Provisional Data Report on Malaria Surveillance and Use of Antimalarial Chemoprophylaxis January – December 2004

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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 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, 2004 to December 31, 2004.

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 six drugs that CDC recommends for travel to malarious areas, which include atovaquone/proguanil, chloroquine, hydroxychloroquine, 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 838 reports of malaria among persons in the United States through NMSS with a date of onset between January 1, 2004 and December 31, 2004.

The infecting species of *Plasmodium* was identified in 642 (76.6%) of these cases (Table 1).

Eight hundred thirty-four (99.5%) of the 838 cases were imported. Four hundred ninty-five (59.3%) of the 834 imported 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 495 cases, 311 (62.8%) were acquired in Africa, 783 (16.8%) in Asia and 8 (15.8%) in the Americas (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 445 (89.9%) of the 495 U.S. residents who had imported malaria. Two hundred sixty-four (59.3%) of the 445 residents had not taken any chemoprophylaxis and 9 residents did not specify what type of chemoprophylaxis was taken. Fifty-two (30.2%) of the remaining 172 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. Only 120 (27.0%) of the 445 U.S. residents had taken a medication recommended by CDC (2).

Of the 120 case-patients who took one of the drugs recommended by CDC, 74 (61.7%) took mefloquine weekly, 24 (20.0%) took doxycycline daily, 14 (11.7%) took Malarone, and 8 (6.7%) took chloroquine.

Of the 52 case-patients who took a non-recommended antimalarial drug, 22 (42.3%) 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. No blood specimen was available for testing drug levels in any of these cases and all adherence data are self-reported by the patients.

At least one of the four *Plasmodium* species (*P. falciparum, P. vivax, P. ovale, P. malariae*) was identified in 86 of the 120 case-patients who took a drug recommended by the CDC; two cases were mixed species which were excluded from the following analyses.

Cases of P. vivax or P. ovale. Among the 84 U.S. residents who developed malaria after using recommended chemoprophylaxis, 43 cases (51.2%) were caused by *P. vivax* (n = 37) or *P. ovale* (n = 6). Twenty-one 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 16 cases were relapsing infections. Six of *P. vivax* and no 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 84 malaria-infected U.S. residents who took recommended prophylaxis who had one species identified, 38 (45.2%) had *P. falciparum* and 3 (3.6%) had *P. malariae.* Details of the country of acquisition, drugs taken, and chemoprophylaxis are shown in Table 4.

Prophylaxis failure rates (Table 5). In the year 2004, there were a total of 105,000 prescriptions sold for chloroquine (Aralen and generic chloroquine), 214,000 prescriptions sold for mefloquine (Lariam and generic mefloquine) and 199,000 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 5.61 per 100,000 prescriptions. Four cases of prophylaxis failures were documented among those who were adherent to Malarone. Additionally, there were 9 cases of prophylaxis failures among those who were adherent to mefloquine. The prophylaxis failure rate for Malarone among cases who reported being adherent was 2.01 per 100,000 prescriptions. The rate for prophylaxis failures among those who were adherent to Malarone and mefloquine was 2.01 and 5.61, respectively with a rate ratio (95% CI) of 0.36 (0.12, 1.05). 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 thirty-four cases of imported malaria between January and December 2004, including 495 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, 316 (71.0%) of the 445 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 persons who reported taking recommended prophylaxis, 21 (17.5%) 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 and would not be included as a chemoprophylaxis failure in this report.

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, fifty (10.1%) of the 495 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 44 (93.6%) of the 47 non-relapsing cases. Seventeen prophylaxis failures occurred among those who reported adherence to prophylaxis.

Mefloquine and Malarone prophylaxis failures among those who reported adherence to prophylaxis translates to a rate ratio (95% confidence interval) of 0.36 (0.12, 1.05), 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.

