Provisional Data Report on Malaria Surveillance and Use of Antimalarial Chemoprophylaxis January – December 2003

Malaria Branch
Division of Parasitic Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Prepared by:

Sonja Mali, M.P.H.
Monica E. Parise, M.D.

Questions should be directed to Malaria Branch, phone 770/488-7755.

TABLE OF CONTENTS

Provisional Data Report on Malaria Surveillance and Use of Antimalarial Chemoprophylaxis

January – December 2003

INTRODUCTION

Malaria is caused by infection with any of four species of the protozoan parasite *Plasmodium* (i.e., *P. falciparum, P. vivax, P. ovale, P. malariae*). The *Plasmodium* parasite is transmitted by the bite of an infected anopheline mosquito. Until the 1940s, malaria was endemic in the United States. Since then, malaria case surveillance has been conducted by CDC to monitor malaria infections and patient characteristics and risk factors, to detect locally acquired cases, and to monitor patterns of antimalarial chemoprophylaxis failures among U.S. travelers.

The Malaria Branch at the Centers for Disease Control and Prevention (CDC) makes recommendations for chemoprophylaxis use for U.S. residents traveling to malarious areas. CDC currently recommends chloroquine as the antimalarial drug of choice for those persons visiting malarious areas that do not have reported strains of chloroquine-resistant *P. falciparum*. Since November 2000, U.S. travelers visiting areas where chloroquine-resistance has been reported have been advised by CDC to use the antimalarial drugs atovaquone proguanil (Malarone), doxycycline, or mefloquine (Lariam) for prophylaxis. In early 2003, primaquine was added as a second line antimalarial drug option.

To monitor for evidence of prophylaxis failure among U.S. travelers, CDC performed analysis of provisional malaria surveillance data on reported cases with onset of illness from January 1, 2003 to December 31, 2003.

METHODS

Definition of Terms

The following definitions are used in this report:

- **Laboratory criteria for diagnosis**: demonstration of malaria parasites in blood films.
- **Confirmed Case**: symptomatic or asymptomatic infection that occurs in the United States in a person who has microscopically confirmed malaria parasitemia, regardless of whether the person had previous attacks of malaria while in other countries. A subsequent attack of malaria is counted as an additional case if the demonstrated *Plasmodium* species differs from the initially identified species.

This report also uses terminology describing antimalarial prophylaxis regimens:

- **Recommended drugs**: one of the five drugs that CDC recommends for travel to malarious areas, which include atovaquone/proguanil, chloroquine, doxycycline, mefloquine, and primaquine (1).

- **Non-recommended drugs**: other drugs that may or may not have antimalarial properties but are not among those recommended by CDC for travelers to malarious areas.
- **Prophylaxis failures**: confirmed case of malaria after return to the U.S. among cases who reported adherence to a CDC-recommended drug for travel to malarious areas. Excludes cases of *P. vivax* and *P. ovale* that occurred more than 45 days after return from travel.

Sources of Data

Data regarding malaria cases are reported to both the National Malaria Surveillance System (NMSS) and the National Notifiable Diseases Surveillance System (2). Although both systems rely on passive reporting, the numbers of reported cases might differ because of differences in the collection and transmission of data and in the timing of case reports. Data received through the NMSS serves as the basis for this report.

NMSS also receives detailed clinical and epidemiological data regarding each case (e.g., information concerning the area to which the infected person has traveled). Healthcare providers and/or laboratories identify cases of blood-smear-confirmed malaria. Each slide-confirmed case is reported to local and/or state health departments and to CDC on a uniform case report form that contains clinical, laboratory, and epidemiological information. CDC staff review all report forms at the time of receipt and request additional information if necessary (e.g., when no recent travel to a malarious country is reported). Reports of other cases may be telephoned directly by healthcare providers to

CDC, usually when assistance with diagnosis or treatment is requested. All cases that have been acquired in the United States are investigated, including all induced and congenital cases and possible introduced or cryptic cases. Information derived from the uniform case report form is entered into a database and analyzed.

Information on numbers of prescriptions sold for chloroquine (Aralen and generic chloroquine), mefloquine and Malarone in the United States was provided by GlaxoSmithKline who acquired the data from Verispan (3).

RESULTS

General Surveillance

CDC has received 857 reports of malaria among persons in the United States through NMSS with a date of onset between January 1, 2003 and December 31, 2003.

The infecting species of Plasmodium was identified in 708 (82.6%) of these cases (Table 1).

