negative blood smear for malaria) had a positive stool culture for *Salmonella* spp. group D. Hospital admission days ranged from 1 to 25 days.

Of the 44 Marines, 14 (32%) were confirmed to have malaria by demonstration of asexual parasites in erythrocytes on peripheral blood smears after arrival at Landstuhl or NNMC (Table 2). Ten (31%) of the initial 32 Marines evaluated at NNMC showed positive results for the NOW ICT test.

Most patients received a preventive medicine briefing before arriving in Liberia, which outlined the measures necessary to avoid malaria (Table 1). However, only 19 (45%) used insect repellent on a regular basis, 5 (12%) applied permethrin to clothing, and no one used bed netting. Only 23 (55%) claimed adherence to weekly MQ dosing on the questionnaire. Poor adherence was attributed to forgetfulness.

Serum MQ levels (determined approximately 25 days after arrival in Liberia and 10 days after onset of symptoms) sufficient to provide 95% prophylactic efficacy (MQ > 794 ng/mL) were detected in 4 (10%) Marines, and 9 (22%) had a MMQ:MQ > 3.79 (Table 1). All MQ tablets analyzed met parameters for identity and dissolution as specified in Abbreviated New Drug Application 76,175. The MQ IC₅₀ values for *P. falciparum* isolates ranged from 3.8 ng/mL to 17.6 ng/mL, which indicated that all isolates were susceptible to the drug (MQ resistance is associated with an IC₅₀ > 45 ng/mL) (Table 2). Molecular characterization failed to identify additional copies of the *pfmdr1* gene in these isolates. Serum results for IgM and IgG against Lassa fever virus and PCR results were negative for 32 Marines tested.

### DISCUSSION

The 14 confirmed and 30 presumptive, cases of malaria among the 44 Marines presented represent the largest single outbreak of *P. falciparum* malaria in the U.S. Military since Operation Restore Hope in Somalia during 1993–1994. If the additional 36 presumptive cases that did not require evacuation from the ship are included, this outbreak in 80 patients was the largest cluster of malaria cases in the U.S. Military since the Vietnam Conflict. We now summarize key clinical findings and review host and parasite factors identified in our outbreak investigation that contributed to this event.

The mean onset of symptoms in this cohort was only 15.4 days after initial exposure in Liberia. This time was significantly shorter than a mean of 28 days recorded among British soldiers deployed to Sierra Leone in 2000. In addition, our cohort contracted malaria after only 10 days ashore, which is a considerably shorter duration of exposure compared that in British and French soldiers in whom malaria developed after months in either Sierra Leone or Côte d’Ivoire. In comparison, U.S. servicemen in Somalia had an attack rate that peaked at 30 cases/1,000 persons/per week, and U.S. servicemen in Afghanistan had an attack rate of 52 cases/1,000 persons. We suspect that the markedly higher attack rate in our cohort and the decrease in time to contract disease and time to onset of symptoms were a reflection of high local transmission intensity and the minimal use of malaria preventative measures.

Five Marines met the World Health Organization criteria for the definition of complicated malaria with parasitemia levels ranging from 2% to 17% combined with pulmonary and/or cerebral complications (Table 2). All five required monitoring in an intensive care unit, mechanical ventilation (range = 4–9 days), and vasopressor support. The remaining 39 Marines with uncomplicated malaria were treated with atovaquone/proguanil per guidelines of the Centers for Disease Control and Prevention. All 44 showed complete recoveries.

