The spread of chloroquine-resistant *Plasmodium falciparum* malaria has led to increased use of mefloquine prophylaxis by US Peace Corps volunteers in sub-Saharan Africa. We compared long-term mefloquine with other drug regimens for effectiveness and tolerance.

The incidence of *Plasmodium falciparum* infections and of adverse reactions was compared in Peace Corps volunteers who took chloroquine weekly, mefloquine weekly, mefloquine every other week, or weekly chloroquine plus daily proguanil. Weekly mefloquine was 94% more effective than chloroquine (95% CI 86% to 97%), 86% more effective than chloroquine plus proguanil (95% CI 67% to 94%), and 82% more effective than prophylaxis with mefloquine when taken every other week (95% CI 68% to 90%). No serious adverse reactions were observed. Mild adverse events were equally frequent in mefloquine users and chloroquine users, and the frequency of these events declined with increasing duration of prophylaxis.

Mefloquine is an effective and well-tolerated drug for prophylaxis of malaria by short-term and long-term travellers.

**Introduction**

Since 1986, more than 1600 *Plasmodium falciparum* infections have been diagnosed among the approximately 2000 US Peace Corps volunteers in sub-Saharan Africa. These infections have been due in part to the geographical spread of chloroquine-resistant *P. falciparum*. Prophylactic mefloquine was made available to these volunteers in September, 1989, because prophylaxis with chloroquine or chloroquine with proguanil was no longer effective. The manufacturer recommended a regimen of 250 mg mefloquine base weekly for the first 4 weeks then to continue with a 250 mg dose every 2 weeks. This regimen was used by Peace Corps volunteers in West Africa from October, 1989, to April, 1990, but resulted in blood concentrations of mefloquine which were too low during the second week after dosing when the every-other-week regimen to suppress parasitaemia. The Centers for Disease Control and Peace Corps therefore recommended that the dosing regimen should be changed to 250 mg mefloquine every week.

Surveillance of malaria among volunteers started in October, 1989, and was continued unchanged when the frequency of dosing was increased.

The effectiveness of mefloquine prophylaxis was defined as the reduction of the incidence of *P falciparum* in mefloquine users compared with that in volunteers who used other regimens. The relative effectiveness of mefloquine was calculated by dividing the difference between the incidence of *P falciparum* infections among mefloquine users (Im) and users of other drugs (Io) by the incidence among users of other drugs (Io/Im = 1-relative risk). Exact confidence intervals (CIs) were calculated by the method of Fisher. Probit analysis based on the prophylaxis failure risks at different blood concentrations of mefloquine was used to estimate the probability of prophylactic effectiveness at different drug concentrations. Differences in proportions were analysed with χ² and Fisher's exact tests, and distributions of continuous variables were compared by Wilcoxon's rank-sum test.

**Results**

**Effectiveness**

Between October, 1989, and May, 1992, an average of 421 Peace Corps volunteers were in West Africa for a total of 13 487 person-months. Between October, 1989, and November, 1990, mefloquine every 2 weeks was used in West Africa for 3328 person-months. Weekly mefloquine was used between December, 1990, and May, 1992, for a total of 6230 person-months (table I). Between October, 1989, and November, 1990, 45 *P falciparum* infections were diagnosed in volunteers using mefloquine every 2 weeks—ie, an incidence of 1.4 cases per 100 volunteers per month. The monthly incidence of infections was 3.1 per 100 volunteers among users of chloroquine alone (table I). Mefloquine prophylaxis used every other week was thus estimated to be 56% more effective than chloroquine prophylaxis (95% CI 29% to 73%, p = 0.0006). Mefloquine every 2 weeks was 37% more effective than prophylaxis with chloroquine and proguanil (95% CI 3% to 59%, p = 0.03).