Eight hundred forty-eight (98.9%) of the 857 cases were imported. Five hundred twenty-six (62.0%) of the 848 cases were in U.S. residents (includes both civilians and military personnel) who acquired the infection outside the United States. The remainder of this report will focus solely on these resident cases. Of the 526 cases, 343 (65.2%) were acquired in Africa, 63 (12.0%) in the Americas and 99 (18.8%) in Asia (Table 2).

The number of imported cases in U.S. residents reported by state or territory is shown in Figure 1.

Use of Chemoprophylaxis in U.S. Residents with Imported Malaria

Information concerning the use of chemoprophylaxis was known for 492 (93.5%) of the 526 U.S. residents who had imported malaria. Two hundred seventy-five (55.9%) of the 492 residents had not taken any chemoprophylaxis, and 93 (42.8%) of the remaining 217 had not taken drugs recommended by CDC for the area visited, which included four people who took a recommended drug in combination with a non-recommended drug and were subsequently excluded from this report. Additionally, three cases did not indicate what type of chemoprophylaxis was taken (n = 3) and one case was a possible transfusion case therefore also excluded from the analysis. Only 120 (24.4%) of the 492 U.S. residents had taken a medication recommended by CDC (2).

Three cases of the 120 case-patients who had taken recommended chemoprophylaxis took a combination of mefloquine and doxycycline, and were excluded from further analysis. Of the 117 case-patients who took one of the drugs recommended by CDC, 65 (55.5%) took mefloquine weekly, 38 (32.5%) took doxycycline daily, 3 (2.6%) took chloroquine, and 11 (9.4%) took Malarone.

Of the 93 case-patients who took a non-recommended antimalarial drug, 40 (43.0%) reported taking chloroquine for travel to areas where chloroquine resistance has been documented.

Malaria Infection After Use of Recommended Prophylaxis

Characteristics of Cases

The characteristics of case-patients who acquired malaria after taking one of the recommended drugs are shown in Table 3.

At least one of the four *Plasmodium* species (*P. falciparum, P. vivax, P. ovale, P. malariae*) was identified in 96 of the 117 case-patients who took a drug recommended by the CDC; three were of mixed species. Cases where there were mixed species or where the species could not be determined (n = 24) were excluded from the following analyses.

Cases of P. vivax or P. ovale. Among the 93 U.S. residents who developed malaria after using recommended chemoprophylaxis, 46 cases (49.5%) were caused by *P. vivax* (n = 41) or *P. ovale* (n = 5). Thirteen of these cases occurred more than 45 days after the patients returned to the United States and thus were consistent with relapsing infections and do not indicate prophylaxis failures. Information was insufficient, because of missing data regarding symptom onset or return date, to assess whether 20 cases were relapsing infections. Eleven cases of *P. vivax* and two cases of *P. ovale* occurred within 45 days after the patient returned to the United States. No cases of *P. vivax* or *P. ovale* occurred before return to the United States. Details of the country of acquisition, drugs taken, and chemoprophylaxis are shown in Table 4. No blood specimen was available for testing drug levels in any of these cases.

Cases of P. falciparum or P. malariae. Among the 93 malaria-infected U.S. residents who took recommended prophylaxis who had one species identified, 43 (46.2%) had *P. falciparum* and 4 (4.3%) had *P. malariae.* Details of the country of acquisition, drugs taken, and chemoprophylaxis are shown in Table 4. No blood specimen was available for testing drug levels in any of these cases and all adherence data are self-reported by the patients.

Prophylaxis failure rates (Table 5). In the year 2003, there were a total of 90,000 prescriptions sold for chloroquine (Aralen and generic chloroquine), 205,000 prescriptions sold for mefloquine (Lariam and generic mefloquine) and 135,000 prescriptions sold for Malarone. We assumed the vast majority of these prescriptions were taken for malaria prophylaxis and not treatment. There were no prophylaxis failures documented for those who were adherent to chloroquine. The prophylaxis failure rate for mefloquine among cases who reported being adherent was 5.85 per 100,000 prescriptions. Three cases of prophylaxis failures were documented among those who were adherent to Malarone. The prophylaxis failure rate for Malarone among cases who reported being adherent was 2.22 per 100,000 prescriptions. The rate for prophylaxis failures among those who were adherent to Malarone and mefloquine was 2.22 and 5.85, respectively with a rate ratio (95% CI) of 0.38 (0.12, 1.25). The method of significance testing used was derived from a Wilson interval estimate for a single proportion (4). Since there are many clinical uses of doxycycline (as opposed to mefloquine and Malarone being solely indicated for malaria prophylaxis or treatment), one cannot

calculate malaria prophylaxis failure rates based on number of prescriptions sold for doxycycline.

