

**Provisional Data Report on Malaria
Surveillance and Use of Antimalarial
Chemoprophylaxis
January – December 2002**

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TABLE OF CONTENTS

Introduction	3
Methods	4
Definition of Terms	4
Sources of Data	5
Results	6
General Surveillance	6
Use of Chemoprophylaxis in U.S. Residents with Imported Malaria	6
Malaria Infection After Use of Recommended Prophylaxis	7
Cases of <i>P. vivax</i> and <i>P. ovale</i>	7
Cases of <i>P. falciparum</i> and <i>P. malariae</i>	8
Prophylaxis failure rates	8
Discussion	9
Acknowledgement	10
Tables & Figure	11

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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 Epidemiology 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.

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, 2002 to December 31, 2002.

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 four drugs that CDC recommends for travel to malarious areas, which include atovaquone/proguanil, chloroquine, doxycycline, and mefloquine (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 serve 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 uniform case report forms is entered into a database and analyzed.

Information on numbers of prescriptions sold for mefloquine and Malarone in the United States was provided by Hoffman-LaRoche who acquired the data from the IMS New Prescription Audit (3).

RESULTS

General Surveillance

CDC has received 912 reports of malaria among persons in the United States through NMSS with a date of onset between January 1, 2002 and December 31, 2002.

The infecting species of Plasmodium was identified in 753 (82.6%) of these cases (Table 1).

Nine hundred ten (99.8%) of the 912 cases were imported. Five hundred ninety-one (64.9%) of the 910 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 591 cases, 395 (66.8%) were acquired in Africa, 63 (10.7%) in the Americas and 99 (16.8%) 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 556 (94.1%) of the 591 U.S. residents who had imported malaria. Three hundred and nine (55.6%) of the 556 residents had not taken any chemoprophylaxis, and 121 (49%) of the remaining 247 had not taken drugs recommended by CDC for the area visited, which included seven people who took a recommended drug in combination with a nonrecommended drug and were

subsequently excluded from this report. Only 126 (22.7%) of the 556 U.S. residents had taken a medication recommended by CDC (2).

Of the 126 case-patients who took one of the drugs recommended by CDC, 86 (68.3%) took mefloquine weekly, 29 (23.0%) took doxycycline daily, 5 (4.0%) took chloroquine, and 6 (4.8%) took Malarone.

Of the 121 case-patients who took a nonrecommended antimalarial drug, 48 (39.7%) 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.

One of the four *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*) was identified in 108 of the 126 case-patients who took a drug recommended by the CDC. In eighteen additional cases the species could not be determined, and these were excluded from the following analyses.

Cases of P. vivax or P. ovale. Among the 108 U.S. residents who developed malaria after using recommended chemoprophylaxis, 65 cases (60.2%) were caused by *P. vivax* (n = 56) or *P. ovale* (n = 9). Thirty-seven 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 18 cases were relapsing infections. Six cases of *P. vivax* and one case of *P. ovale* occurred within 45 days after the patient returned to the United States, and an additional two cases of *P. vivax* and one case of *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 108 malaria-infected U.S. residents who took recommended prophylaxis, 40 (37.0%) had *P. falciparum* and 3 (2.8%) 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 2002, a total of 295,401 and 119,269 prescriptions were sold for mefloquine (Lariam and generic) and Malarone, respectively. We assumed the vast majority were for malaria prophylaxis, and not treatment. No prophylaxis failures were documented among those who were adherent to Malarone. Prophylaxis failure rate for mefloquine among cases who reported being adherent was 0.68 per 100,000 prescriptions. This number was 3.39 per 100,000 for mefloquine failures among all cases, regardless of adherence to prophylaxis. 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

Nine hundred ten cases of imported malaria between January and December 2002, including 591 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, 422 (75.9%) of the 556 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 nonrecommended prophylaxis for the region to which they were traveling. Of the 129 (23.2%) persons who reported taking recommended prophylaxis, 37 (28.7%) 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.

One of the limitations of this report was that some case-surveillance data were missing. Even after contacting healthcare providers or local/ state departments of health, thirty-five (5.9%) of the 591 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. However, data on adherence were only available for 40 (75.5%) of the 53 non-relapsing cases. More importantly, only four prophylaxis failures occurred among those who reported adherence to

prophylaxis suggesting continued efficacy of these drugs. Two of these were *P. vivax* cases that occurred more than 21 days after return from travel; these could still possibly have been relapsing infections although not characterized as such in the current report which uses >45 days as the cut-off to define a relapsing infection. No prophylaxis failures occurred on Malarone, and that for mefloquine was 0.68 per 100,000 prescriptions which is lower than reported last year (1.85 per 100,000). In summary, when travelers take appropriate chemoprophylaxis, prophylactic failures rates are incredibly low.