The monthly incidence of *P falciparum* infections between December, 1990, and May, 1992, is shown in table I. Prophylaxis with weekly mefloquine was 94% more effective than prophylaxis with chloroquine (95% CI 86% to 97%, p < 0.0001) and 86% more effective than prophylaxis with chloroquine plus proguanil (95% CI 67% to 94%, p < 0.0001). The addition of daily proguanil to weekly chloroquine did not significantly increase the effectiveness of chloroquine during either time period (table I) although there was a trend towards increased effectiveness. Weekly mefloquine was 82% more effective than mefloquine every 2 weeks (95% CI 68% to 90%, p < 0.0001). The wide range of the confidence intervals of the relative risk for users of chloroquine and pyrimethamine-sulfadoxine was due to the small number of person-months in this group.

Blood samples were obtained within 5 days of diagnosis from 25 of the 60 volunteers who developed malaria while taking mefloquine prophylaxis. Mean (SD) mefloquine blood concentration was 384 (176) ng/mL. The clinical presentation of malaria in these volunteers was mild (one volunteer was asymptomatic) and there were few parasites in the blood films.

Our probit analysis suggests that 99% prophylactic efficacy can be achieved at a blood mefloquine concentration of about 915 ng/mL, 95% efficacy at a concentration of 620 ng/mL, and 90% efficacy at 462 ng/mL.

**Compliance**

Compliance with chemoprophylaxis as reported in the questionnaires was not complete. 5% of volunteers who used weekly mefloquine, 6% of volunteers who used mefloquine every 2 weeks, and 10% of volunteers using chloroquine said that they had missed or delayed one or more doses. None said that they had missed chemoprophylaxis frequently but the reported compliance could not be independently verified.

**Malaria in Peace Corps volunteers**

Use of mefloquine by volunteers increased from 37% in November, 1989, to 76% in January, 1991, and 97% in May, 1992. Two years after the introduction of mefloquine the incidence had declined to a pre-epidemic level (figure).

**Side-effects**

No serious adverse drug reactions or hospital admissions associated with any chemoprophylaxis regimen were reported. Apart from nausea, the frequency and type of the mild adverse events reported were similar in mefloquine users and users of chloroquine alone (table II). Only 6

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**TABLE I—INCIDENCE OF INFECTIONS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Person-months</th>
<th>Incidence (month/100 volunteers)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oct 1989-Nov 1990</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>844</td>
<td>26</td>
<td>3.1</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>3328</td>
<td>45</td>
<td>1.4</td>
</tr>
<tr>
<td>Mefloquine every 2 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1818</td>
<td>39</td>
<td>2.1</td>
</tr>
<tr>
<td>Chloroquine and proguanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine and pyrimethamine-sulfadoxine</td>
<td>422</td>
<td>9</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Dec 1990-May 1992</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>236</td>
<td>9</td>
<td>3.8</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>6230</td>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>Mefloquine weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>574</td>
<td>10</td>
<td>1.7</td>
</tr>
<tr>
<td>Chloroquine and proguanil</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II—SIDE-EFFECTS (%)**

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Mefloquine (n = 802)</th>
<th>Chloroquine* (n = 520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strange dreams</td>
<td>24.7</td>
<td>26.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.71</td>
<td>22.11</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Weakness</td>
<td>5.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Visual difficulties</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Any event</td>
<td>40.6</td>
<td>45.8</td>
</tr>
</tbody>
</table>

*With or without proguanil. tp < 0.0001.
prophylactic mefloquine use; such events occurred with the knowledge of no evidence that severe neuropsychiatric reactions result from this prophylaxis caused concern. However, verification of a causal relation requires formal investigations, such as cohort or case-control studies. The results of this study and those of a European cohort study of 140,000 travellers who used malaria chemoprophylaxis indicate that prophylactic mefloquine use is well tolerated. The self-reported minor adverse events are unlikely to be associated specifically with use of mefloquine, since users of chloroquine with or without proguanil reported the same events at the same frequency as mefloquine users. Also, the frequency of these side-effects declined with continued mefloquine prophylaxis. Such events are frequently experienced by Peace Corps volunteers: a random sample survey of 1242 volunteers around the world found that during a 4-month period dizziness was experienced by 33% of volunteers, unsteadiness by 28%, insomnia by 37%, strange dreams by 48%, and depression by 46% (J. Moore, personal communication). However, the questionnaire methods used in our study and the random sample survey may not be sufficiently specific to identify reliably such subjective adverse events as disturbances in the sleep and dream patterns.