Fever and headache were the most common initial symptoms in this cohort. Loose stools, a less frequently recognized but common symptom of *P. falciparum* infection, were observed in 62% of the Marines. Of interest, severe diarrhea was a prominent initial symptom among several of the first Marines in which illness developed. This symptom mis-

---

**Table 1**  
Characteristics (n = 44) of U.S. Marines with confirmed or presumed malaria, Liberia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory abnormalities (n = 44)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Anemia (hematocrit &lt; 42%)</td>
<td>35 (80)</td>
</tr>
<tr>
<td>Alanine aminotransferase elevation (&gt; 56 U/L)</td>
<td>22 (50)</td>
</tr>
<tr>
<td>Prothrombin time prolonged (&gt; 14 seconds)</td>
<td>20 (45)</td>
</tr>
<tr>
<td>Partial prothrombin time prolonged (&gt; 42 seconds)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt; 150,000 cells/μL)</td>
<td>19 (43)</td>
</tr>
<tr>
<td>Hypoglycemia (glucose &lt; 76 mg/dL)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Leukopenia (&lt; 4 cells/μL)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Leukocytosis (&gt; 10.5 cells/μL)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Acute renal failure (creatinine &gt; 1.4 mg/dL)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Serum mefloquine measurements (n = 41)</td>
<td></td>
</tr>
<tr>
<td>Mefloquine &gt; 794 ng/mL*</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Carboxy metabolite/mefloquine &gt; 3.79†</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Clinical symptoms (n = 42)</td>
<td></td>
</tr>
<tr>
<td>Fever (&gt; 38°C)‡</td>
<td>35 (83)</td>
</tr>
<tr>
<td>Headache</td>
<td>35 (83)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (62)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Preventive measure (n = 42)</td>
<td>No. (%) compliance</td>
</tr>
<tr>
<td>Attended preventive medicine briefing</td>
<td>39 (93)</td>
</tr>
<tr>
<td>Regularly used insect repellent</td>
<td>19 (45)</td>
</tr>
<tr>
<td>Wore permethrin-treated clothing</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Used bed nets</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adherence to weekly mefloquine</td>
<td>23 (55)</td>
</tr>
<tr>
<td>Reason for poor adherence with mefloquine (n = 19)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Psychiatric concerns</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Mefloquine concentration > 794 ng/mL confers 95% protective efficacy.
† Carboxy metabolite/mefloquine > 3.79 implies steady-state kinetics.
‡ Clinical improvements reported are those recalled by patients; all evacuated marines were reported by the medical staffs of ships to have had temperatures > 38°C.
led shipboard physicians to initially diagnose them with travelers’ diarrhea and treat them empirically with ciprofloxacin while their conditions continued to worsen. In retrospect, the failure to recognize diarrhea as a symptom of malaria led to a delay in diagnosis and prompt initiation of correct treatment.

The use of malaria rapid testing (NOW ICT test) proved to be essential in expeditiously evaluating the first 32 Marines who arrived at NNMC. Because rapid test kits offer speed and accuracy when compared with traditional microscopy, these tests are critical in making a timely diagnosis of malaria in resource-limited environments or in the setting of an outbreak of a febrile illness in travelers returning from the tropics. As a case in point, in the chaotic setting of preparing and reading blood smears for the first 32 Marines arriving at NNMC, one patient was originally reported as having a negative thin blood smear. For the first 32 Marines arriving at NNMC, 15 positive. After further review of the thin blood smear, one patient was originally reported as having a negative thin blood smear. These tests are critical in making a timely diagnosis of malaria and accuracy when compared with traditional microscopy.

Table 2
Clinical characteristics of 14 U.S. Marines with confirmed (smear positive) malaria, Liberia*