ACKNOWLEDGMENT

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References

1. Centers for Disease Control and Prevention. Health information for international travel, 2001-2002. 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. IMS New Prescription Audit, June 2003

**Table 1. Total number of reported malaria cases -- United States,
January - December 2002**

<i>Plasmodium</i> Species	Number	(%)
P. falciparum	413	45.3
P. vivax	277	30.4
P. malariae	27	3.0
P. ovale	28	3.1
Undetermined	159	17.4
Mixed	8	0.9
Total	912	100.0

Table 3. Characteristics of imported malaria cases in U.S. residents who took recommended prophylactic regimens (n=126), January - December 2002

Characteristic*	Mefloquine (n = 86)	Doxycycline (n = 29)	Chloroquine** (n = 5)	Malarone (n = 6)
Age in years; mean (SD)	26.0 (16.1)	28.9 (12.0)	24.8 (22.2)	23.3 (22.7)
Gender (male); no (%)	56 (65.1)	16 (55.2)	3 (60.0)	4 (66.7)
Species (%)				
P. falciparum	24 (27.9)	14 (48.3)	0 (0)	2 (33.3)
P. vivax	41 (47.7)	9 (31.0)	4 (80.0)	2 (33.3)
P. ovale	9 (10.5)	0 (0)	0 (0)	0 (0)
P. malariae	1 (1.2)	2 (6.9)	0 (0)	0 (0)
Unknown	11 (12.8)	4 (13.8)	1 (20.0)	2 (33.3)
Mixed	0 (0)	0 (0)	0 (0)	0 (0)
Top 2 States reporting highest number of malaria cases	California (n=28) Michigan, Florida (n=6 each)	California (n=14) Wisconsin (n=3)	Five states (n=1 each)	California, Florida, Hawaii, North Carolina, Vermont, Washington (n=1 each)
Top 2 Countries or regions of acquisition with highest number of cases	PNG [‡] (n=13) India, Nigeria (n=8 each)	Uganda (n=5) Ghana, PNG [‡] (n=3 each)	Honduras (n=6) Guatemala (n=2)	Kenya (n=2) Indonesia, Nigeria, PNG, Thailand (n=1 each)
Patients who were hospitalized; no (%)	36 (41.9)	15 (51.7)	4 (80.0)	4 (66.7)
Patients with complicated malaria; no (%)***	0 (0)	1 (3.5)	0 (0)	0 (0)
Fatal Cases	1 (1.2)	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.

[‡] Papua New Guinea

Table 4. Imported non-relapsing* malaria infections in U.S. residents after use of recommended prophylaxis, (n =53)

<i>Plasmodium</i> Species	Month of Onset	Country of Acquisition	Drug Taken	Adherence to Prophylaxis	No. of days after return to the U.S.
<i>P. vivax</i>					
1	April	Burma	Doxycycline	No	17
2	July	Burma	Mefloquine	No	Ill before return
3	April	Ethiopia	Mefloquine	Unkown	Ill before return
4	January	Liberia	Mefloquine	Unknown	6
5	July	Malagasy Republic	Doxycycline	Unkown	30
6	April	Nigeria	Mefloquine	No	9
7	May	PNG	Mefloquine	Yes	27
8	October	PNG	Doxycycline	Yes	41
<i>P. falciparum</i>					
1	April	Africa, Unspecified	Doxycycline	Unkown	28
2	November	Africa, West	Doxycycline	No	219
3	Unkown	Africa, West	Mefloquine	No	Unknown
4	January	Cameroon	Doxycycline	Unknown	12
5	July	Central African Rep	Mefloquine	No	21
6	November	Ghana	Doxycycline	No	0
7	June	Ghana	Doxycycline	No	5
8	August	Ghana	Doxycycline	No	8
9	September	Ghana	Mefloquine	No	18
10	August	Ghana	Mefloquine	Unkown	22
11	October	Ghana	Mefloquine	No	44
12	June	Ghana	Mefloquine	Yes	Ill before return
13	September	Ivory Coast	Mefloquine	No	21
14	October	Ivory Coast	Mefloquine	No	44
15	September	Ivory Coast	Mefloquine	No	Ill before return
16	July	Kenya	Mefloquine	Unknown	18
17	January	Kenya	Mefloquine	No	28
18	Unknown	Kenya	Malarone	No	Unknown
19	December	Laos	Doxycycline	No	0
20	June	Laos	Doxycycline	No	Unknown
21	December	Liberia	Mefloquine	No	Ill before return
22	January	Malagasy Republic	Mefloquine	No	16
23	April	Malawi	Mefloquine	Unknown	6
24	August	Mali	Mefloquine	No	4
25	Unknown	Niger	Mefloquine	No	Unknown
26	August	Nigeria	Mefloquine	Unknown	5