DISCUSSION

Eight hundred forty-eight cases of imported malaria between January and December 2003, including 526 in U.S. residents, were reported to CDC.

One reason for conducting malaria surveillance is to monitor for failures of chemoprophylaxis, which may indicate the emergence of drug resistance in new areas. However, 368 (74.8%) of the 492 imported malaria cases among U.S. residents who had information available regarding chemoprophylaxis occurred in persons who were either not taking prophylaxis or were taking non-recommended prophylaxis for the region to which they were traveling. Of the 120 (24.4%) persons who reported taking recommended prophylaxis, 13 (10.8%) were likely relapses of *P. vivax* or *P. ovale* infections that would not be prevented by most of the available drugs such as mefloquine or doxycycline, which are blood schizonticides.

A minor limitation of this report was that a small amount of case-surveillance data was missing. Even after contacting healthcare providers or local/ state departments of health, thirty-four (6.5%) of the 526 malaria case surveillance reports of imported malaria in U.S. residents had missing information on whether or not chemoprophylaxis was used.

The current form also includes information on self-reported adherence to prophylactic regimens that was incorporated in the definition of prophylaxis failure. Data on adherence were available for 53 (88.3%) of the 60 non-relapsing cases. Only 18 prophylaxis failures occurred among those who reported adherence to prophylaxis, suggesting continued efficacy of these drugs.

Mefloquine and Malarone prophylaxis failures among those who reported adherence to prophylaxis translates to a rate ratio (95% confidence interval) of 0.38 (0.12, 1.25), and thus there appear to be no differences among the rates. In summary and most importantly, when travelers take appropriate chemoprophylaxis, prophylactic failures rates, as demonstrated here, are very low.

ACKNOWLEDGMENT

The authors gratefully acknowledge those health-care providers, laboratories, and local or state health departments for reporting data to the CDC.

References

1. Centers for Disease Control and Prevention. Health information for international travel, 2002-2003. Atlanta: US Department of Health and Human Services, Public Health Service, 2001.
2. Louise CM. et al. Malaria Surveillance – United States, 2000. In: CDC Surveillance Summaries, July 12, 2002. MMWR 2002; 51 (No. SS-05): 9-21.
3. Verispan Prescription Audit, June 2003
4. Newcombe, R. G. (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine, 17, 857–872.

Table 1. Total number of reported malaria cases -- United States, January - December 2003

Plasmodium Species	Number	(%)
P. falciparum	416	48.5
P. vivax	232	27.1
P. malariae	27	3.1
P. ovale	23	2.7
Undetermined	149	17.4
Mixed	10	1.2
Total	857	100.0

Figure 1. Number of imported malaria cases in U.S. residents, by state in which malaria was diagnosed – United States, January– December 2003 (n=526)