<table>
<thead>
<tr>
<th>Patient no./site of initial medical evaluation</th>
<th>Clinical presentation</th>
<th>Peak parasitemia, %</th>
<th>NOW ICT rapid assay result</th>
<th>IC_{50} ng/mL</th>
<th>Serum MQ† level, ng/mL</th>
<th>MMQ/MMQ‡ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Landstuhl, Germany</td>
<td>ARDS</td>
<td>5</td>
<td>ND</td>
<td>Culture not performed</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2/Landstuhl</td>
<td>ARDS</td>
<td>2</td>
<td>ND</td>
<td>9.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3/Bethesda, Maryland</td>
<td>Cerebral malaria</td>
<td>15</td>
<td>+</td>
<td>12.9</td>
<td>80</td>
<td>0.57</td>
</tr>
<tr>
<td>4/Bethesda</td>
<td>ARDS</td>
<td>17</td>
<td>+</td>
<td>17.6</td>
<td>191</td>
<td>0.42</td>
</tr>
<tr>
<td>5/Bethesda</td>
<td>Cerebral malaria</td>
<td>12</td>
<td>+</td>
<td>10.1</td>
<td>Below detection</td>
<td>Below detection</td>
</tr>
<tr>
<td>6/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>–§</td>
<td>No growth</td>
<td>759</td>
<td>0.96</td>
</tr>
<tr>
<td>7/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>16.7</td>
<td>89</td>
<td>7.36</td>
</tr>
<tr>
<td>8/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>3.8</td>
<td>131</td>
<td>1.52</td>
</tr>
<tr>
<td>9/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>16.0</td>
<td>205</td>
<td>6.55</td>
</tr>
<tr>
<td>10/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>12.8</td>
<td>291</td>
<td>2.96</td>
</tr>
<tr>
<td>11/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>Culture not performed</td>
<td>Below detection</td>
<td>Below detection limit</td>
</tr>
<tr>
<td>12/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>0.25</td>
<td>+</td>
<td>Culture not performed</td>
<td>69</td>
<td>2.85</td>
</tr>
<tr>
<td>13/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>+</td>
<td>No growth</td>
<td>79</td>
<td>3.38</td>
</tr>
<tr>
<td>14/Bethesda</td>
<td>Uncomplicated malaria</td>
<td>&lt;0.1</td>
<td>–§</td>
<td>Culture not performed</td>
<td>8999</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*IC_{50} = 50% inhibitory concentration IC_{50} > 45 ng/mL indicates MQ resistance; MQ = mefloquine (corrected serum level); MMQ = mefloquine metabolite (ratio of serum inactive carboxyl metabolite to MQ level). ARDS = acute respiratory distress syndrome; ND = not determined.
†MQ ≥ 794 ng/mL (protective); MQ < 794 ng/mL (not protective).
‡MMQ/MMQ ≥ 3.79 (steady state); MMQ/MMQ < 3.79 (not steady state).
§Determined in Bethesda 48 hours after blood smears were obtained on a ship.
¶Marine resumed MQ prophylaxis as he became ill.

Procedures

Marines were issued MQ without an established plan for DOT, which undoubtedly contributed to only a 55% self-reported adherence rate. Of note, the only explanation reported for missed doses was forgetfulness and not a concern about the highly publicized neuropsychiatric side effects related to MQ (this deployment occurred one year after reports of severe adverse events in soldiers that were initially linked to MQ). The adherence rate to chemoprophylaxis in our cohort was similar to that noted in U.S. service members infected with malaria after deployments to Somalia and Afghanistan.

To explain such poor adherence, it is important to note that these Marines were issued MQ while deployed in Iraq and Djibouti in the months before deployment to Liberia and, regardless of adherence in those settings, malaria did not develop in any of them. Poor adherence in regions with low transmission intensity often has no negative consequences, which may have led the Marines to believe that malaria preventative measures in general are unnecessary. This outbreak accentuates the challenge military and civilian providers face when determining the true need for chemoprophylaxis because malaria transmission intensity varies significantly throughout the world. In addition, it emphasizes the importance of DOT in an operational setting.

Barriers to attaining serum MQ levels high enough to kill blood-stage parasites include poor absorption because of vomiting and increased clearance secondary to diarrhea (an interruption in enterohepatic cycling leads to increased clearance). Although several Marines had loose stools as an initial symptom, none had gastrointestinal symptoms before becoming ill, which suggests that altered absorption (or pharmacokinetics of MQ) and resultant decreased serum levels were factors in this outbreak.

Low serum levels may have resulted from deficiencies in the MQ tablets. However, at the time of admission, all blister packs examined were intact and none had exceeded the stamped expiration date. Although most Marines carried the tested MQ in their pockets for several weeks under a variety of climactic conditions (desert, shipboard, and jungle...
environments), we found no evidence to suggest that a lack of drug potency or bioavailability contributed to low serum MQ levels. In addition, each of the five tablets tested met the FDA recommended dissolution criteria established for MQ hydrochloride.