27	May	Nigeria	Mefloquine	No	11
28	July	Nigeria	Mefloquine	No	16
29	August	Nigeria	Doxycycline	No	Ill before return
30	May	Nigeria	Mefloquine	No	Unknown
31	April	Philippines	Doxycycline	No	2
32	November	Sierra Leone	Doxycycline	No	0
33	February	Sudan	Mefloquine	Unknown	9
34	August	Tanzania	Mefloquine	No	Unknown
35	May	Thailand	Malarone	No	Ill before return
36	May	Uganda	Doxycycline	Unknown	2
37	May	Uganda	Doxycycline	No	3
38	May	Uganda	Doxycycline	No	14
39	June	Zambia	Mefloquine	No	7
40	July	Zambia	Mefloquine	No	36

P. malariae

1	August	Malawi	Doxycycline	Unknown	12
2	March	Philippines	Mefloquine	No	18
3	June	South Africa	Doxycycline	Yes	Ill before return

P. ovale

1	January	Cameroon	Mefloquine	Unknown	18
2	March	Ghana	Mefloquine	No	Ill before return

* 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 2002

<i>Plasmodium</i> Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	malarone	
P. vivax	1	1	0	0	2
P. falciparum	1	0	0	0	1
P. malariae	0	1	0	0	1
P. ovale	0	0	0	0	0
Total	2	2	0	0	4

*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 2002

<i>Plasmodium</i> Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	malarone	
P. vivax	2	1	0	0	3
P. falciparum	5	3	0	0	8
P. malariae	0	1	0	0	1
P. ovale	1	0	0	0	1
Total	8	5	0	0	13

Figure 1. Number of imported malaria cases in U.S. residents, by state in which the disease was diagnosed – United States, January– December 2002 (n=591)