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Table 1. Total number of reported malaria cases -- United States, January - December 2004

Plasmodium Species	Number	(%)
P. falciparum	368	43.9
P. vivax	217	25.9
P. malariae	27	3.2
P. ovale	21	2.5
Undetermined	196	23.4
Mixed	9	1.1
Total	838	100.0

Figure 1. Number of imported malaria cases in U.S. residents, by state in which malaria was diagnosed – United States, January– December 2004 (n=495)

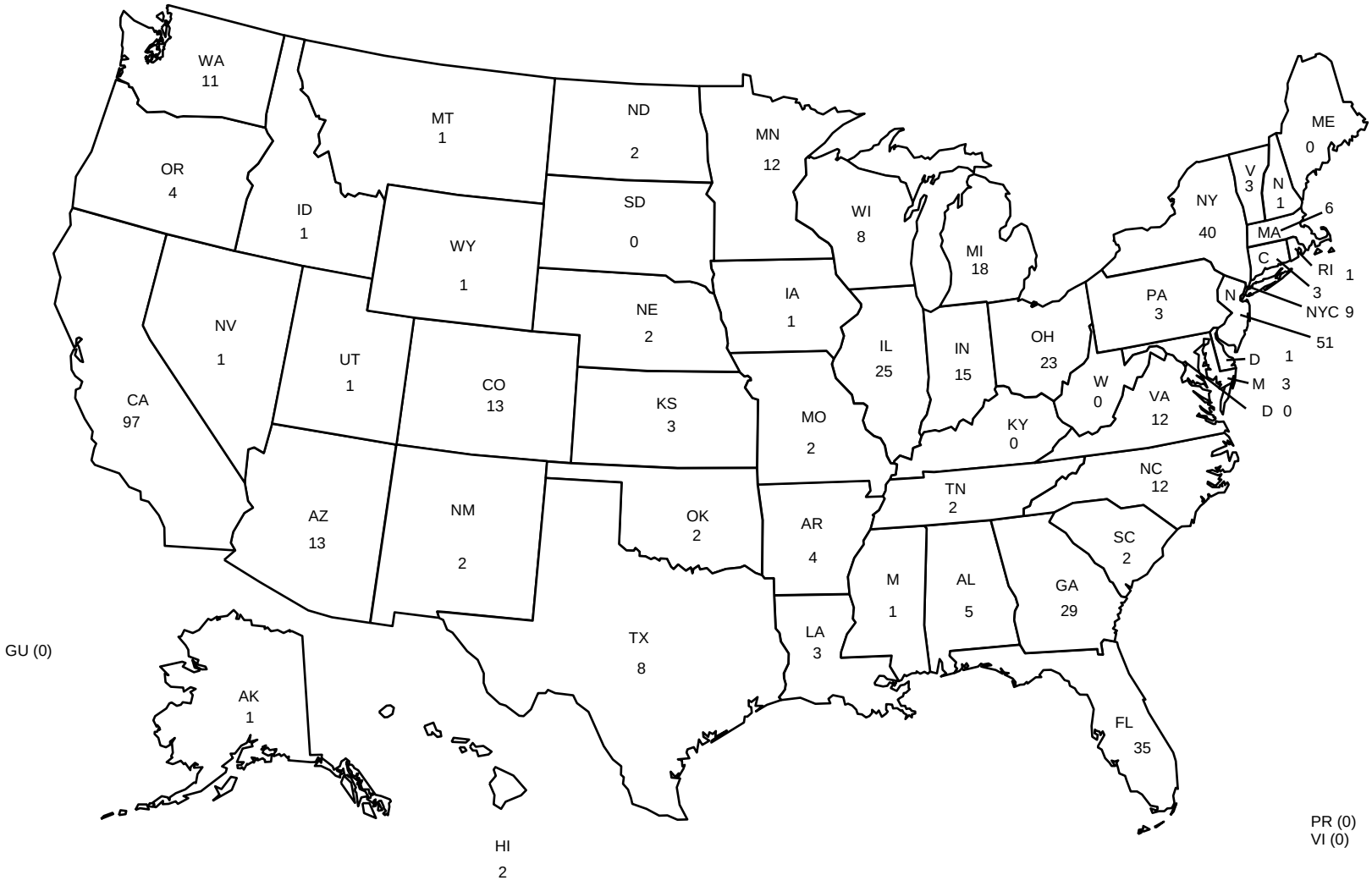

Table 2. Number of imported malaria cases in U.S. residents, by *Plasmodium* species and area of acquisition - United States, January - December 2004