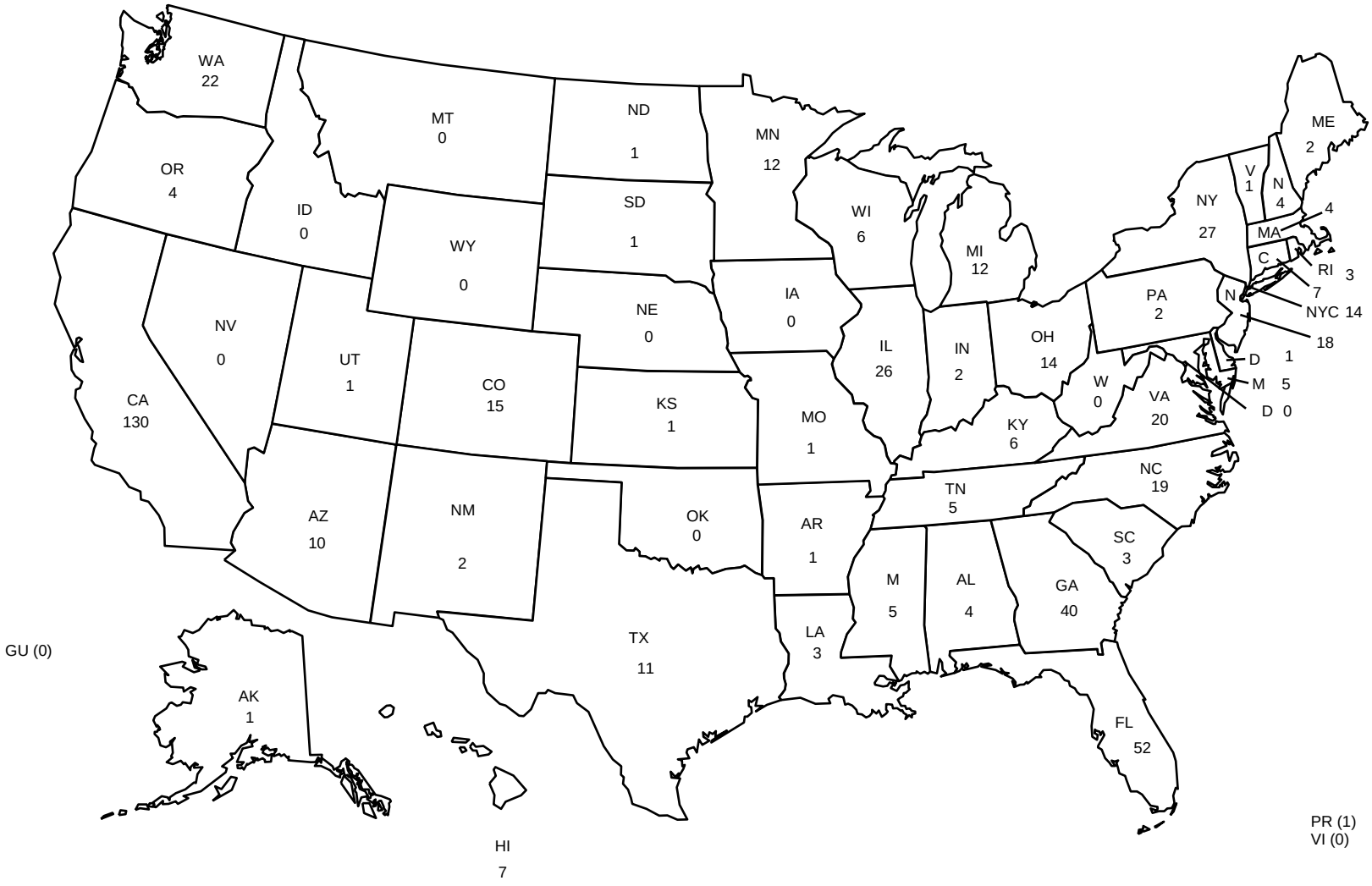

Table 2. Number of imported malaria cases in U.S. residents, by *Plasmodium* species and area of acquisition - United States, January - December 2003

Country	P. falciparum	P. vivax	P. malariae	P. ovale	Unknown	Mixed	Total
Africa	**248**	**16**	**11**	**13**	**52**	**3**	**343**
Angola	1	0	0	0	0	0	1
Benin	0	0	0	0	0	1	1
Burkina Faso	1	0	0	0	0	0	1
Cameroon	8	2	1	1	0	0	12
Central African Republic	1	0	0	0	0	0	1
Comoros	0	0	0	0	1	0	1
Congo	6	0	0	0	0	0	6
Equatorial Guinea	2	0	0	0	1	0	3
Ethiopia	0	0	0	2	2	0	4
Gabon	0	0	0	0	0	2	2
Gambia	2	0	2	0	0	0	4
Ghana	43	1	0	1	3	0	48
Guinea	2	1	0	0	2	0	5
Ivory Coast	7	0	0	1	1	0	9
Kenya	23	2	0	1	4	0	30
Liberia	4	0	0	0	1	0	5
Malagasy Republic	1	0	0	0	0	0	1
Malawi	1	0	0	0	0	0	1
Mali	1	0	0	0	0	0	1
Mozambique	1	0	1	0	0	0	2
Niger	1	0	0	0	1	0	2
Nigeria	84	2	2	3	17	0	108
Senegal	6	1	0	0	4	0	11
Sierra Leone	11	0	1	0	1	0	13
Somalia	1	0	0	0	0	0	1
South Africa	2	1	1	0	0	0	4
Sudan	1	0	0	0	0	0	1
Tanzania	1	0	1	0	1	0	3
Uganda	8	3	1	2	6	0	20
Zambia	3	0	0	0	0	0	3
Zimbabwe	4	0	0	0	0	0	4
Africa, West Unspecified	9	0	0	1	2	0	12
Africa, Unspecified	13	3	1	1	5	0	23
Asia	**6**	**80**	**2**	**1**	**9**	**1**	**99**
Afghanistan	0	8	0	0	3	0	11
Cambodia	0	2	0	0	0	0	2
China	0	1	0	0	0	0	1
India	2	37	1	0	2	0	42
Indonesia	1	9	0	1	1	0	12
Iraq	0	7	0	0	1	0	8
South Korea	0	7	0	0	0	0	7
Laos	1	0	0	0	0	0	1
Pakistan	1	7	1	0	0	0	9
Phillippines	0	0	0	0	1	0	1
Thailand	0	1	0	0	0	1	2
Vietnam	1	1	0	0	0	0	2
Southeast Asia, Unspecified	0	0	0	0	1	0	1