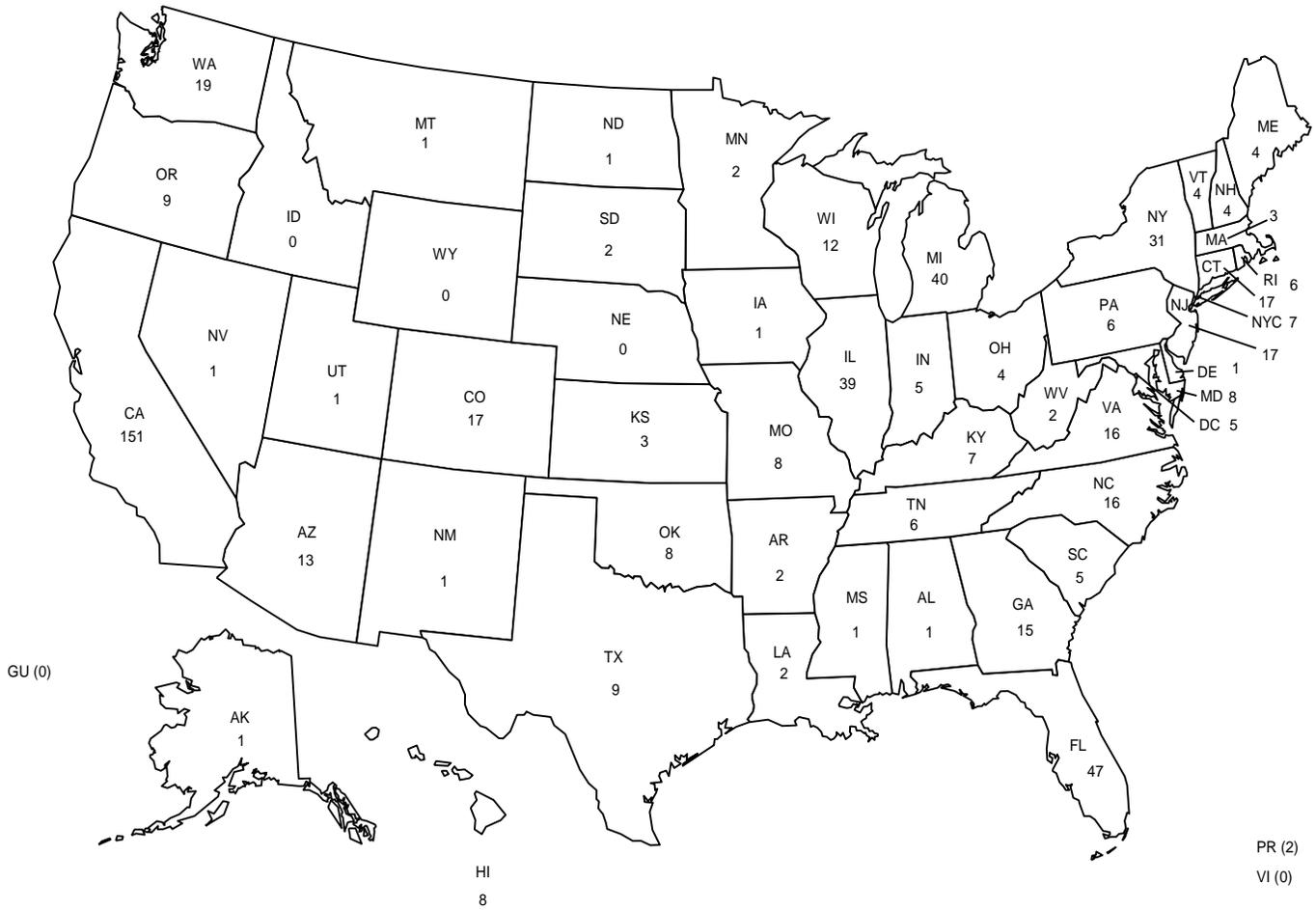


Table 2. Number of imported malaria cases in U.S. residents, by Plasmodium species and area of acquisition - United States, January - December 2002

Country	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. malariae</i>	<i>P. ovale</i>	Unknown	Mixed	Total
Africa	256	36	16	13	71	3	395
Benin	1	0	0	0	1	0	2
Burkina Faso	4	0	0	0	0	0	4
Burundi	0	0	1	0	0	0	1
Cameroon	16	2	0	2	1	0	21
Central African Republic	2	0	0	0	0	0	2
Chad	0	0	1	0	0	0	1
Congo	2	1	0	1	2	0	6
Equatorial Guinea	1	0	0	0	0	0	1
Ethiopia	1	5	0	0	0	0	6
Gambia	1	0	0	0	1	0	2
Ghana	43	2	3	3	9	2	62
Guinea	4	0	0	0	2	0	6
Ivory Coast	12	2	0	1	2	0	17
Kenya	17	3	1	1	7	0	29
Liberia	6	2	1	0	2	0	11
Malagasy Republic	2	1	0	0	0	0	3
Malawi	4	0	1	0	0	0	5
Mali	4	0	0	0	0	0	4
Mauritania	0	0	0	0	0	1	1
Niger	1	1	0	0	0	0	2
Nigeria	89	5	5	2	25	0	126
Senegal	5	2	0	0	0	0	7
Sierra Leone	5	0	0	0	0	0	5
South Africa	2	1	1	0	0	0	4
Sudan	2	1	0	0	0	0	3
Tanzania	3	2	0	0	2	0	7
Togo	1	0	0	0	2	0	3
Uganda	5	1	0	1	6	0	13
Zaire	0	0	0	0	1	0	1
Zambia	5	0	0	1	2	0	8
Zimbabwe	1	0	1	0	0	0	2
Africa, East	0	2	0	0	0	0	2
Africa, West Unspecified	5	0	0	0	0	0	5
Africa, Unspecified	12	3	1	1	6	0	23

Asia	10	74	2	3	9	1	99
Afghanistan	0	2	0	0	0	0	2
Burma	0	3	0	0	0	0	3
China	0	1	0	0	0	0	1
India	1	32	1	1	6	0	41
Indonesia	0	10	0	1	1	0	12
South Korea	0	17	0	0	2	0	19
Laos	2	1	0	0	0	0	3
Pakistan	0	3	0	1	0	1	5
Philippines	3	2	1	0	0	0	6
Thailand	2	1	0	0	0	0	3
Yemen	1	0	0	0	0	0	1
Asia, Unspecified	0	1	0	0	0	0	1
Southeast Asia, Unspecified	1	1	0	0	0	0	2
Central America and Caribbean	14	29	1	1	3	0	48
Costa Rica	0	3	0	0	0	0	3
Dominican Republic	0	1	0	0	0	0	1
El Salvador	0	2	0	0	0	0	2
Guatemala	1	3	0	0	0	0	4
Haiti	11	1	0	0	1	0	13
Honduras	2	11	1	1	2	0	17
Nicaragua	0	1	0	0	0	0	1
Panama	0	6	0	0	0	0	6
America, Central Unspecified	0	1	0	0	0	0	1
North America	0	1	0	0	0	0	1
Mexico	0	1	0	0	0	0	1
South America	1	8	1	0	4	0	14
Argentina							0
Brazil	0	3	0	0	1	0	4
Ecuador	1	3	1	0	2	0	7
Venezuela	0	1	0	0	1	0	2
America, South Unspecified	0	1	0	0	0	0	1

Oceania	3	20	1	0	5	0	29
Papua New Guinea	3	18	1	0	4	0	26
Solomon Islands	0	0	0	0	1	0	1
Vanuatu	0	2	0	0	0	0	2
Unknown	2	2	0	0	0	1	5
Total	286	170	21	17	92	5	591