Finally, despite the FDA-approved regimen of taking MQ at least one week before entering a malarious area, it can take up to 7–9 weeks to reach protective serum concentrations.36 However, an inadequate lead time was not an explanation for subtherapeutic levels because these Marines had been issued MQ for their brief deployment in Djibouti at least a month before entering Liberia. Because MQ regimens also require taking the drug for four weeks after leaving the malarious area, if the Marines were adherent with their chemoprophylaxis, they should have had protective levels upon arriving in Liberia. Consequently, it appears that low serum MQ levels in these Marines were unlikely to be a reflection of a pharmacokinetic problem and most likely resulted from inadequate adherence with weekly dosing.

A drug-resistant strain of *P. falciparum* could have altered the expected efficacy of MQ and been responsible for breakthroughs of prophylaxis. Occasional breakthroughs in non-immune travelers with therapeutic serum levels of MQ have been reported from sub-Saharan Africa, including west Africa.37–39 Although MQ is not widely used in west Africa, halofantrine, a structurally related drug, is widely available and used for treatment of persons with acute *P. falciparum* malaria.40 Resistance to halofantrine may confer cross-resistance to MQ *in vitro* and *in vivo*.41 Confirmation of emerging drug resistance relies on four pillars of proof: molecular markers, confirmatory drug levels, elevated ICs, and known clinical outcome (not reinfection). *In vitro* susceptibility measures the ability of a drug to inhibit the replication of asexual parasites and is often reported as an IC. The ICs values for MQ in strains from west Africa are often higher than other strains worldwide (this had been reported before FDA approval and use of MQ), which suggests that MQ resistance could have contributed to this outbreak.37

Specimens sent for laboratory analysis of MQ levels and for drug susceptibility testing were blinded with regard to clinical symptoms and other laboratory data. Although one parasite in this cohort had an IC of 2-fold more resistant than a control clone from west Africa (Sierra Leone), all isolates were sensitive (IC90 < 45 ng/mL) to MQ, and molecular markers for amplification of the pfmdr1 gene showed no unusual results. On the basis of these findings, we conclude that a MQ-resistant strain of *P. falciparum* was not responsible for this outbreak.

Several important limitations of our outbreak investigation must be considered. First, we report a case series of patients who were evacuated from ships off the coast of Africa to military hospitals. These ships had rudimentary laboratory capacity and limited medical expertise aboard. As a result, we were unable to obtain clinical, laboratory, or epidemiologic data from Marines who remained healthy. Ideally, a case–control study may have increased the power of our conclusions.

Second, only 14 (32%) of the 44 Marines (and 18% of the 80 Marines with febrile illness) were confirmed to have malaria by blood smear. We speculate that the broad-based initiation of empiric antimalarial therapy for febrile Marines while still shipboard (and 1–2 days before at Landstuhl or Bethesda where definitive testing was performed) is the most likely explanation for the low number of confirmed cases of malaria. We acknowledge that there would be a clearer sense of the true incidence of malaria in our cohort if peripheral blood smears were made for all febrile Marines before initiation of therapy and were available for review by expert microscopists.

When considering this second limitation, it is important to note that this outbreak was remarkable for the simultaneous presentation of 80 febrile patients, several of whom were critically ill, on a ship at sea. In light of this situation, once malaria was diagnosed in the initial patients who sought treatment, broad-based empiric antimalarial treatment was initiated to prevent further morbidity, and possible mortality, in this cohort of non-immune persons. Although we presume that all febrile patients had malaria, some Marines with negative blood smears could have been infected with another infectious disease endemic to Liberia such as leptospirosis, a ricketsial illness (that responded to doxycycline), or self-limiting gastroenteritis.

Third, adherence rates to malaria preventative measures were self-reported and based on a non-anonymous questionnaire, which raises questions concerning the true validity of marine responses. We suspect compliance with malaria preventative measures may have been even lower than reported because some Marines may have overestimated their adherence for fear of administrative sanctions.