Central America and Carribbean	**15**	**17**	**1**	**0**	**10**	**0**	**43**
Costa Rica	1	0	0	0	1	0	2
Dominican Republic	0	1	0	0	0	0	1
El Salvador	0	1	0	0	0	0	1
Guatemala	1	2	0	0	1	0	4
Haiti	11	1	0	0	2	0	14
Honduras	2	11	1	0	6	0	20
Nicaragua	0	1	0	0	0	0	1
North America	**1**	**5**	**0**	**0**	**0**	**0**	**6**
Mexico	1	5	0	0	0	0	6
South America	**2**	**7**	**0**	**0**	**3**	**2**	**14**
Brazil	1	3	0	0	1	0	5
Ecuador	0	0	0	0	1	1	2
Guyana	1	2	0	0	0	1	4
Peru	0	1	0	0	1	0	2
America, South Unspecified	0	1	0	0	0	0	1
Oceania	**0**	**12**	**2**	**0**	**6**	**0**	**20**
Marshall Islands	0	0	1	0	0	0	1
Papua New Guinea	0	10	1	0	6	0	17
Solomon Islands	0	1	0	0	0	0	1
Pacific, South Unspecified	0	1	0	0	0	0	1
Unknown	**1**	**0**	**0**	**0**	**0**	**0**	**1**
Country	**P. falciparum**	**P. vivax**	**P. malariae**	**P. ovale**	**Unknown**	**Mixed**	**Total**
Total	**273**	**137**	**16**	**14**	**80**	**6**	**526**

Table 3. Characteristics of imported malaria cases in U.S. residents who took recommended prophylactic regimens (n=117), January - December 2003

Characteristic*	Mefloquine (n =65)	Doxycycline (n = 38)	Chloroquine** (n = 3)	Malarone (n = 11)
Age in years; mean (SD)	31.5 (18.6)	33.7 (18.4)	31.3 (34.9)	36.4 (18.3)
Gender (male); no (%)	42 (64.6)	28 (73.7)	1 (33.3)	3 (27.3)
Species (%)				
P. falciparum	31 (48.4)	8 (21.1)	0 (0)	4 (36.4)
P. vivax	19 (29.7)	19 (50.0)	1 (50.0)	2 (18.2)
P. ovale	3 (4.7)	0 (0)	0 (0)	2 (18.2)
P. malariae	2 (3.1)	2 (5.3)	0 (0)	0 (0)
Unknown	10 (15.4)	8 (21.1)	2 (33.3)	3 (27.3)
Mixed	0 (0)	1 (2.6)	0 (0)	0 (0)
Top 2 States reporting highest number of malaria cases	Illinois (n=5) New Jersey (n=4)	California (n=12) Virgina (n=5)	Washington, Virginia, New Mexico (n=1 each)	California, New York (n=1 each)
Top 2 Countries or regions of acquisition with highest number of cases	Nigeria (n=14) Afghanistan, Ghana (n=6 each)	Indonesia (n=7) Ghana, Iraq (n=5 each)	Honduras (n=3)	Kenya (n=5) Cameroon, Ethiopia, India, Iraq,Uganda (n=1 each)
Patients who were hospitalized; no (%)	37 (56.9)	19 (50.0)	1 (33.3)	5 (45.5)
Patients with complicated malaria; no (%)***	0 (0)	0 (0)	0 (0)	0 (0)
Fatal Cases	1 (1.5)	0 (0)	0 (0)	1 (9.1)

* There were no statistically significant differences in age, gender, whether hospitalized, presence of complications, or whether case resulted in a fatal outcome among the different drugs.

** Includes only those persons who used chloroquine for travel to areas where chloroquine resistance has not been documented.