Country	P. falciparum	P. vivax	P. malariae	P. ovale	Unknown	Mixed	Total
Africa	198	24	10	13	62	4	311
Angola	0	0	0	0	1	0	1
Benin	3	0	0	0	0	0	3
Burkina Faso	2	0	0	0	3	0	5
Cameroon	7	2	0	1	1	0	11
Chad	1	0	0	0	0	0	1
Congo	1	0	0	0	0	1	2
Djibouti	0	2	0	0	0	1	3
Ethiopia	0	1	0	0	1	0	2
Gambia	1	1	0	0	0	0	2
Ghana	17	2	2	4	1	0	26
Guinea	3	0	0	0	0	0	3
Ivory Coast	3	2	0	0	2	0	7
Kenya	16	0	2	2	4	1	25
Liberia	7	0	0	0	2	0	9
Malagasy Republic	1	2	1	0	0	0	4
Malawi	1	0	0	0	0	0	1
Mali	1	0	0	0	0	0	1
Mozambique	2	0	0	0	0	0	2
Niger	2	0	1	0	1	0	4
Nigeria	75	2	2	2	17	1	99
Rwanda	0	1	0	0	1	0	2
Senegal	2	0	0	0	1	0	3
Sierra Leone	15	1	0	0	6	0	22
South Africa	1	2	0	0	0	0	3
Sudan	0	0	0	1	1	0	2
Tanzania	1	0	0	0	0	0	1
Togo	4	0	0	0	1	0	5
Uganda	14	1	1	1	8	0	25
Zambia	1	0	0	0	2	0	3
Zimbabwe	1	0	0	0	0	0	1
Africa, West Unspecified	3	1	0	0	5	0	9
Africa, Unspecified	13	4	1	2	4	0	24
Asia	10	57	1	1	12	3	84
Afghanistan	0	8	1	0	0	0	9
Burma	0	1	0	0	0	0	1
Cambodia	0	1	0	0	0	0	1
China	0	0	0	0	1	0	1
India	8	34	0	0	7	2	51
Indonesia	1	3	0	0	1	0	5
Iraq	1	0	0	0	0	0	1
South Korea	0	3	0	0	1	0	4
Pakistan	0	5	0	0	1	0	6
Phillippines	0	2	0	0	0	0	2
Saudi Arabia	0	0	0	1	0	0	1
Sri Lanka	0	0	0	0	1	0	1
Vietnam	0	0	0	0	0	1	1

Country	P. falciparum	P. vivax	P. malariae	P. ovale	Unknown	Mixed	Total
Central America and Carribbean	19	20	1	1	16	0	57
Belize	0	1	0	1	0	0	2
Costa Rica	2	1	0	0	3	0	6
Dominican Republic	2	0	0	0	0	0	2
El Salvador	0	1	0	0	2	0	3
Guatemala	0	4	0	0	2	0	6
Haiti	11	0	1	0	1	0	13
Honduras	3	12	0	0	6	0	21
Nicaragua	0	0	0	0	1	0	1
Panama	0	1	0	0	0	0	1
Central America, Unspecified	1	0	0	0	1	0	2
North America	0	3	0	0	1	0	4
Mexico	0	3	0	0	1	0	4
South America	4	8	0	0	4	1	17
Brazil	1	3	0	0	1	1	6
Colombia	1	0	0	0	0	0	1
Ecuador	0	1	0	0	1	0	2
Guyana	2	1	0	0	2	0	5
Peru	0	3	0	0	0	0	3
Oceania	2	13	0	1	5	0	21
American Samoa	0	0	0	0	1	0	1
Papua New Guinea	2	10	0	1	4	0	17
Solomon Islands	0	1	0	0	0	0	1
Vanuatu	0	2	0	0	0	0	2
Unknown	1	0	0	0	0	0	1
Country	P. falciparum	P. vivax	P. malariae	P. ovale	Unknown	Mixed	Total
Total	234	125	12	16	100	8	495

Table 3. Characteristics of imported malaria cases in U.S. residents who took recommended prophylactic regimens (n=120), January - December 2004