The absence of effective and well-tolerated drugs in the 1980s to prevent malaria resulted in varying recommendations for travel to malarious areas and for various categories of travellers. This inability to offer simple, uniform recommendations was confusing for the medical profession and short-term travellers and expatriates and led to widely varying prevention practices. For instance, 68 different drug regimens were used by European and North American short-term travellers to Kenya and use of chemoprophylaxis by expatriates has varied widely. Because mefloquine is highly effective against chloroquine-resistant *P. falciparum* malaria in Africa and is well tolerated, the recommendations for malaria prophylaxis for short-term travellers and expatriate residents can now be simplified.

Mefloquine is the drug of choice for malaria prophylaxis in Africa. Mefloquine use is contraindicated only for people with a known hypersensitivity to the drug. Several cautions are listed for use of mefloquine by drivers, pilots, machine operators, people on beta-blockers, pregnant women, children who weigh less than 15 kg, and those with a history of neuropsychiatric illness. However, these precautions are based on limited evidence or theoretical concerns. If mefloquine cannot be tolerated, daily 100 mg doxycycline is an effective alternative drug, but it is not recommended for pregnant women and children under 8 years. If neither mefloquine nor doxycycline can be used, chloroquine (with or without proguanil) may be recommended; however, these travellers must be advised of chloroquine's limited effectiveness and therefore how to manage febrile illness. Such travellers are often recommended to carry a drug with them (pyrimethamine/sulfadoxine or halofantrine) for self-treatment if medical attention is not available.

Although mefloquine is highly effective in Africa, resistance may develop against this drug. Thus, continued monitoring and detailed documentation of malaria in people who use mefloquine for prophylaxis is essential. Such documentation should include microscopic confirmation of the malaria diagnosis and determination of the mefloquine blood concentration shortly after the onset of symptoms.
The extent of non-capsulate, non-serotypable Haemophilus influenzae (NST) as a cause of serious invasive disease in children has not been fully defined. We describe the epidemiology of these childhood infections from cases identified during a continuing prospective survey of invasive H influenzae disease in children of different age groups have not been fully described. Furthermore, the relative importance of such organisms may increase because of the general introduction of Hib vaccines, which will greatly diminish invasive Hib disease7,8 but not systemic infection caused by NST strains or related non-capsulate variants but not in NST strains belong to one of two distinct groups of organisms—non-capsulate H influenzae (NC) strains that are phylogenetically distinct and separate from the population of capsule strains, and non-capsulate derivatives of Hib9 or possibly other capsule types. Serotyping will not differentiate between these two groups. The genetically distinct populations of NC strains and capsule H influenzae types a-f (including their non-capsulate progeny) can be distinguished by various molecular typing methods. Capsule genes are present in capsule strains or related non-capsulate variants but not in non-capsulate strains or related non-capsulate variants but not in

**Population-based study of non-typable Haemophilus influenzae invasive disease in children and neonates**

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**Introduction**

Whereas capsulate Haemophilus influenzae type b (Hib) causes serious invasive disease in young children, the importance of non-capsulate, non-serotypable H influenzae (NST) is less well established. Although there are numerous reports of children and neonates with NST systemic infections, the attack rate, mortality, and pattern of disease in children of different age groups have not been fully described. Furthermore, the relative importance of such organisms may increase because of the general introduction of Hib vaccines, which will greatly diminish invasive Hib disease but not systemic infection caused by NST or H influenzae of other capsular types.

NST strains belong to one of two distinct groups of organisms—non-capsulate H influenzae (NC) strains that are phylogenetically distinct and separate from the population of capsule strains, and non-capsulate derivatives of Hib or possibly other capsule types. Serotyping will not differentiate between these two groups. The genetically distinct populations of NC strains and capsule H influenzae types a-f (including their non-capsulate progeny) can be distinguished by various molecular typing methods. Capsule genes are present in capsule strains or related non-capsulate variants but not in

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