*** Includes cerebral malaria, renal failure, or adult respiratory distress syndrome.

Table 4. Imported non-relapsing* malaria infections in U.S. residents after use of recommended prophylaxis, (n =60)

Plasmodium Species	Month of Onset	Country of Acquisition	Drug Taken	Adherence to Prophylaxis	No. of days after return to the U.S.
P. vivax					
1	October	Africa	Mefloquine	Yes	1
2	August	Iraq	Doxycycline	No	3
3	October	Indonesia	Doxycycline	No	4
4	July	Solomon Islands	Doxycycline	No	9
5	August	Mexico	Doxycycline	Unknown	9
6	May	Brazil	Doxycycline	Yes	9
7	October	Indonesia	Doxycycline	No	10
8	May	Iraq	Doxycycline	No	10
9	December	Guyana	Mefloquine	No	13
10	September	Indonesia	Doxycycline	No	30
11	October	Kenya	Mefloquine	No	36
P. falciparum					
1	April	Ghana	Mefloquine	Yes	0
2	November	Ghana	Mefloquine	Yes	0
3	Unknown	Nigeria	Mefloquine	No	0
4	January	Ghana	Mefloquine	No	0
5	July	Kenya	Malarone	Yes	1
6	November	Nigeria	Mefloquine	No	1
7	June	Liberia	Mefloquine	No	1
8	August	Mali	Mefloquine	Yes	2
9	September	Ghana	Doxycycline	No	3
10	August	Nigeria	Mefloquine	No	3
11	October	Cameroon	Mefloquine	No	5
12	June	Africa, West	Doxycycline	No	7
13	September	Uganda	Mefloquine	Yes	7
14	October	Nigeria	Mefloquine	No	8
15	September	Ghana	Mefloquine	No	9
16	July	Ghana	Doxycycline	No	12
17	January	Uganda	Mefloquine	No	13
18	Unknown	Africa, West	Mefloquine	No	16
19	December	Nigeria	Doxycycline	No	17
20	June	Kenya	Mefloquine	No	17
21	December	Nigeria	Mefloquine	No	19
22	January	Kenya	Malarone	Yes	23

23	April	Ghana	Mefloquine	Unknown	24
24	August	Kenya	Mefloquine	Yes	34
25	Unknown	Malawi	Mefloquine	Yes	42
26	December	Nigeria	Mefloquine	Yes	Ill before return
27	March	Ghana	Mefloquine	Yes	Ill before return
28	April	Kenya	Mefloquine	No	400
29	April	Nigeria	Mefloquine	Yes	86
30	Unknown	Kenya	Malarone	No	Unknown
31	August	Sierra Leone	Mefloquine	Yes	Unknown
32	October	Brazil	Mefloquine	No	86
33	May	Guyana	Doxycycline	No	Unknown
34	October	Nigeria	Mefloquine	Yes	Unknown
35	July	Ghana	Doxycycline	Unknown	Unknown
36	July	Nigeria	Mefloquine	No	Unknown
37	August	Ivory Coast	Mefloquine	No	Unknown
38	August	Africa	Mefloquine	Unknown	Unknown
39	October	Nigeria	Doxycycline	Yes	Unknown
40	Unknown	Kenya	Malarone	Yes	Unknown
41	August	Africa	Mefloquine	No	Unknown
42	Unknown	Congo	Mefloquine	Unknown	Unknown
43	July	Zimbabwe	Doxycycline	No	Unknown

P. malariae

1	August	South Africa	Mefloquine	Unknown	43
2	August	Mozambique	Doxycycline	No	54
3	July	Uganda	Doxycycline	Yes	Unknown
4	August	Tanzania	Mefloquine	No	Unknown

P. ovale

1	April	Ethiopia	Mefloquine	Unknown	32
2	April	Ethiopia	Mefloquine	No	40

* Excludes *P. vivax or P. ovale* infections occurring more than 45 days after return from travel.
Data include all non-relapsing infections, whether or not adherence to recommended prophylaxis was reported

Table 5a. Number of prophylactic failures*, by *Plasmodium* species and recommended drug among those who reported adherence to prophylaxis -- United States, January - December 2003

Plasmodium Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	Malarone	
P. vivax	1	1	0	0	2
P. falciparum	11	1	0	3	15
P. malariae	0	1	0	0	1
P. ovale	0	0	0	0	0
Total	12	3	0	3	18

*only includes cases that reported adherence to recommended drug

Table 5b. Number of prophylactic failures, by *Plasmodium* species and recommended drug among those whose adherence status is unknown-- United States, January - December 2003

Plasmodium Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	Malarone	
P. vivax	0	1	0	0	1
P. falciparum	3	1	0	0	4
P. malariae	1	0	0	0	1
P. ovale	1	0	0	0	1
Total	5	2	0	0	7