Characteristic*	mefloquine (n =74)	doxycycline (n = 24)	chloroquine** (n = 8)	Malarone (n = 14)
Age in years; mean (SD)	31.3 (16.4)	34.2 (14.2)	32.1 (19.7)	34.1 (12.6)
Gender (male); no (%)	48 (64.9)	15 (62.5)	7 (87.5)	8 (57.1)
Species (%)				
P. *falciparum*	23 (31.1)	11 (45.8)	1 (12.5)	3 (21.4)
P. *vivax*	25 (33.8)	3 (12.5)	4 (50.0)	5 (35.7)
P. *ovale*	4 (5.4)	0 (0)	0 (0)	2 (14.3)
P. *malariae*	1(1.4)	2 (8.3)	0 (0)	0 (0)
Unknown	19 (25.7)	8 (33.3)	3 (37.5)	4 (28.6)
Mixed	2 (2.7)	0 (0)	0 (0)	0 (0)
Top 2 States reporting highest number of malaria cases	California (n=12) New York (n=9)	California (n=5) Georgia (n=3)	Indiana (n=2)	California (n=7)
Top 2 Countries or regions of acquisition with highest number of cases	Kenya, Papua New Guinea (n=7 each) India, Nigeria (n=6 each)	Uganda (n=3) Burkina Faso, Ghana, India, Ivory Coast, Kenya, Liberia (n=2 each)	Honduras (n=4) Guatemala (n=2)	Brazil (n=3) Ghana (n=2 each)
Patients who were hospitalized; no (%)	37 (50.0)	10 (41.7)	7 (87.5)	7 (50.0)
Patients with complicated malaria; no (%)***	2 (2.7)	0 (0)	1 (12.5)	0 (0)
Fatal Cases	2 (2.7)	0 (0)	0 (0)	0 (0)

* 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 =47)

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	February	Pakistan	Mefloquine	Unknown	0
2	December	Peru	Mefloquine	Yes	4
3	December	Burma	Malarone	Unknown	14
4	May	Indonesia	Mefloquine	No	16
5	April	Brazil	Malarone	Yes	38
6	April	Papua New Guinea	Doxycycline	Yes	44
P. falciparum					
1	April	Iraq	Doxycycline	No	1
2	June	Ivory Coast	Doxycycline	No	3
3	June	Mozambique	Malarone	Yes	3
4	June	Kenya	Mefloquine	No	3
5	January	Ghana	Mefloquine	No	5
6	January	Nigeria	Mefloquine	No	6
7	August	Mali	Mefloquine	No	6
8	February	Guinea	Mefloquine	Yes	7
9	September	Uganda	Doxycycline	No	9
10	March	Nigeria	Mefloquine	No	9
11	December	Honduras	Chloroquine	No	10
12	September	Sierra Leone	Mefloquine	No	11
13	June	Chad	Doxycycline	Yes	14
14	August	Kenya	Doxycycline	No	16
15	January	Nigeria	Malarone	Yes	16
16	February	Ghana	Doxycycline	No	19
17	September	Africa, West	Malarone	Yes	22
18	August	Kenya	Doxycycline	Yes	25
19	August	Nigeria	Mefloquine	No	28
20	March	India	Doxycycline	No	34
21	February	Sierra Leone	Mefloquine	No	45
22	October	Nigeria	Mefloquine	Yes	64
23	May	Guyana	Doxycycline	Yes	Ill before return

24	August	West Africa	Mefloquine	No	Ill before return
25	November	Ghana	Mefloquine	Yes	Ill before return
26	Unknown	Uganda	Doxycycline	No	Unknown
27	April	Liberia	Doxycycline	No	Unknown
28	Unknown	Kenya	Mefloquine	No	Unknown
29	Unknown	Kenya	Mefloquine	No	Unknown
30	Unknown	Sierra Leone	Mefloquine	No	Unknown
31	Unknown	Kenya	Mefloquine	No	Unknown
32	July	Nigeria	Mefloquine	No	Unknown
33	May	Mozambique	Mefloquine	Yes	Unknown
34	Unknown	Congo	Mefloquine	Yes	Unknown
35	Unknown	Niger	Mefloquine	No	Unknown
36	August	Africa	Mefloquine	Yes	Unknown
37	Unknown	Ghana	Mefloquine	No	Unknown
38	Unknown	Papua New Guinea	Mefloquine	Yes	Unknown

P. malariae

1	June	Kenya	Doxycycline	Unknown	26
2	April	Uganda	Doxycycline	No	65
3	April	Niger	Mefloquine	Yes	459

P. ovale**

* Excludes *P. vivax or P. ovale* infections occurring more than 45 days after return from travel.
** No *P. ovale* cases occurred within < 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 2004

Plasmodium Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	Malarone	
P. vivax	1	1	0	1	3
P. falciparum	7	3	0	3	13
P. malariae	1	0	0	0	1
P. ovale	0	0	0	0	0
Total	9	4	0	4	17

*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 2004

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