As seen in the past, this most recent outbreak of malaria in military members resulted from poor adherence with personal protective measures and chemoprophylaxis. In the current political climate, we must assume that U.S. servicemen will be called on again to deploy to regions of the world in which malaria is endemic. Clearly, military members and their leadership must ensure that malaria prevention measures are viewed as equally importantly as other key elements of deployment, e.g., supplies and communications. Additionally, chemoprophylaxis should be given by DOT and, as advocated by Lieutenant General William Slim after witnessing the effects of malaria on British soldiers in World War II, leadership must be held accountable when servicemen do not adhere to DOT.41 Pre-travel discussions with all travelers should address differences in malaria transmission intensity in various regions of the world to guard against complacency with preventive measures and pill fatigue. Providers should use rapid diagnostic tests (e.g., NOW ICT test) and have a low threshold to initiate empiric treatment of malaria when evaluating a febrile patient returning from a tropical environment.

Ultimately, the development of new chemoprophylactic agents and an effective malaria vaccine will aid in the prevention of malaria in all travelers at risk, military and civilian alike. Until then, for the next precipitous deployment into a high transmission area, such as these Marines experienced in Liberia, the use of a drug that is dosed weekly, can take up to 7–9 weeks to achieve protective concentrations, and requires four weeks of post-exposure dosing is clearly suboptimal. Loading-dose regimens of MQ achieve protective drug levels in four days, but using MQ in this manner is not FDA approved.36 Although clearly supported by the peer-reviewed medical literature, Department of Defense policy does not permit the U.S. military to use medical products in a manner that is not FDA approved.42 Therefore,
prescribing a loading dose of MQ cannot be used operationally by the U.S. military.42 The use of chemoprophylactic drugs such as atovaquone/proguanil or doxycycline, which provide protection after the first dose, would offer more rapidly attainable malaria chemoprophylaxis in deployment circumstances such as those encountered by the 26th Marine Expeditionary Unit.

Received December 19, 2009. Accepted for publication April 23, 2010.

Acknowledgments: We thank countless members of the U.S. Navy, Marine Corps, Army, and Air Force who aided in the clinical care of the Marines and in our outbreak investigation; Drs. Peter Jahrling and C. J. Peters for providing expertise in the field of Lassa fever; Michael T. O’Neil, Patrick Rozmajzl, Ted Hadfield, and all the expert malaria slide readers at the Naval Medical Research Center and Walter Reed Army Institute of Research. Silver Spring, MD, for assistance; the Office of Compliance, Center for Drug Evaluation and Research, U.S. Food and Drug Administration for assistance analysis of mefloquine tablets; and Nicholas G. Conger for help with data collection.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, or the U.S. Government. We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document; and that each takes public responsibility for it. NNMC public affairs office reviewed October 2009.

Disclosure: None of the authors have any potential conflicts of interest.

Authors’ addresses: Timothy J. Whitman, David L. Blazes, Sybil A. Tasker, and Ramzy G. Azar, Infectious Diseases Department, Division of Medicine, National Naval Medical Center, Bethesda, MD. Alan J. Magill, Division of Experimental Therapeutics, Walter Reed Army Institute of Research. Silver Spring, MD. Philip E. Coyne and Gregory J. Martin, Infectious Diseases Clinical Research Program, Uniformed Services University, Bethesda, MD. Michael D. Green, Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, GA. Wilber K. Milhous, College of Public Health, University of South Florida, Tampa, FL. Timothy H. Burgess and Daniel Freilich, Naval Medical Research Center, Silver Spring, MD. Timothy P. Endy, Infectious Diseases Division, Department of Medicine, State University of New York, Upstate Medical University, Syracuse, NY. Christopher D. Clagett, U.S. Navy Environmental and Preventive Medicine Unit Seven, Naples Italy. Gregory A. Deye, Walter Reed Army Institute of Research, Silver Spring, MD. G. Dennis Shanks, Army Malaria Institute, Gallipoli Barracks, Enoggera, Brisbane, Queensland, Australia.

REFERENCES


